Siegfried Mense
Robert D. Gerwin
Editors

Muscle Pain

Understanding the Mechanisms

Springer

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Foreword

This edition of the companion volumes *Muscle Pain: Understanding the Mechanisms* and *Muscle Pain: Diagnosis and Treatment* is essential reading for those interested in clinical approaches to acute and chronic pain conditions involving muscle tissues and in the mechanisms underlying these conditions. The volumes cover a very important topic in pain medicine, since muscle pain is very common and can often be difficult to diagnose and treat effectively. Furthermore, chronic pain involving muscle and other components of the musculoskeletal system increases with age, such that it is a common complaint of those of us who are middle-aged or older. Indeed, as changing population demographics in "westernized" countries result in higher proportions of the population living longer and being middle-aged and elderly, chronic muscle pain will likely become even more of a health problem.

In the case of acute muscle pain, this can often be very intense, and in the short term can limit or modify the use of components of the musculoskeletal system associated with the sensitive muscle. Chronic muscle pain can also be intense, as well as unpleasant and disabling, and it is in many cases the over-riding symptom of most musculoskeletal disorders that are associated with long-term deleterious changes in musculoskeletal function. This can present a challenge both to the patient who has to live with the condition and to the clinician called upon to assist the patient, not only because of the physical or biomechanical impediment but also because of the presence of chronic pain reflecting persistent alterations in the peripheral muscle tissues and/or central nervous system. Chronic pain is now recognized as a multidimensional experience encompassing cognitive, emotional and motivational aspects as well as the sensory or perceptual dimension. Thus, as the editors of this work note in their preface, it can distort the patient's life, including work, family and social relationships, and can change the patient's perception of himself or herself from being an effective and independent human being to one who is ineffective and dependent. These features apply especially to patients with chronic muscle pain, and the range and impact of most musculoskeletal disorders and the pain that they manifest dictate that clinicians need to have a

good knowledge base about pain and adopt a broad biopsychosocial perspective in order to provide effective management of the patient. These companion volumes provide this knowledge base and perspective.

Although the etiology and pathogenesis of several muscle pain conditions are still unclear, recent advances have been made in understanding muscle pain mechanisms and in the management of the conditions. The chapters in these books collectively provide up-to-date details of these mechanisms and management approaches. The anatomy and neurophysiology relevant to muscle pain is covered in *Muscle Pain: Understanding the Mechanisms*. It offers a solid basic science underpinning for the more clinically oriented second volume, *Muscle Pain: Diagnosis and Treatment,* which outlines present knowledge of etiologic and pathophysiologic processes, and which also deals with current approaches to the management of the various conditions manifesting muscle pain.

Like its predecessor, these companion volumes should prove to be an invaluable resource not only to clinical practitioners wanting to have a basic understanding of pain mechanisms and clinical approaches currently available to diagnose and manage muscle pain problems, but also to basic and clinical pain scientists who are interested in an up-to-date and comprehensive review of the diagnostic and management approaches to muscle pain.

Toronto Barry J. Sessle

Preface

Disorders of the musculoskeletal system are the leading causes of disability in western societies. Musculoskeletal pain syndromes can be divided into two broad categories: (1) myalgias, which include the major condition of myofascial pain syndromes, as well as inflammatory and other myosites, and (2) articular disorders, which include all of the arthritides. Fibromyalgia has long been considered a chronic musculoskeletal pain syndrome, but recent research supports categorizing fibromyalgia as a widespread chronic pain syndrome. Ergonomic and postural and other structural dysfunctions, including pain associated with the hypermobility syndromes, can bridge these two categories, although they tend to fall more into the myalgic group of disorders.

A problem for the practitioner trying to understand a patient's pain is that pain is a subjective sensation that is colored by the patient's personal life experience, and ethnic and cultural background. Chronic pain is not simply a sensation, but a global experience that involves suffering and a distortion of the patient's role in all phases of life, including family, work and social relationships, and can change the patient's self perception of him- or herself from being an independent, effective human being, to being a dependent, ineffective person. Communication is particularly difficult with chronic pain patients, because chronic pain is such a personal experience of global suffering, rather than a simple sensation like touch. There is a definite effect of gender on pain perception. Therefore, when examining muscles in patients for painful conditions, the greater sensitivity of women to painful stimuli has to be taken into account.

Pain from muscle and skin is subjectively and objectively distinct. Muscle pain is described as aching and cramping, diffuse and poorly localized, whereas cutaneous pain is described as sharp and pricking, and precisely localized. Cutaneous pain is usually not referred to other body regions, while muscle pain is commonly referred to other deep somatic structures like tendons and fascia or other muscles, and viscera (viscerosomatic pain syndromes). Objective differences between muscle and cutaneous pain exist in the processing of neuronal information at the

spinal and brainstem level and continue up to the brain, where nociceptive activity from skin and muscle terminates in different regions. Some of the established pain terms used in this book are defined in chapter 1 of the volume "Muscle Pain: Understanding the Mechanisms".

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Chapter 1
Introduction

Siegfried Mense and Robert D. Gerwin

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Abstract The introduction presents the terms and concepts that underlie the chapters that follow. Many complex and unique terms have arisen in the field of muscle pain; they must be clearly understood when studying this phenomenon. For example, there is a difference between nociception, the activation of the neural matrix that responds specifically to noxious stimuli, and the sensation of pain that is subjective and of chronic pain in particular that evokes an affective and emotional response reflected in activation of specific areas of the brain. The terms associated with nociception are defined, and the mechanisms of transduction and transmission of nociceptive impulses through the nervous system cranially to activate the cortex resulting in the perception of pain are introduced. The differences between acute and chronic pain, and the unique features of muscle pain in contrast to cutaneous pain, are addressed in the introduction. Peripheral and central sensitization is of great importance in the transition from acute to chronic pain. The principles that underlie sensistization that results in increased intensity of pain, and in the spread of pain sensation spatially and temporally, summarized in the term referred pain, are introduced in this section. Muscle pain is associated with muscle hardness (specifically in myofascial pain syndrome) that is associated with muscle hardness. Muscle contracture, muscle spasm, cramp and stiffness are differentiated in the introduction. The mechanisms that underlie contracture, important in such conditions as myofascial pain syndrome, are explained. Finally, it is recognized that nociception does not simply follow a direct ascending path from peripheral stimulation to activation of the dorsal horn neuron and then thalamic and cortical neurons. The introduction lays the groundwork for the later discussion in the text of descending pain modulation mechanisms that are essential to understanding the sensation that we finally call pain.

1.1 Subjective Nature of Pain Terms

There is no objective standard against which to test the extent to which the sensation which one individual describes as an aching pain is physiologically the same as that which another individual means when describing aching pain. The problems presented by the subjective quality of pain perception and the lack of a precise descriptive terminology regarding it are more than semantic. The official definition of pain by the International Association for the Study of Pain (IASP) emphasizes this aspect:

> *Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage*
>
> (Merskey and Bogduk 1994).

Cortical imaging studies show that individuals with pain due to the same stimulus in the same part of the body may exhibit activations in different parts of the brain or different degrees of activity in the same part. Pain is an individual experience, particularly if it is chronic, and is influenced by past life experiences and several other factors (e.g., genetic, emotion, attention, etc).

Chronic pain has a dimension of suffering not characteristic of acute pain. Apparently, patients describing their chronic "pain" actually describe suffering caused by the persistence of pain. Most practitioners do not have a comparable experience, and therefore are likely to have difficulty understanding what the patient is trying to communicate. Chronic pain activates brain areas that are distinct from those activated by acute pain. This has been demonstrated by cortical imaging studies (see May 2007 for review). Generally, acute pain mainly activates the primary sensory cortex, whereas chronic pain elicits strong activation in the anterior cingulate gyrus, and in other cortical areas that are associated with the affective–motivational component of pain.

The subjective nature of pain makes it impossible to prove or disprove that the patient is in pain. For these reasons, the examiner must accept the patients' pain at face value. Validation of the patient's complaint of pain by the examiner is critical in establishing a therapeutic relationship. If patient's descriptions seem exaggerated, it may be due to the patient's impression that the examiner is discounting what is reported. It is also possible that peripheral and central sensitization (see Chaps. 3 and 4) results in pain complaints that may seem out of proportion to the cause of the pain or to the physical findings.

1.2 Established Pain Terms (partly after Merskey and Bogduk 1994; Loeser and Treede 2008)

1.2.1 General Terms

1.2.1.1 Nociception

Pain originates in the cortex; therefore, all the processing of neuronal information about a noxious stimulus in the central nervous system (CNS) below the cortex is called nociception. Nociception can be studied in an anesthetized individual, but pain cannot (under anesthesia, there is nociception but no pain). Fibers conducting the information about a noxious stimulus are called nociceptive fibers; when a sufficiently high level of activity in these fibers reaches the cortex, pain may be perceived.

1.2.1.2 Noxious Stimulus

An actual or potential tissue-damaging event.

1.2.1.3 Nociceptor

A sensory receptor that is capable of transducing and encoding noxious stimuli.

1.2.1.4 Nociceptive Neuron

A central or peripheral neuron that is capable of encoding noxious stimuli. Nociceptive central neurons are

1. Wide-dynamic range (WDR) neurons, which have a low threshold for activation and reach maximum discharges during noxious stimulation, and
2. High-threshold (HT) or nociceptive specific (NS) neurons, which have a high stimulation threshold in the noxious range. These neurons require noxious stimuli for activation.

1.2.1.5 Pain Matrix

The term includes all structures of the brain that are activated – more or less specifically – by painful stimuli. The matrix includes the insula, prefrontal cortex, anterior cingulate cortex and amygdala (parts of the limbic system), and the thalamus.

1.2.1.6 Central Pain

Pain initiated or caused by a primary lesion or dysfunction in the CNS.

1.2.2 Increased Sensitivity

1.2.2.1 Allodynia

Pain due to a stimulus that does not normally evoke pain. Pain threshold is decreased, and the stimulus and the response are of different sensory modalities (categories). An example is pain evoked by gentle tactile stimulation.

1.2.2.2 Hyperalgesia

An increased pain response to a stimulus that is normally painful (stimulus and response are of the same modality). Many cases of hyperalgesia have also features of allodynia**.** The IASP (Loeser and Treede 2008) proposes to use hyperalgesia as an "umbrella term" for all cases of increased pain sensitivity, because it is often difficult to know if a stimulus is capable of activating nociceptors.

1.2.2.3 Hyperesthesia

Increased sensitivity to stimulation. The increased sensation is of the same category as the applied stimulus.

1.2.2.4 Hyperpathia

A painful syndrome characterized by abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. There is an increased threshold and increased response, and stimulus and response are of the same category.

1.2.3 Decreased Sensitivity

1.2.3.1 Analgesia

Absence of pain in response to stimulation which would normally be painful.

1.2.3.2 Hypoalgesia

Diminished pain in response to a normally painful stimulus. There is an increased threshold and decreased response, and stimulus and response are of the same category.

1.3 Established, But Often Ill-Defined, Pain Terms

1.3.1 Contracture (in the Physiological Sense)

Sliding of the actin and myosin filaments of a muscle without preceding activation of the neuromuscular endplate. For instance, contractures can occur when Ca++ is released from the sarcoplasmic reticulum (the intracellular calcium store of the muscle cell) not by action potentials propagating along the muscle fiber, but by chemical agents (e.g., high doses of caffeine; for details see chaps. 2–4 in the companion volume by Mense and Gerwin 2010).

1.3.2 Muscle Spasm

Spasm can be defined as an involuntary, longer-lasting contraction of a muscle or a muscle group. If the contraction is painful, it is often called cramp. Spasm and cramp in the sense of this definition are associated with electromyograph (EMG) activity. If chronic involuntary shortening of a muscle occurs without EMG activity, the term contracture is more appropriate.

1.3.3 Muscle Stiffness

The term is used to describe discomfort with movement of a joint. It is also used in the engineering sense: with increased stiffness, greater force is required to produce the same movement. In this sense, spastic muscles have increased stiffness.

1.3.4 Muscle Tone

The tone of a muscle is usually defined as its resting tension, clinically determined as resistance to passive movement. Muscle tone has two main components: (1) the viscoelastic component. It is independent of nerve activity and reflects the passive physico-chemical properties of muscle tissue (tension of elastic fibers, osmotic pressure of cells). (2) The contractile component. It is due to a low-frequency activation of a small number of motor units. Its presence can be detected in the EMG. Note that a completely relaxed muscle has only viscoelastic tone, i.e., it is "silent" in the surface EMG. (In the needle EMG, however, there is low-level activity in some motor units).

1.3.5 Projected Pain

Pain caused by a lesion of nerve fibers (compression or inflammation) along their course in a peripheral nerve or dorsal root. At the site of the lesion, action potentials are generated that reach central nervous neurons via the same afferent fibers that normally signal the presence of a stimulus at the receptive ending. The central neurons cannot recognize the origin of the action potentials, and interpret any activity in a nerve fiber as coming from the receptive ending. Therefore, projected pain is felt in the innervation territory of the damaged nerve fibers.

1.3.6 Referred Pain

Referred pain is not felt at the site of a tissue lesion but remote from it. The area of referred pain is often discontinuous with the site of the lesion. Referred pain can occur together with local pain (at the lesion site) or in isolation. Since pain originating in a given muscle tends to exhibit a relatively constant pattern of referral, it is often possible to identify the muscle from which the pain originates if the pattern is known. If the pain is referred from one site to several remote locations it is often described as "radiating." Referred pain is usually – but not always – segmental, occurring in myotomes innervated by the same nerve root or neighboring nerve roots which innervated the original source of pain. Trigger points

in axial (trunk) muscles can thus refer pain through the body, so TrPs in dorsal muscles can have a ventral body representation. Thus, referred pain is due to a central nervous mechanism (see Chap. 5) and does not necessarily occur in the same segment, whereas projected pain occurs exclusively in the innervation territory of a lesioned nerve or dorsal root.

1.3.7 Spread of Pain

The term used by patients for describing the expansion of a body region in which pain is felt. In contrast to referred pain (see above) the expansion is often continuous with the original site of pain. The mechanisms underlying spread of pain are probably identical to those leading to referral of pain, and probably involve central sensitization.

1.4 General Aspects of Pain and Nociceptor Function

Centuries ago, pain was assumed to be an emotion like pleasure and fear. In the nineteenth century, the hypothesis was put forward that pain is due to activation of a set of specialized nerve endings, i.e., pain is a sensation like touch. Max von Frey (1896) was the first to link pain to fine nerve terminals in the skin. Recently, the old view has returned in a certain way: pain is often viewed "more like a motivational drive than a sensation, resembling hunger, thirst or sexual drive" (Scholz and Woolf 2002). Pain is not a homogenous entity. Pain is classified by its underlying mechanisms. Thus, there is nociceptive pain (due to excitation of nociceptors by external stimuli), inflammatory pain (mediated by inflammatory mediators released by an inflamed organ), and neuropathic pain (evoked by lesions of the central or peripheral nervous system). Pain can arise from different organ systems. Thus, cutaneous, visceral, and musculoskeletal (somatic) pain can be distinguished.

The term "nociceptor" is derived from the Latin word "noxius" for damaging or harmful. It denotes a sensory ending that detects actual or potential tissue damage. Usually, the stimulation threshold of a nociceptor is just below tissue-damaging intensity. The nociceptive system is supposed not to signal tissue damage but to have primarily a warning function: it is activated when stimuli approach tissue-threatening intensity. However, not all pain is associated with potential tissue damage. Distension of hollow viscera such as the bladder, and stretching of organ capsules can give rise to nociceptive activity. Excitation of nociceptors may cause pain in humans and pain-related behavior in animals. The information originating in a nociceptor together with the neuronal structures carrying this information are called nociceptive ("measuring harmful stimuli"); the stimulus exciting a nociceptor is a "noxious" one.

A nociceptor can also be defined by its capability of distinguishing between an innocuous and a noxious stimulus. This means that a nociceptor's discharge frequency increases with the intensity of a stimulus, not only until pain threshold

is reached but also within the noxious range. (In contrast, the discharge of a sensitive mechanoreceptor levels off when the stimulus reaches noxious intensities). The term "pain receptor" instead of nociceptor should be avoided, because receptive endings are named after the stimulus they measure and not after the sensation they can cause. Thus, pain is the result of an activation of nociceptors, but nociceptors do not measure pain.

Excitation of nociceptors does not always evoke pain. Actually, the link between nociceptor activation and induction of pain is relatively loose: there are situations in which massive traumas do not cause pain (e.g., in soldiers in combat), and in other situations there can be pain without activation of nociceptors (e.g., in patients with phantom pain (Nikolajsen and Jensen 2006)). Moreover, there are pain-modulating pathways in the CNS that enhance or reduce pain. Therefore, the occurrence of pain depends on the balance between pain-promoting and pain-inhibiting influences, and not only on the presence of a noxious stimulus or excitation of nociceptors.

Nociceptive free nerve endings are present in almost all tissues and organs of the body. Exceptions are the brain, parenchyma of the lung, liver, and cartilage, where nociceptors are missing. Conversely, pain is the predominant or only sensation that can be elicited by stimulation of cornea, dura mater, and tooth pulp.

The great majority of nociceptors are connected to the CNS by unmyelinated afferent fibers. (An afferent fiber, or "afferent" for short, conducts action potentials from the periphery to the CNS). In morphological studies of the endings of unmyelinated fibers, it may be difficult to distinguish postganglionic sympathetic (efferent) fibers from unmyelinated afferent ones. The presence of neuropeptides is an important criterion, since = calcitonin gene-related peptide (CGRP), for example, is absent from postganglionic sympathetic fibers (Ju et al. 1987), but is present in and released from most unmyelinated nociceptive nerve endings.

Not all unmyelinated afferent fibers supply nociceptors. In cutaneous nerves, there are thermoreceptors and low-threshold mechanoreceptors with unmyelinated afferent fibers, and low-threshold mechanoreceptors with unmyelinated afferents can also be found in skeletal muscle (Light and Perl 2003; Hoheisel et al. 2005). The latter ones are assumed to mediate pressure and tension sensations from muscle tissue (Graven-Nielsen et al. 2004). Another important function for these non-nociceptive endings in muscle is to adjust circulation and respiration to the requirements of muscle work. In contrast to nociceptive fibers, these slowly-conducting muscle afferents are activated by a physiological degree of exercise (moderate contraction force and physiological stretch) and send their information to the circulatory and respiratory centers in the medulla (McCloskey and Mitchell 1972).

1.5 Muscle Pain Versus Skin Pain

While painful sensations derived from the human skin are associated with brisk movements, with rise of pulse rate, and with a sense of invigoration, those derived from deeper structures are often associated with quiescence, with slowing of the pulse, a fall of blood

pressure, sweating, and nausea. The last phenomenon, nausea, is responsible for the common designation "sickening," which is applied to pain derived from the deeper structures but never to cutaneous pain. This syndrome, or vasovagal response, to deep pain occurs frequently when joints are painfully stimulated; it has also been witnessed in painful stimulation of muscle, deep fascia, and periosteum and in puncturing arteries. ..... It never occurs, apparently, with cutaneous pain

Thomas Lewis 1942

1.5.1 Subjective Differences

1.5.1.1 First and Second Pain

Some of the subjective differences between muscle and skin pain are listed in Table 1.1. First plus second pain occurs when a fast, short-lasting stimulus acts on a cutaneous nerve or innervation territory of a skin nerve, for instance an electrical stimulus or a sudden blow to a skin region. The first pain has as a sharp, pricking character, whereas the second pain is felt much later, has a dull or aching character and often includes after-sensations. The first pain in the skin is due to impulses in the relatively fast-conducting thin myelinated fibers. In muscle, activity in these fibers is apparently not felt, and therefore there is no first pain from muscle.

1.5.1.2 Pain Localization

In contrast to cutaneous pain, which is localized with great accuracy, muscle pain is difficult to localize. However, in older studies on pain from other deep somatic structures (subcutaneous tissues excluding viscera), e.g., fascia and periosteum, the painful sensations are often described as originating in a single spot (Kellgren 1938; Staff 1988).

From a teleological point of view, there is no need for a good localization of muscle pain, because the typical body reaction to this type of pain is guarding or immobilization of the painful muscle. In contrast, cutaneous pain typically exhibits the good localization necessary for removing external noxious stimuli by well-directed motor reflexes and voluntary body movements. Muscle pain is not avoided or abolished by such reflexes or movements.

Table 1.1 Subjective differences between muscle and skin pain

Muscle pain	Skin pain
No first and second pain upon electrical stimulation	First and second pain upon electrical stimulation
Ill localizable	Well localizable
Tearing, cramping, pressing character	Stinging, burning, cutting character
Strong tendency for pain referral	No pain referral
Hard to tolerate, strong affective component	Better tolerable, weak affective component

One possible explanation why a painful stimulus to muscle is less easy to localize than a stimulus to the skin is the lower innervation density of muscle tissue (see also Chap. 2). However, direct quantitative comparisons between the innervation density of muscle and skin have not been published so far and are difficult to make, because muscle tissue is three-dimensional and skin largely two-dimensional. It is generally assumed that innervation density decreases in the order: skin, muscle, and viscera. Nevertheless, the innervation density of muscle tissue is high enough to ensure a multiplicity of sensory functions. In the rat gastrocnemius–soleus muscle nerve, more than half of all fibers are afferent, i.e., they conduct impulses from receptive nerve endings to the spinal cord (Baron et al. 1988). These data underline the function of skeletal muscle as a sense organ.

Moreover, in addition to innervation density, many other factors determine the capacity to localize a stimulus, e.g., the degree of convergence in the CNS. Convergence means that many afferent fibers from different tissues contact one central neuron. A high spatial resolution of a neuronal network requires a combination of a high innervation density of the peripheral tissue with little convergence in the CNS.

1.5.1.3 Nature of Pain

Typically, muscle pain is described as aching and cramping, while cutaneous pain is characterized by its sharp, pricking, and stabbing nature. For the differences in the character of muscle and skin pain, no ready explanations are available, except the speculation that both pains activate different areas in the cortex, which may lead to different sensations (Svensson et al. 1997a).

1.5.1.4 Referral of Pain

Electrical stimulation of muscle nerve fascicles with a needle electrode has been shown to elicit localized muscle pain at low intensities of stimulation; at high intensities, the area of pain first expanded, and then pain referral to regions not innervated by the stimulated nerve appeared (Torebjörk et al. 1984). High-intensity stimulation of a cutaneous nerve fascicle did not lead to pain referral (Marchettini et al. 1990). The skin very rarely refers pain to other regions.

Visceral pain resembles muscle pain in that it is difficult to localize. The main difference between these two types of pain is that visceral pain is mainly referred to the skin, whereas muscle pain is referred generally to deep somatic structures. Another difference is that tissue-threatening (noxious) stimulation of muscle and of skin always elicits pain, if strong enough. However, noxious stimulation of viscera, e.g., cutting or crushing – which are effective pain stimuli for muscle and skin – do not produce pain, if the area of stimulation is small (Bielefeldt and Gebhart 2006). Both muscle and visceral pains are associated with autonomic symptoms

such as drop in blood pressure, sweating, and nausea. In cutaneous pain, these reactions are missing.

The strong tendency of muscle pain to be referred may be due to the spinal connectivity of nociceptive fibers from muscle, and their capacity to induce changes in the excitability of neurons in the CNS. Nociceptive input from muscle is known to be more effective in this regard than cutaneous input (Wall and Woolf 1984). This view is supported by the finding that temporal summation is more pronounced with stimulation of periosteum and muscle than skin (Nie et al. 2005). Temporal summation of pain means that the pain increases when painful stimuli of constant intensity are repeated at short intervals (seconds).

1.5.1.5 Affective Pain Component

Muscle pain is typically harder to tolerate than cutaneous pain; the affective–emotional (suffering) component of the pain sensation is stronger with muscle pain (Svensson et al. 1997b). This difference may be due to the different supraspinal centers to which the nociceptive neurons project: the centers for muscle pain appear to have stronger connections with the limbic system, which is responsible for the affective–emotional component of pain.

1.5.2 Objective Differences

Most of the objective differences listed in Table 1.2 were discovered in animal experiments.

1.5.2.1 Flexion Reflexes

When the skin of a limb is painfully stimulated, a flexion reflex is elicited. The reflex consists of a contraction of flexor muscles of the limb, resulting in withdrawal of the limb from the noxious stimulus (an example is the reflex removal of the

Table 1.2 Objective differences between muscle and skin pain

Muscle pain	Skin pain
No flexion reflexes when muscle is stimulated	Marked flexion reflexes when skin is stimulated
Weak synaptic contacts of unmyelinated muscle afferents with dorsal horn neurons	Strong synaptic contacts of unmyelinated cutaneous afferents with dorsal horn neurons
Supraspinal processing of muscle nociception mainly in mesencephalon, strong projection to anterior cingulate gyrus in cortex	Supraspinal processing of cutanous nociception mainly in thalamus, weak projection to anterior cingulate gyrus
Strong effect of descending antinociceptive system on nociception from muscle	Weak effect of descending antinociceptive system on nociception from skin

hand from a flame). Teleologically, the lack of flexion reflexes elicited from muscle makes sense, because a painful lesion in muscle is not influenced by flexing the limb.

1.5.2.2 Differences in Synaptic Effectiveness and CNS Targets of Afferent Fibers

In animal experiments, the weak synaptic contacts between unmyelinated muscle afferents and dorsal horn neurons become obvious when the action potentials of dorsal horn neurons are recorded. Approximately 10% of the dorsal horn neurons respond to the stimulus when unmyelinated muscle afferents are stimulated electrically; the proportion is greater than 30% to stimulation of a cutaneous nerve (sural n.) (Hoheisel et al. 1997). One of the reasons for this difference is the tonic inhibition of nociceptive fibers from muscle by activity in thick afferent fibers from the skin. When the thick fibers are blocked pharmacologically, the unmyelinated fibers from muscle have much stronger synaptic effects (Lambertz et al. 2006). This means that generally the excitatory action of nociceptive fibers from muscle in the spinal cord is small, but their modulating effects on dorsal horn neurons are strong.

Dorsal horn cells driven by muscle nociceptors show marked convergence of input from skin and other deep somatic tissues and probably also from viscera (Grubb et al. 1993; Yu and Mense 1990), i.e., these neurons can be excited by stimulation of all these tissues. This applies particularly to neurons having input from soft tissues in the low back (Taguchi et al. 2008).

Dorsal horn cells processing information from cutaneous nociceptors show little convergence, i.e., they cannot be driven by input from different types of tissue (e.g., skin, muscle, viscera). Many appear to receive input exclusively from nociceptors in the skin. The highly convergent input from various tissues to neurons processing information from muscle nociceptors may contribute to the diffuse nature of muscle pain in comparison to cutaneous pain.

In the CNS, the information from muscle and cutaneous nociceptors is processed differently. One example is that the nociceptive information carried in spinal afferent fibers from deep tissues and the skin, respectively, terminates in different regions of the spinal cord: noxious stimulation of skin excites neurons in all laminae of the dorsal horn, whereas following muscle stimulation, no neurons in lamina II (substantia gelatinosa) are activated (Ohtori et al. 2000). In the mesencephalon, there are similar differences: Neurons responding to stimulation of muscle nociceptors are located in the ventral periaqueductal gray matter (PAG), whereas cells responding to cutaneous nociceptors are located in the lateral PAG (Keay and Bandler 1993; Ohtori et al. 2000). Thalamic nuclei with strong spinal nociceptive input from the skin are the ventral posterolateral (VPL) and medial intramedullary nuclei, whereas for nociceptive input from muscle, the ventrolateral (VL) nucleus is an important relay (Gholami et al. 2006).

In other brain areas, too, differences in the termination between nociceptive input from muscle and skin were found. In the rat, a particularly strong input from muscle

nociceptors was found in the accumbens and amygdala nuclei as well as the paraventricular nucleus of the hypothalamus (Ohtori et al. 2000). In an fMRI study of the cortex in humans, a stronger activation of the anterior cingulate gyrus was found when a skeletal muscle was stimulated in comparison to stimulation of the overlying skin. However, in this study the differences were not significant (Svensson et al. 1997a). The authors concluded that "the perceived differences between acute skin and muscle pain are mediated by differences in the intensity and temporospatial pattern of neuronal activity within similar sets of forebrain structures."

1.6 Descending Pain-Modulating Influences

The PAG in the mesencephalon – one of the main supraspinal centers for the processing of nociceptive impulses from muscle – is also the site of origin of descending pain-modulating pathways (Fields 2004). There are not only pathways that inhibit pain sensation (antinociceptive tracts) but also those that facilitate (enhance) them (pronociceptive tracts). In electrophysiological experiments on rats, a stronger action of the descending antinociceptive system on dorsal horn neurons mediating nociception from muscle was found (Yu and Mense 1990). This finding may relate to the observation that long-lasting physical exertion (e.g., in sports competitions) which is known to activate the descending antinociceptive tracts, reduces pain sensations from deep somatic tissues to an extent that lesions of the musculoskeletal system go unnoticed.

1.7 Transition from Acute to Chronic Pain

One definition of chronic pain is that pain which persists past the normal time of healing; in clinical practice, a period of 3–6 months is accepted as a dividing line between acute and chronic pain (Merskey and Bogduk 1994). Muscle pain is well-known for its tendency to become chronic.

In chronic pain patients, the pain has lost the function of a warning system; it has become a disease of its own. The factors controlling the transition from acute to chronic muscle pain are still under investigation. In Chap. 4, some of the mechanisms governing this transition are presented in more detail.

1.8 Interactions Between Psychosocial and Somatic Factors

There can be no doubt that psychosocial factors modulate pain perception. This is particularly valid for chronic pain. Since it is likely that affective status has some influence on pain perception, the remaining questions are by what mechanisms and by what magnitude do psychosocial influences cause somatic dysfunctions.

This problem may be linked to another question, namely why one patient with an acute lesion recovers normally and another patient with the same lesion develops chronic pain. The answer that in one patient the lesion resolved, relieving the pain, whereas in the other the lesion did not resolve and the pain persisted, is much too simple. There is general agreement that exactly the same lesions in two patients can show quite different time courses, one resolving completely and the other leading to chronic pain. Therefore, as well as somatic factors, other influences must be involved. A possible explanation is that in different patients the descending pain-inhibiting or -facilitating pathways have different degrees of activity. It is conceivable that a low tonic discharge rate in neurons of the descending pain-inhibiting pathway is associated with a propensity to develop chronic pain.

Another explanation is the influence of psychosocial factors. This does not mean that in these cases the chronic pain is psychogenic; pain is aggravated and perpetuated by psychosocial problems and dysfunctions. The neuroanatomic basis of these influences is strong connections between the limbic system (e.g., the amygdala which is involved in fear and stress reactions) and those mesencephalic nuclei that mediate muscle pain. The psychosocial factors are often overlooked because they are so varied, and it takes great experience to identify them. In some patients, psychological stressors can be potent aggravating factors (for instance, in fibromyalgia and chronic temporomandibular pain). For details, see Chaps. 4–7 in companion volume by Mense and Gerwin (2010).

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Chapter 2
Functional Anatomy of Muscle: Muscle, Nociceptors and Afferent Fibers

S. Mense

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Abstract Nociceptors are free nerve endings, but not all free nerve endings in skeletal muscle are nociceptive. Nociceptive free nerve endings are connected to the CNS by thin myelinated fibers or unmyelinated afferent fibers. In the light microscope, free nerve endings look like a string of beads, i.e., they consist of axonal expansions (varicosities) connected by thin axonal segments. The neuropeptide substance P has been reported to be present predominantly in nociceptive afferent fibers.

In the electron microscope, a prominent feature of nociceptive nerve endings is that they are not free in the strict sense but ensheathed by Schwann cells.

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At present, there are no clear ultrastructural differences between non-nociceptive free nerve endings (e.g., sensitive mechanoreceptors and thermoreceptors) and nociceptive ones.

Functionally, different free nerve endings are assumed to possess different sets of receptor molecules in their axonal membrane. Receptor molecules that are particularly important for the function of muscle nociceptors are acid-sensing ion channels (ASICs) that open at a low tissue pH, P2X3 receptors that are activated by binding adenosine triphosphate (ATP), and the transient receptor potential receptor subtype 1 (TRPV1) that is sensitive to high temperatures and low pH.

2.1 Structure and Basic Function of Skeletal Muscle

A skeletal muscle is ensheathed by tight connective tissue, the epimysium, which in some muscles forms a dense fascia. An example is the anterior tibial muscle, which contracts inside the tube-like fascia with minimal distortion of the skin. Each muscle is composed of several fascicles (groups of muscle fibers or fiber bundles) that are surrounded by less dense connective tissue, the perimysium. The smallest macroscopic unit of a muscle is the muscle fiber (or muscle cell), each being separated from the others by a thin layer of loose connective tissue, the endomysium. Altogether, the connective tissue of a muscle can be viewed as a continuum that extends from the epimysium to the endomysium, and which has spaces in between that are filled by the muscle fibers. The connective tissue of muscle is functionally important, because it contains elastic fibers and maintains the shape and length of a muscle after deformation (contraction, stretch, pressure). Moreover, many pathologic processes take place not in the muscle cells proper but in the connective tissue where the blood vessels are located.

Each muscle fiber is composed of many myofibrils which consist of a chain of sarcomeres (Fig. 2.1). A sarcomere is the smallest functional unit of a skeletal muscle; it is approximately 2.5 μm (micrometers or microns) long in resting muscle. Inside the sarcomeres, the molecular filaments of actin and myosin are located, which interdigitate and slide against each other during contraction and relaxation of a muscle. The thin actin filaments are fixed to the Z band or Z disk that forms the border of a sarcomere in the direction of the long axis of the muscle cell. The myosin filaments are thicker than the actin filaments; they bridge the gap between two actin filaments. A third important molecule inside a sarcomere is titin, a long coiled molecule that is assumed to act like a spring, and brings the sarcomere back to its original length after stretch (Fig. 2.2). Titin also contributes to the elastic stiffness of a muscle.

The myofibrils in a muscle fiber are arranged in a way that the myosin and actin filaments of adjacent fibrils are in alignment. Thus, the myosin filaments of many myofibrils lie beside each other, and form the dark band (the anisotrope or A band) of the striations in skeletal muscle fibers that can be seen with a light microscope. Anisotrope means that the band is birefringent in polarized light. Without such an

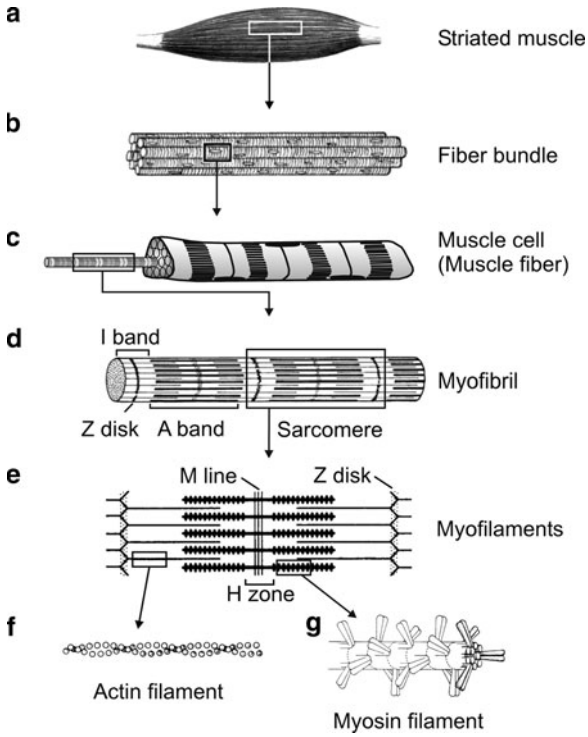

Fig. 2.1 Composition of skeletal muscle tissue. (**a**) Whole muscle showing longitudinally arranged muscle fiber bundles. The bundles are separated from each other by loose connective tissue (perimysium, not shown). (**b**) Muscle fiber bundle containing several muscle fibers (muscle cells). Each muscle fiber is enveloped by a fine layer of loose connective tissue (endomysium, not shown). (**c**) Single muscle cell showing the typical striations and three nuclei close to the cell membrane. The round profiles at the cut left end of the cell indicate cross-sections of myofibrils that contain the contractile filaments. One of the fibrils is shown protruding from the cell; it consists of a chain of sarcomeres. The *box* marks two sarcomeres that are shown in (**d**) at a higher magnification. Sarcomeres are the smallest functional units of a striated muscle; they extend from one Z line (or Z disk) to the next. (**e**) Components of a sarcomere. Thick myosin molecules with spiny heads lie in the center. They interdigitate with thin actin molecules that are fixed to the Z disk. The isotropic (I) band on both sides of the Z line contains actin filaments, only (see **d**). The anisotropic (A) band contains both actin and myosin filaments with the exception of its middle portion (the lighter H zone) which is free from actin. The M-line (M-band) consists of proteins that are important for the stability of the sarcomere structure; they crosslink the myosin filaments. During contraction, the actin and myosin filaments slide against each other; thus, the I band and H zone become narrower whereas the A band maintains a constant width. (**f, g**) An actin filament consists of two chains of globular proteins, whereas the myosin filament is a bundle of many threadlike proteins from which the myosin heads protrude. A single myosin molecule consists of two heavy protein chains and two pairs of light chains the latter forming the myosin head

accurate alignment of the fibrils – as is the case in smooth muscles – no striations would be visible. The filaments themselves can not be seen at the light microscopic level.

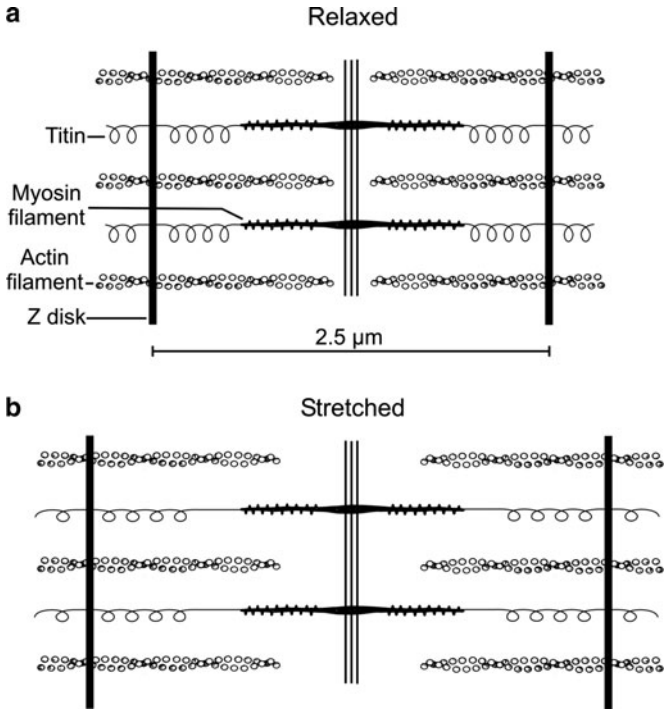

Fig. 2.2 The function of titin. Titin is the largest protein molecule of the human body; it consists of approximately 30,000 amino acids. The protein connects the myosin filaments with the Z disks (**a**) and has also connections with the actin filaments (not shown). It has a coiled structure, and functions as a spring that – together with the other elastic elements of muscle tissue – brings the sarcomere back to its original length after muscle stretch (**b**). Titin is probably an important factor contributing to the elastic stiffness of the muscle

The A band has a darker outer zone (closer to the Z disk) which is due to the overlap between myosin and actin filaments, and a paler inner zone, the H band or zone which marks that region of the A band where only myosin filaments are present. Sarcomere regions close to the Z disk contain actin filaments only; they look pale in the light microscope and form the isotropic (I) band (Fig. 2.1).

The contraction of a skeletal muscle cell is initiated by an action potential that arrives via the α-motor fiber at the neuromuscular endplate or junction. The action potential releases acetylcholine (ACh) from the terminal branches of the motor fiber (Fig. 2.3). The ACh diffuses across the synaptic cleft to the muscle cell membrane, and binds to specific receptor molecules on the surface of the membrane. The ACh binding opens ion channels, and positive ions (mainly Na^+) enter the muscle cell. This causes a depolarization of the muscle cell membrane, i.e., makes the inner side of the muscle cell membrane more positive. The depolarization is called endplate potential (EPP). Normally, the amount of ACh molecules released by a single action potential is large enough to depolarize the muscle cell membrane beyond firing threshold, and elicits an action potential. The normally suprathreshold potential at

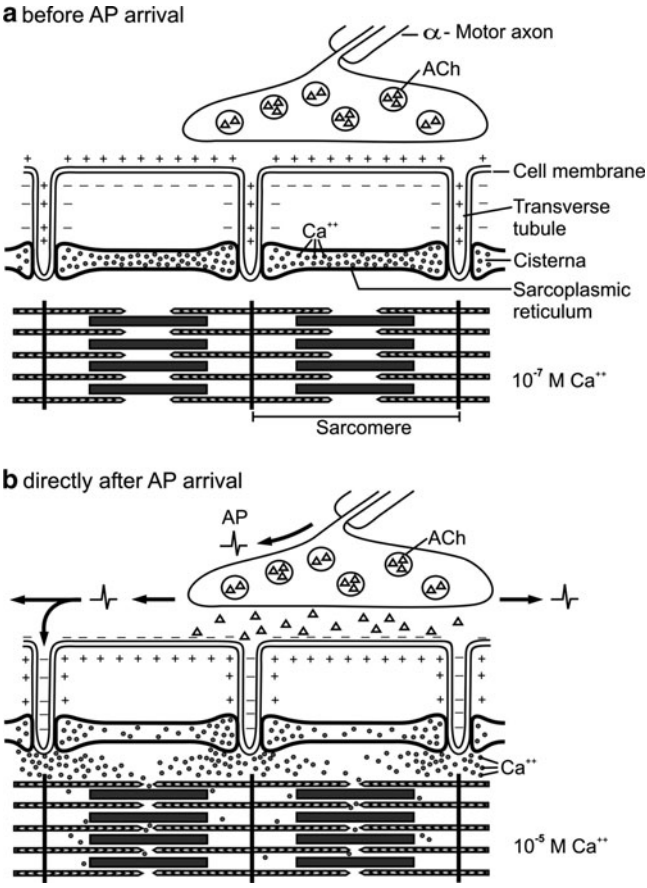

Fig. 2.3 Events leading to the sliding of the contractile filaments. The α-motor axon forms a presynaptic expansion, the neuronal part of the neuromuscular junction or endplate. The vesicles in the expansion contain acetylcholine (ACh, *open triangles*), the transmitter substance of the neuromuscular junction (**a**). When an action potential of the motor axon arrives at the endplate, it causes fusion of the vesicles with the presynaptic membrane and release of ACh into the synaptic cleft. The ACh molecules diffuse to the postsynaptic membrane, and bind to ACh receptor molecules in the membrane of the muscle cell. This induces opening of membrane channels, and influx of positively charged ions into the muscle cell. The result is a depolarization of the postsynaptic membrane, i.e., the negative electric charges on the inner surface of the muscle cell membrane (**a**) are replaced by positive ones. Normally, the postsynaptic depolarization induced by a single action potential in the α-motor axon is large enough to elicit an action potential in the membrane of the muscle cell adjacent to the endplate (**b**). The action potential is propagated over the entire muscle cell, enters the invaginations of the cell membrane (the transverse tubule) and releases calcium ions (Ca^{2+}) from the cisternae of the sarcoplasmic reticulum, which functions as an intracellular calcium store. The resulting increase in intracellular calcium concentration (from approximately 10^{-7}–10^{-5} M) is the signal for the myosin filaments to pull at the actin filaments by rowing movements of the myosin heads, and thus shorten the sarcomere (see Fig. 2.4). The ACh molecules in the synaptic cleft are cleaved by acetylcholine esterase which is present in the cleft. If the number of accessible postsynaptic ACh receptors is reduced by curare, which blocks the receptors, the depolarization does not reach firing threshold, and the muscle cell does not contract

the neuromuscular endplate is a clear difference to the postsynaptic potentials in CNS neurons, which are typically subthreshold.

In the muscle cell membrane, the EPP elicits a pair of action potentials that travel along the muscle cell in opposite directions. They make sure that all sarcomeres of the muscle cell contract at about the same time. The action potentials also reach the inside of the cell by following the transverse tubules. Transverse tubules are invaginations of the cell membrane; they have close contact with the sarcoplasmic reticulum (SR). The SR consists of a network of branching and anastomosing tubules that fill the space between the myofibrils. The reticulum has terminal expansions (cisternae) close to the transverse tubules which function as calcium stores of the muscle cell. The action potentials that enter the transverse tubules release Ca^{2+} from these cisternae. This leads to an increase of the Ca^{2+} concentration in the cytoplasm outside the SR from about 10^{-7} M to approximately 10^{-5} M. The high Ca^{2+} causes the molecules troponin and tropomyosin – which mask the binding sites for myosin on the actin filament in resting muscle – to change their positions on the actin molecule and unmask the binding sites (Fig. 2.4). Now, the heads of the myosin filaments can bind to actin, and as soon as they have done so, the neck of the myosin molecule makes a flexing movement. The sequence: attachment of the myosin heads to actin – flexion of the myosin neck – detachment of the myosin head – attachment of the myosin head to another site of the actin molecule results in a "rowing" movement of the myosin heads as long as the high Ca^{2+} concentration is present in the cytoplasm. The rowing movements pull the actin filament in between the myosin filaments, thus shortening the sarcomere.

The myosin heads possess an ATP-binding site and contain ATPase, an enzyme that splits adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and a phosphate group (P) plus energy. ATP is present in the cytoplasm, and in resting muscle is bound to the myosin head, which in this state cannot attach to the actin molecule. The enzyme ATPase cleaves ATP, and the myosin–ADP-P complex can bind to actin, if the binding sites are made available by high Ca^{2+}. The binding process is followed by the release of P, which results in a flexing of the myosin head (the so-called power stroke which moves the actin to the center of the sarcomere). The attached myosin head binds ATP again, the myosin–ATP complex is detached from the actin, the ATP is cleaved by ATPase, and the neck of the myosin head returns to its initial angle. This cycle continues as long as enough ATP is available and the Ca^{2+} is high enough. Please note that the energy released by the ATP molecule is not used for the shortening process as such (the flexing of the myosin heads) but for changing the angle of the neck of the myosin heads back to the unflexed position, and for the detachment of the myosin heads from the actin). If after detachment of the myosin head the cytoplasmic Ca^{2+} concentration is still high, the heads can attach again to the actin filament. Many successive cycles of this attaching–flexing–separating process lead to a movement of the actin filament along the myosin. Since the actin filaments are attached to the Z disk, the sarcomere is shortened.

When the cytoplasmic calcium concentration drops to the initial value, the rowing movements of the myosin heads stop. The drop in Ca^{2+} is due to the action of a molecular calcium pump which transports the Ca^{2+} back into the SR. After

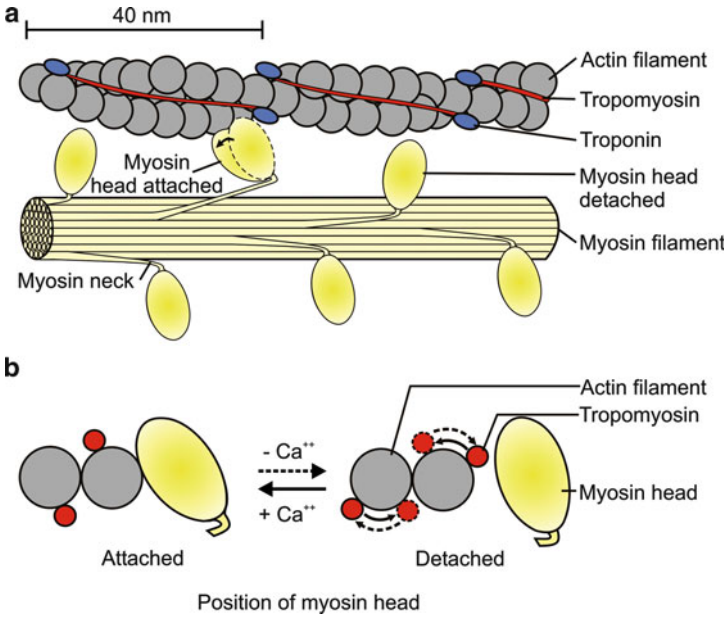

Fig. 2.4 The "sliding filament" mechanism during contraction. In the resting state, the binding sites for the myosin heads on the globular molecules of the actin chain are masked by the threadlike tropomyosin molecule and therefore not accessible (**a, b**). When an action potential of the muscle cell releases Ca^{2+} from the sarcoplasmic reticulum and the Ca^{2+} concentration in the cytoplasm of the cell rises, the tropomyosin that covers the binding sites moves aside, and the myosin heads attach to the actin molecules (**b**). Subsequently, the neck of the myosin heads make a bending movement, and thus pull the myosin filament towards the Z line (**a**). Since the attached myosin heads have the action of an ATPase (an enzyme splitting adenosine triphosphate, ATP), energy-rich ATP molecules are cleaved. The released energy is used for separating the myosin heads from the actin. By repeating this sequence of attaching, bending, and separating, the myosin heads make a rowing movement which leads to the sliding movement of the filaments that shortens the sarcomere

death, there is a general lack of metabolic energy, and the cytoplasmic ATP concentration is very low. Therefore, the myosin heads cannot separate from the actin, and rigor mortis ensues. In rigor mortis, all myosin heads are attached to actin, a situation which never occurs during life because the myosin heads take turns and some heads are always not attached.

In the microscope, a contracted muscle fiber can be recognized by the unchanged width of the A band and a narrower I and H band. There is evidence in the literature showing that in resting muscle a small proportion of the myosin heads are attached to the actin filaments (Campbell and Lakie 1998). These attached myosin heads probably contribute to the viscoelastic component of muscle tone (see Chap. 6).

Physiologically, a skeletal muscle can perform four types of contraction.

1. *Shortening (concentric) contraction*. This is characterized by reduction in muscle length produced by a generation of muscle force. An example is the

quadriceps femoris muscle extending the knee during walking uphill. These contractions, which are characterized by simultaneous length and force changes, have been termed auxotonic contractions (Li and Stephens 1994). Most contractions performed in daily life are auxotonic.

2. *Isotonic contraction.* This is defined as length change without change in the force exerted. Isotonic contractions are rare in the normal environment, because almost all movements are associated with a change in force. For instance, when lifting an arm without any load, the force of gravity, against which the contraction has to be performed, will increase until a horizontal position is reached and then decrease again. Pure isotonic contractions can be performed on an exercise machine which provides constant resistance through the range of movement.
3. *Isometric contraction*. The term describes an increase in force without length change. Isometric contractions are rare in daily life. An example is activation of the masseter muscle when the maxillary and mandibular teeth are in contact. The teeth and their supporting tissues have limited compressibility; therefore, the contraction is largely isometric. Under these conditions, the myosin heads perform their movements and pull at the actin filament, but the developed force is used not for shortening of the muscle but for putting tension on the insertion points and for stretching the elastic tissue components of the muscle. Thus, the sarcomeres shorten, but the muscle as a whole does not.
4. *Lengthening (eccentric) contraction*. This is defined as a lengthening of muscle by external forces, with the muscle resisting the lengthening. In eccentric contractions, the force developed by the muscle is smaller than that causing the lengthening (otherwise the muscle would not be lengthened). The muscle contracts to slow the lengthening. An example is the contraction of the quadriceps muscle during walking downhill. This type of contraction is particularly important for the development of muscle soreness (see below).

Skeletal muscle is composed of two main types of muscle fibers, namely "white" and "red" fibers. The proportion of each fiber type varies between muscles. White fibers look pale because they contain less myoglobin than red ones. They contain large amounts of phosphorylases and glycogen, and produce energy mainly by degrading glucose, i.e., they obtain energy by the glycolytic metabolism. One of the end products of the glycolytic metabolism is lactate, which after a short bout of contractions accumulates in such an amount that the tissue pH drops and the work has to be terminated, i.e., white fibers fatigue quickly. When white fibers are activated by a short impulse, they contract in the form of a fast twitch (approximately 25 ms duration). They are used in movements of high velocity and short duration. Examples are flight reactions of animals or short distance running in humans. The gastrocnemius muscle is a typical white muscle that is used for the fast movements of the legs.

Red muscle fibers contain more myoglobin and oxidative enzymes but less phosphorylases. When activated, they contract with slow twitches (75 ms duration), and are more resistant to fatigue. They are able to contract for long periods, because

they make use of the oxidative metabolism, i.e., they consume oxygen and obtain ATP from the mitochondria. Ideally, red fibers degrade glucose to CO_2, water, and energy. Fibers of this type are numerous in postural muscles, because they are well-suited for slow contractions of long duration. The true muscles of the back are typical examples of muscles with a high proportion of red fibers. The white fibers correspond largely to Type II fibers, and the red fibers to Type I fibers.

Small lesions of skeletal muscle can be repaired by satellite cells that are present underneath the cell membrane of each muscle cell. They are assumed to be myoblasts, i.e., cells that develop into muscle cells during development. The muscle fibers formed by these cells during regeneration of a damaged muscle are indistinguishable from the original ones. Larger areas of damaged muscle can not regenerate; they are replaced with connective tissue.

2.2 Morphology of Muscle Nociceptors

The fact that small-diameter afferent fibers have to be activated in order to elicit muscle pain is well-established (Weddell and Harpman 1940). These fibers conduct at a velocity of below 20–30 m/s (depending on the species studied), which is relatively slow in comparison to the fastest conducting fibers, which reach 100 m/s. Histologically, they consist of thin myelinated (group III) and nonmyelinated (group IV) fibers. The conduction velocity of group IV fibers is approximately 0.5–2.5 m/s in the cat, that of group III, 2.5–30 m/s. The nomenclature with Roman numerals (group I–IV) was introduced by Lloyd (1943) for muscle afferent fibers, but is now generally used for fibers from deep somatic tissues in general (muscle, joint, fascia, tendon, ligaments). Group III fibers correspond to cutaneous Aδ-, and group IV to C fibers. It is worth mentioning that not all of these small-caliber or slowly conducting fibers are nociceptive; they also include thermoreceptive and mechanoreceptive fibers. Therefore, the terms “slowly conducting fibers” or “small-caliber fibers” must not be used as synonyms for “nociceptive.”

In cutaneous nerves, there are thermoreceptors and low-threshold mechanoreceptors that have unmyelinated afferent fibers, and low-threshold mechanoreceptors with group IV afferents have also been found in skeletal muscle (Light and Perl 2003; Hoheisel et al. 2005). The presence of certain neuropeptides such as CGRP does not distinguish between high- and low-threshold mechanosensitive group IV-fiber units, because the neuropeptide is found in both functional types (Hoheisel et al. 1994).

2.2.1 Structure of Muscle Nociceptors in the Light and Electron Microscope

The first comprehensive report on the morphology of free nerve endings in skeletal muscle was published by Stacey (1969). He focused on endings supplied by

group III and IV fibers. As mentioned above, nociceptors have the morphological appearance of free nerve endings. The term "free nerve ending" indicates that in the light microscope no (corpuscular) receptive structure (Stacey 1969) can be recognized. When immunohistochemical staining for neuropeptides is used, the receptive ending looks like a string of beads, with the beads (so-called varicosities) having relatively wide diameter connected by very thin stretches of axon. The diameter of a branch of a free nerve ending is 0.5–1.0 μm, i.e., at the limit of the spatial resolution of the light microscope (Fig. 2.5a, b). A receptive ending together with its afferent fiber is called an "afferent unit."

In Stacey's study, the majority of the group IV fibers had a diameter of approximately 0.35 μm. The unmyelinated afferents were numerous and outnumbered the myelinated ones by a factor of 2. The predominant location of free nerve

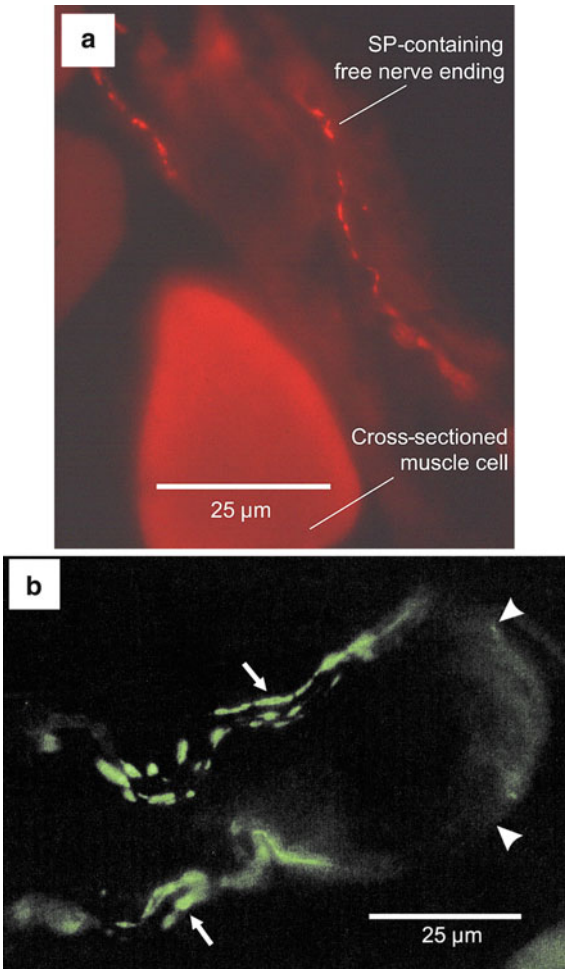

Fig. 2.5 Histology of free nerve endings in muscle. Photographs of histological sections of the rat gastrocnemius muscle show free nerve endings that contain the neuropeptide substance P (SP, **a**) and calcitonin gene-related peptide (CGRP, **b**) respectively. The fibers were visualized using antibodies to SP (**a**) or CGRP (**b**) coupled to a fluorescent marker. Please note the typical appearance of the endings as a string of beads with localized widenings of the axon (so-called varicosities) that contain vesicles filled with SP- or CGRP-immunoreactive material. From these varicosities, the neuropeptides are released when the nerve fibers are electrically active. The CGRP-containing ending was located in the connective tissue around an arteriole (*arrowheads*), the typical location of free nerve endings in muscle

endings supplied by group IV fibers was the adventitia of arterioles and venules. Surprisingly, muscle fibers themselves did not receive direct innervation by free nerve endings. Group III afferents generated not only free nerve endings but also paciniform corpuscles, whereas group IV fibers terminated exclusively in free nerve endings. The high sensitivity of the free nerve endings to chemical stimuli, particularly to those accompanying inflammatory lesions or disturbances of the microcirculation, may be related to their location on or in the walls of the blood vessels. The finding that the muscle fibers proper are not supplied by free nerve endings (Reinert et al. 1998) may relate to the clinical experience that muscle cell death is usually not painful, at least not if it occurs slowly, as for instance during muscular dystrophy, polymyositis, or dermatomyositis. A different situation is tearing of a muscle fiber bundle, which can be extremely painful. In this condition, many muscle cells are destroyed simultaneously and release their contents (e.g., K^+ ions and ATP) in the interstitial space, from where they can diffuse to the next nociceptive endings.

Usually, a single group IV fiber has several branches, each of which possesses various receptive sites. All branches that are located closely together in a small volume of tissue form a receptive ending. An ending can extend over relatively long distances and can have several receptive branches which again have several receptive sites. The physiological term receptor refers to an entire morphological ending.

At present, it is not possible to correlate morphological features of free nerve endings with the functional types found in electrophysiological experiments (see Chap. 3). There is general agreement that muscle nociceptors are free nerve endings, but their exact ultrastructure is unknown and no electronmicroscopic criterion exists that allows a distinction between a nociceptive free nerve ending and a thermoreceptive or mechanoreceptive one. However, the notion that there are several morphological types of free nerve ending in muscle supports the assumption that these receptors do not form a homogeneous group, but consist of functionally different types.

In skeletal muscle, the free nerve endings appear to be distributed quite evenly in the proximodistal direction. At least, in a quantitative evaluation of the innervation density by neuropeptide-(SP- and CGRP-) containing fibers, no difference between the proximal and distal portions of the rat gastrocnemius–soleus (GS) muscle was found (Reinert et al. 1998). Therefore, a higher innervation density at the transition zone between muscle and tendon is not a probable explanation for the frequent pain in this region. However, in the same study the nerve fiber density in the peritendineum (the connective tissue around a tendon) of the rat calcaneal tendon was found to be several times higher than that in the GS muscle. In contrast, the collagen fiber bundles of the tendon tissue proper were almost free of free nerve endings. The high fiber density in the peritendineum may explain the high prevalence of tenderness or pain in the tissue around the tendon and the insertion site. The scarcity of nerve endings in the center of the tendon may relate to the clinical observation that (incomplete) ruptures of the tendon may occur without pain.

In an electron microscopic investigation on sympathectomized cats, von Düring and Andres (1990) reported that group III and IV endings were predominantly located in the perimysium surrounding larger or smaller bundles of muscle fibers. Other locations were the adventitia of arterioles, venules, and lymphatic vessels, and finally the sheath of nerve fiber bundles. These latter terminals were assumed to originate from nervi nervorum (nerves supplying the nerves themselves). In muscle, the terminals of group III fibers were generally larger than those of group IV fibers, and they contained more mitochondria and a more distinct receptor matrix (see below). The authors suggested that those terminals (mainly originating from group III fibers) that had a close association with connective tissue may have a mechanoreceptive function mediating stretch or pressure, whereas endings that lacked this feature, but had a spatial relation to mast cells, were nociceptors.

Electronmicroscopic data demonstrate that the varicosities of free nerve endings contain mitochondria and vesicles, and show other structural specializations characteristic of receptive structures. However, free nerve endings are not free in the strict sense, because most of them are ensheathed by a single layer of Schwann cells. In contrast to myelinated fibers where each Schwann cell is wrapped in multiple layers around a small stretch of the axon, the Schwann cells of unmyelinated fibers form a single layer. The Schwann cells of unmyelinated fibers leave parts of the axon membrane uncovered (Andres et al. 1985). Here, the only structure that separates the axon membrane from the interstitial fluid is the basal membrane. The exposed membrane areas are assumed to be the sites where external stimuli (particularly chemical stimulants) act (Fig. 2.6; Andres et al. 1985; Messlinger 1996; see also Heppelmann et al. 1990a, b for free nerve endings in the joint).

The arrangement of cell organelles [mitochondria, vesicles, and axonal reticulum (a network of fluid-filled vacuoles or channels)] embedded in the axonal cytoplasm of the varicosities was called *receptor matrix* by Andres and von Düring (1973)) (see also Kruger et al. 2003). Often, nociceptive endings exhibit granular or dense core vesicles containing neuropeptides. The function of the round clear vesicles in the peripheral ending is still obscure. They may contain the same transmitters as the central synaptic terminal, which is glutamate for nociceptive afferent units.

2.2.2 Receptor Molecules in the Membrane of Nociceptors

In the following paragraphs, a distinction is made between "receptor" as a term for a receptive nerve ending, and "receptor molecule" (or "membrane receptor") for a molecule that binds a specific stimulant or is activated by a thermal or mechanical stimulus. In the biochemical literature, the term "receptor" describes the receptor molecule.

The specific receptor molecules in the membrane of nociceptive endings (Fig. 2.7) are divided into two main classes: ionotropic and metabotropic receptors.

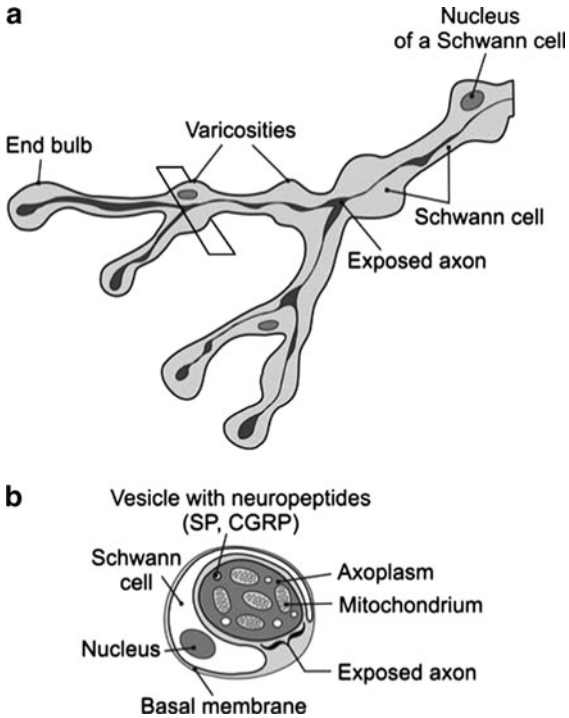

Fig. 2.6 Ultrastructure of free nerve endings. (**a**) Reconstruction of a free nerve ending from electron microscopic sections. The ending has several branches and exhibits the typical varicosities. Schwann cell processes ensheath the ending almost completely, and leave only small patches of axon uncovered (exposed axon areas). The exposed areas are the site where chemical stimuli are assumed to act. (**b**) Cross-section through a varicosity of the ending (*boxed* in **a**). The varicosity resembles a presynaptic terminal in that it contains many mitochondria (providing energy) and vesicles containing neuropeptides that are released when the ending is excited

Ionotropic receptors are large proteins that form a channel or pore that spans the entire width of the axonal membrane. Usually the channel is closed; after binding a specific stimulating molecule (its ligand), the channel opens, and ions flow across the membrane according to their concentration difference inside and outside the membrane (Na^+ ions will enter the ending, K^+ and Cl^--ions leave the ending). Binding of the ligand to a metabotropic receptor on the outer surface of the membrane activates a G protein (guanine nucleotide-binding protein) on the inside of the membrane. G proteins alternate between an inactive guanosine diphosphate (GDP) and active guanosine triphosphate (GTP) bound state; in the activated state, they regulate intracellular metabolic cascades. For instance, they change the state of activation of intracellular second messenger systems such as phospholipase C (PLC), cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), and protein kinases (PKs). One sequel of the activation of these messengers, particularly the PKs, is the phosphorylation of ion channels. Phosphorylation means that a phosphate residue is coupled to another molecule, for instance a channel protein. The phosphorylation increases the opening time or opening probability of the channels, i.e., it leads to increased ion fluxes across the membrane. Collectively, the processes lead either to direct excitation of the ending or to a changed reaction of the nerve ending to external stimuli [sensitization (increased excitability) or desensitization (decreased excitability)].

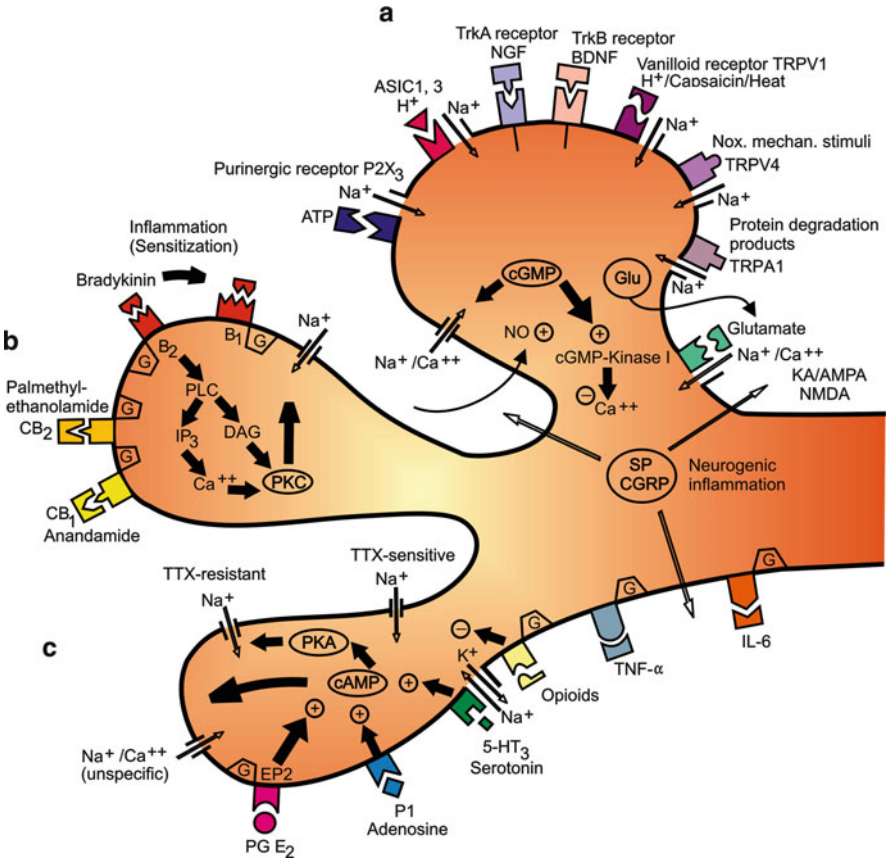

Fig. 2.7 Membrane receptors of a nociceptive nerve ending. Of particular importance for muscle pain are the receptor molecules and processes shown in branches **a**, **b** and **c**. (**a**) There are two main receptors sensitive to H^+ ions: acid-sensing ion channels (*ASIC 1, 3*) and the transient receptor potential subtype V1 (*TRPV1*). The purinergic receptor *P2X3* binds *ATP*, a molecule that is present in each cell of the body but has a particularly high concentration in muscle cells. ATP could serve as a general pain signal, because it is released by any cell damage. All these receptor molecules are ion channels which span the axonal membrane and are permeable to Na^+ and other cations (Ca^{2+} and/or K^+). (**b**) Shows the change of the bradykinin receptor B2 to B1. In intact tissue, *bradykinin* (BKN) excites or sensitizes the ending by acting on the B2 receptor; in inflamed tissue, it binds to the newly synthesized B1 receptor. BKN exerts its action not by opening an ion channel but by activating a G protein that regulates intracellular metabolic changes. These changes lead to an increased excitability of the ending (sensitization). The change from B2 to B1 shows that even in the very periphery there are neuroplastic changes, i.e., functional or morphological changes of neurons brought about by pathological tissue alterations. (**c**) In addition to BKN there are other sensitizing substances such as prostaglandin E2 (*PGE_2*) and serotonin (*5-HT*) which likewise bind to specific membrane receptors. The receptors for $5\text{-}HT_3$ and PGE_2 induce intracellular cascades of events that increase the sensitivity of the Na^+ channels by activating protein kinase A (*PKA*). The larger ion currents that flow through the channel proteins of a sensitized ending render the ending more sensitive to external stimuli. Branch c also shows that tetrodotoxin(TTX)- resistant Na^+ channels are present in the membrane of nociceptive endings. *cAMP*, cyclic adenosine monophosphate, a second messenger

Figure 2.7 shows a large number of receptor molecules that have been detected in the membrane of nociceptors in a variety of tissues. Judging from their responsiveness to pain-producing agents, the following receptor molecules are likely to be relevant for muscle pain and tenderness (Mense and Meyer 1985; Caterina and David 1999; McCleskey and Gold 1999; Mense 2007).

Bradykinin (BKN) receptors (B1 and B2). BKN is cleaved from blood plasma proteins when a blood vessel breaks or increases its permeability so that plasma proteins enter the interstitial space. In intact tissue, BKN excites nerve endings by the activation of the BKN receptor molecule B2, whereas under pathological conditions (e.g., inflammation) the receptor B1 is the predominant one (Perkins and Kelly 1993; for a review of receptor molecules mediating the effects of classic inflammatory (pain-producing or algesic) substances, see Kumazawa 1996). This means that in a pathologically altered muscle, for instance during inflammation, the damaged tissue sends a signal (probably nerve growth factor (NGF)) to the cell body (the soma or perikaryon) of the primary afferent neuron, which then synthesizes B2 receptors that are transported in the cytoplasma of the axon to the receptive ending and built into its membrane. The de-novo synthesis of a receptor molecule is a neuroplastic change; it demonstrates that neuroplastic changes occur not only in the CNS but also in the peripheral afferent neuron. It is often overlooked that many of the so-called pain-producing substances such as BKN excite not only nociceptors but also low-threshold mechanosensitive (presumably non-nociceptive) endings. Therefore, BKN cannot be considered a specific excitant of nociceptors.

Serotonin receptors (particularly 5-HT_3). Serotonin (5-hydroxytryptamin, 5-HT) is released from blood platelets during blood clotting. The stimulating effects of serotonin on nociceptive terminals in the body periphery are predominantly mediated by the 5-HT_3 receptor (at present, more than 15 different 5-HT receptors are known in the CNS). The serotonin concentrations released in the tissue are usually not sufficient to excite nociceptors directly, but they can sensitize them, i.e., make them more sensitive to other pain-producing agents such as BKN.

Prostaglandins, particularly prostaglandin E2 (PGE_2). Prostaglandins (PGs) are released in a pathologically altered muscle by the enzymatic action of cyclooxigenases. PGE_2 binds to a G protein-coupled prostanoid receptor (EP2) in the membrane of the nociceptive ending. Similarly to serotonin, PGE_2 sensitizes nociceptors rather than exciting them under (patho)physiological circumstances (Mense 1981).

Acid-sensing ion channels (ASICs). ASICs constitute a family of receptor molecules that are sensitive to a drop in pH and open at various pH values. The channel proteins react already to small pH changes, for instance from pH 7.4 to 7.1. This receptor family (for instance ASIC1 and ASIC3) is particularly important for muscle pain, because almost all pathologic changes in muscle are accompanied by a drop in tissue pH, e.g., exhausting exercise, ischemia, and inflammation (Immke and McCleskey 2003). In these conditions, the pH of the muscle tissue can drop to 5–6. The proton-sensitive nociceptors may also be of

importance for the induction of chronic muscle pain. Repeated intramuscular injections of acidic solutions have been reported to induce a long-lasting hyperalgesia (Sluka et al. 2001).

P2X3 receptors. This receptor is a subtype of the purinergic receptors that are activated by ATP and its derivatives (Burnstock 2007; Ding et al. 2000). ATP is the energy-carrying molecule in all cells of the body; accordingly, it is present in every tissue cell. It is released from all tissues during trauma and other pathologic changes that are associated with cell death. For this reason, ATP has been considered a general signal substance for tissue trauma and pain (Cook and McCleskey 2002). ATP is particularly important for muscle pain, because it is present in muscle cells in high concentration (Stewart et al. 1994). When injected into human muscle, ATP causes pain (Mörk et al. 2003).

Transient receptor potential receptor subtype 1 (TRPV1) formerly called VR1. This receptor is one of the most important molecules for the induction of pain. The natural stimulant for the TRPV1 receptor is Capsaicin, the active ingredient of chilli peppers (Caterina and Julius 2001). The receptor is also sensitive to an increase in H^+-concentration and to heat, with a threshold of approximately 39°C. Its endogenous ligands are H^+-ions. As for ASICs, the sensitivity of this receptor to protons is important under conditions in which the pH of the tissue is low. Acidity of the tissue increases the sensitivity of the receptor molecule to heat. For instance, in tissue with a pH of 6.3, a temperature of 26°C is sufficient for activating the receptor. Under these conditions, the normal body temperature can cause pain (Reeh and Kress 2001). This finding offers an explanation for the aching of the whole body in general infections such as flu, where the body temperature is raised (and the tissue pH probably lowered).

In microneurographic recordings from muscle nerves in humans, muscle nociceptors have been found that could be activated by i.m. injections of capsaicin (Marchettini et al. 1996). The capsaicin injections were associated with strong muscle pain. Since capsaicin is assumed to be a specific stimulant for the TRPV1 receptor, these data show that this receptor molecule is also present in human muscle nociceptors.

Other TRP receptors. TRPV4 is a mechanosensitive ion channel that is sensitive to both weak and strong (noxious) intensities of local pressure (Liedtke 2005). It may be the receptor for mediating pain evoked by pinching and squeezing. Another candidate for this function is the degenerin/epithelial sodium channel (DEG/ENaC; Goodman et al. 2004). TRPA1 has been reported to mediate pain elicited by protein degradation products that are present during many pathological tissue alterations, and during experimental induction of a tissue lesion, e.g., by injection of formaldehyde (Macpherson et al. 2007). The TRPA1 receptor is considered by some to be the central molecule for chemically induced pain (Tai et al. 2008).

Tyrosine kinase A (TrkA) receptor. The ligand of this receptor is NGF (Caterina and David 1999). NGF is well-known for its sensitizing action on nociceptors in the body periphery and neurons in the CNS; it is synthesized in muscle, and its synthesis is increased during pathophysiological changes of the muscle (e.g., inflammation, Menetrey et al. 2000; Pezet and McMahon 2006).

Glutamate receptors. There is evidence indicating that the NMDA receptor (one of the receptors for glutamate) is present on nociceptive endings in masticatory muscles. Injections of glutamate into the masseter muscle in human subjects induced a reduction in pressure pain threshold which was attenuated by coinjection with ketamine, an NMDA receptor antagonist (Cairns et al. 2006). The glutamate-induced mechanical sensitization did not spread outside the injection site; therefore, the glutamate effect likely resulted from a peripheral mechanism, i.e., from an action of glutamate on peripheral NMDA receptors.

Substances exciting muscle nociceptors independent of membrane receptors.

Hypertonic saline: injections of NaCl solutions (4.5–6.0%) have long been and still are used to elicit pain from deep somatic tissues (Kellgren 1938; for review, see Graven-Nielsen 2006). Single injections or infusions of the hypertonic solution reliably elicit a medium level of pain in patients and healthy controls. The traditional explanation for the pain-eliciting action of hypertonic saline is that when injected in high concentrations, Na^+ ions enter the ending through sodium channels and reduce the negative potential on the inside of the axonal membrane. Recently, the notion that hypertonic solutions excite nociceptors through an unspecific mechanism (e.g., by osmotic volume changes of the receptive ending) has been challenged, because there are data showing that two members of the TRP receptor family are sensitive to osmotic stimuli, namely TRPV4 (Liedtke 2005) and TRPA1 (Zhang et al. 2008). As mentioned above, both channel proteins appear to be also implicated in nociception in general.

Potassium ions: The most likely explanation for the excitatory action of high concentrations of extracellular potassium ions is a depolarization of the membrane potential due to a reduction of the inside–outside potassium gradient (usually the potassium concentration inside the axon is much higher).

Even at the electron microscopic level, no morphological specializations can be recognized among free nerve endings of different function (mechano-nociceptors, thermo-nociceptors, mechanoreceptors, thermoreceptors). Therefore, the functional differences have been attributed to the presence of special combinations of receptor molecules in the membrane of the endings (Cesare and McNaughton 1997).

2.2.3 Neuropeptide Content of Nociceptors

Most of the following data were obtained in experiments at the spinal level. Trigeminal afferents are not mentioned specifically, but most results are valid also at the trigeminal level.

Whether or not a particular neuropeptide or combination of neuropeptides is associated with a particular functional type of free nerve ending is obscure. Studies on DRG cells indicate that substance P (SP) – and to a lesser extent, also calcitonin gene-related peptide (CGRP) – is present predominantly in nociceptive units (Lawson et al. 1997; Djouhri and Lawson 2004). A strong argument supporting a

nociceptive function of SP is that noxious stimulation in the body periphery is followed by a release of SP in the dorsal horn of the spinal cord and brainstem. On the other hand, there is also evidence speaking against a relation between nociceptive function and the presence of SP. In a study by Leah et al. (1985), ten out of 12 individually identified nociceptive DRG cells of the cat did not exhibit immunoreactivity (IR) for SP. Virtually all afferent units with SP–IR also showed CGRP–IR (Garry et al. 1989); both peptides are presumably released together when the fiber is active. In the spinal cord, CGRP prolongs the action of SP by inhibiting its degradation and by facilitating synaptic transmission in general.

Data from animal experiments in which single DRG cells with receptive endings in muscle were first functionally identified, and then injected with a dye, showed that at least some cell bodies whose peripheral processes terminated in presumable nociceptors contained CGRP (Hoheisel et al. 1994). However, SP, CGRP and other neuropeptides were not only present in nociceptive units but also in other types of muscle receptor (e.g., in some muscle spindles and other low-threshold mechanosensitive (non-nociceptive) units). The only condition for the presence of CGRP seemed to be a small soma size in the DRG and/or a slow conduction velocity of the afferent fiber. Collectively, these data indicate that the correlation between a particular neuropeptide – or a combination of neuropeptides – and the afferent function of the neuron is relatively weak.

Likewise, no neuropeptide has been found that is specific for afferent fibers from a particular tissue. DRG cells projecting in a cutaneous nerve have been reported to contain SP, CGRP, and somatostatin (SOM). The same peptide pattern was found in muscle nerves, whereas visceral afferent units lack SOM (Molander et al. 1987; O'Brien et al. 1989). In comparison to skin nerves, muscle nerves appear to contain less SP. This finding makes sense, because the vasodilatation and plasma extravasation caused by the release of SP and CGRP from free nerve endings (see below) would be dangerous for skeletal muscles, since many of them are surrounded by a tight fascia. Therefore, an SP-induced muscle edema would result in a high increase in interstitial pressure, and could cause muscle necrosis.

On the other hand, there can be no doubt that a relatively high proportion of free nerve endings in muscle exhibit IR to SP and CGRP (Reinert et al. 1998). In a study on functionally identified DRG cells employing a combination of electrophysiological and immunohistochemical techniques, Lawson et al.(1997) reported that cells terminating in cutaneous nociceptive endings showed a strong tendency to express SP, particularly if they had a slow conduction velocity or a small soma in the DRG.

In the CNS, neuropeptides function as so-called neuromodulators, i.e., substances that enhance or attenuate the action of neurotransmitters. Glutamate is generally assumed to be the main neurotransmitter of nociceptive afferents in the spinal cord and trigeminal brainstem, and – with few exceptions – the neuropeptides enhance the central nervous effects of peripheral noxious stimuli (Hökfelt et al. 1980; Kow and Pfaff 1988). The peptides are synthesized in the somas of the DRG or in ganglion cells of cranial nerves. They are transported to both the central and the peripheral terminal of the primary afferent unit. In presynaptic terminals of the

spinal cord and the trigeminal nuclei, neurotransmitters and neuropeptides often coexist, and are released together when action potentials arrive at the terminal.

In a quantitative evaluation of neuropeptide-containing free nerve endings and preterminal axons (both characterized by varicosities) in the GS muscle of the rat, most endings were found around small blood vessels (arterioles or venules), whereas capillaries and the muscle cells proper were not contacted by these endings. Most numerous were the endings containing CGRP followed by SP-positive, VIP (vasoactive intestinal polypeptide) -positive, NGF-positive, and GAP-43 (growth associated protein 43)- positive endings (Reinert et al. 1998). Many endings contained more than one peptide, e.g., SP and CGRP or SP and VIP.

After 12 days of an experimental myositis, the innervation density of the muscle with neuropeptide-containing free nerve endings was significantly increased. The effect was particularly marked for endings containing SP, GAP-43, and NGF (Reinert et al. 1998). The density of the SP-positive fibers doubled in inflamed muscle. Of course, the question arises as to whether this increase was due to inflammation-induced sprouting of the nerve fibers or to an increase in the neuropeptide content of the individual fiber, so that a higher proportion of fibers were above detection threshold in the microscope. The finding that the density of NGF-positive and GAP-43-positive endings increased together with that of an SP-containing one was interpreted as indicating that sprouting had occurred, because NGF and GAP-43 are strongly expressed in growth cones.

2.3 The Nociceptive Afferent Fiber

A nerve fiber consists of an axon [a cylinder of excitable nerve membrane filled with cytoplasm (the axoplasm)] plus a sheath of Schwann cells. Unmyelinated fibers are not naked axons; they are covered by a single layer of Schwann cells. In myelinated fibers, the sheath similarly consists of a single layer of Schwann cells, but here each cell is wrapped around the axon in multiple turns and its cytoplasm squeezed out, so that the membranes of each turn contact each other. This densely packed spiral of Schwann cell membrane is the myelin. In thin myelinated fibers, the myelin consists of a few spiral turns, in thick myelinated ones the number of turns can amount to several dozen. Afferent or sensory fibers conduct action potentials from the periphery to the CNS; their cell body (soma) is located in the dorsal root ganglion (DRG), and the central process of these cells enters the CNS via the dorsal root (in the case of spinal nerves). Some cranial nerves such as the trigeminal, vagus and glossopharyngeal nerve similarly have sensory ganglia that contain the cell bodies of the afferent fibers. The entire neuron from the nerve ending in muscle to the presynaptic terminals in the spinal cord including the cell body in the DRG is a primary afferent neuron. However, there are also unmyelinated afferent fibers in the ventral root: approximately 15% of all ventral root fibers are unmyelinated afferents, the soma of which is situated in the DRG (Applebaum et al. 1976).

Efferent or motor fibers conduct action potentials from the CNS to the periphery; their soma is located in the spinal cord or brainstem and the fibers leave the CNS via the ventral root or cranial nerve motor roots. An exception are postganglionic sympathetic fibers whose cell bodies are mostly located in the sympathetic trunk (e.g., vasomotor fibers that constrict blood vessels).

In the DRG, the correlation between soma diameter and axonal conduction velocity is weaker than generally thought. This correlation was studied in intracellularly stained DRG cells of the cat (Hoheisel and Mense 1987). For group III units (DRG cells having axons conducting at 2.5–30 m/s), there was no significant correlation between soma size and conduction velocity, and for group IV units (with axons conducting at less than 2.5 m/s), the correlation was even negative. Thus, the axonal diameter or conduction velocity of a given group III or IV afferent fiber cannot be inferred from the soma size in the DRG. Usually, the majority of nociceptive free nerve endings will originate from small-diameter DRG cells, but there are also relatively large somata that have nociceptive peripheral endings.

Nociceptive afferent fibers differ from other fibers in that they are equipped with a special type of sodium channel that cannot be blocked by tetrodotoxin (TTX), the toxin of the puffer fish. These channels are called TTX-resistant (TTX-r); they are phylogenetically old, and are characterized by a slow time-course of the sodium currents and long action potential duration (Matsutomi et al. 2006). TTX blocks the conduction of action potentials in nerve fibers that possess TTX-sensitive sodium channels (mostly non-nociceptive small- and large-diameter fibers). Therefore, one of the first symptoms of TTX poisoning is numbness in the affected body region. In contrast, nociceptive fibers are equipped with many TTX-r channels; therefore, TTX has no blocking action on these fibers. Two TTX-r Na^+ channels important for nociception are the voltage-gated sodium channels (Nav) 1.9 and 1.8. Nav 1.9 has been found exclusively in nociceptive primary afferent neurons, whereas Nav 1.8 is present in both nociceptive and non-nociceptive ones (for review, see Djouhri and Lawson 2004). However, the functional distinction between Nav 1.8 and Nav 1.9 may not be as strict as formerly thought, because recently Nav 1.8 has been reported to be involved in neuropathic pain caused by compression or inflammation of DRG cells (Hudmon et al. 2008).

There is evidence indicating that nociceptive fibers from muscle are equipped with TTX-r sodium channels (Steffens et al. 2003). As TTX-resistant Na^+ channels are characteristic for nociceptive fibers, a substance that specifically blocks TTX-r Na^+ channels would be a perfect analgesic.

One of the typical functional properties of a nociceptor is its high mechanical stimulation threshold, i.e., it is not excited by light pressure or muscle movement but requires strong, subjectively painful stimuli for activation. The high mechanical threshold is surprising, considering the fact that a free nerve ending is a fragile structure with a semifluid membrane. The mechanosensitive TRPV4 receptor is being discussed as the main receptor of mechano-nociceptors (Liedtke 2005), but some doubts remain, because the receptor has been described to have a relatively low threshold to the mechanical component of osmotic stimuli (see above).

Possibly, low-threshold receptors can mediate pain sensations under certain circumstances. Recently, a discussion started about how strictly "labeled" the nociceptive endings and central pathways really are (actually, this discussion is very old and never stopped completely). The labeled line theory (or specificity theory) states that there are (high-threshold) nociceptive pathways that elicit pain and non-nociceptive (low-threshold) pathways that mediate nonpainful sensations such as touch and warmth. However, there are clinical and basic research observations indicating that sometimes non-nociceptive stimuli can cause pain in healthy normal subjects (Yarnitsky 2008). One explanation is that the final decision on the nature of a subjective sensation is made by the brain, which uses the *pattern* of the input from the periphery for this decision (and not just the activity in one specialized pathway). At present, the bulk of the available data suggest that in muscle pain research, nociceptive endings and pathways can be distinguished from non-nociceptive ones. Therefore, in this book the distinction between high-threshold nociceptors and low-threshold non-nociceptive endings has been maintained.

2.4 Fiber Composition of a Muscle Nerve

Table 2.1 shows a list of the fiber types that are present in a muscle nerve**.** Two nomenclatures are used: one classifies the nerve fibers after the diameter of the fibers and labels them with the Roman numerals I–IV (Lloyd 1943). This labeling system is generally used for sensory fibers. The other nomenclature uses the conduction velocity as a criterion and labels them with capital Roman letters or a combination of capital Roman letters and Greek letters in lower case (Erlanger and Gasser 1930).

The nerve to a locomotor muscle in the cat (the lateral GS) is composed of approximately one-third myelinated (720) and two-thirds unmyelinated (2,480) fibers (Table 2.2; Mitchell and Schmidt 1983; Stacey 1969). Nearly one quarter of the myelinated (group III) fibers had nociceptive properties in neurophysiological experiments (Mense and Meyer 1985). Of the unmyelinated fibers, 50% are sensory (group IV), and of these, approximately 55% have been found to be nociceptive in the rat (Hoheisel et al. 2005). In the sternomastoid nerve of the rat, the sensory group IV fibers likewise constitute approximately half of all the unmyelinated fibers, and thus account for the great majority of afferent units in that nerve (Sandoz and Zenker 1986).

Data obtained from one muscle nerve cannot be transferred directly to other muscle nerves, because considerable differences exist between different muscles. For instance, neck muscle nerves of the cat contain unusually high numbers of sensory group III receptors (Abrahams et al. 1984). One possible explanation for these differences is that the muscles have different functions and environmental conditions: in contrast to the neck muscles, which must register the orientation of the head in relation to the body in fine detail, the locomotor hindlimb muscles often have to contract with maximal strength and under ischemic conditions. Another

Table 2.1 Fiber types in a muscle nerve

		Type	Function (examples)	Diameter including sheath (μm)	Mean conduction velocity (m/s)
a					
Sensory fibers	Thick myelinated	Group I	Muscle spindle primary (Ia)	15	100
			Golgi tendon organ (Ib)	15	100
		Group II	Muscle spindle secondary	8	50
	Thin myelinated	Group III	Nociceptors	<3	15
			Paciniform corpuscles	<3	15
				<3	15
	Unmyelinated	Group IV	Nociceptors	1	1
			Mechanoreceptors	1	1
b					
Motor fibers	Thick myelinated	Aα	α-Motoneuron	15	100
		Aβ	Skeleto- and fusimotor	8	50
	Thin myelinated	Aγ	Fusimotor to muscle spindle	5	20
		B	Sympathetic preganglionic	<3	15
	Unmyelinated	C	Sympathetic and parasympathetic postganglionic (vasomotor)	1	1

For muscle afferent (sensory) fibers the nomenclature by Lloyd (Group I–IV) has been used (**a**). This system is based on the diameter of the fibers. The other common nomenclature uses Latin and Greek letters and is based on the conduction velocity of the fibers. It is normally applied to efferent (motor) fibers (**b**). For reasons of comparison, the mean conduction velocity is given for both sensory and motor fibers. The two systems are similar in the following respects: Group I and II are thick myelinated and correspond largely to Aα− and Aβ−fibers. Aγ- and Aδ-fibers are thin myelinated and correspond largely to Group III. The unmyelinated C fibers are identical to the Group IV afferents

Table 2.2 Composition of the nerve to the lateral gastrocnemius–soleus muscle in the cat. Notice that the unmyelinated fibers outnumber the myelinated ones by a factor of almost two, and that approximately one-third of all nerve fibers are unmyelinated sensory ones. The majority of the latter are likely be nociceptors (modified after Mitchell and Schmidt 1983)

Fiber numbers (GS nerve)			
Myelinated		Unmyelinated	
Sensory	Motor	Sensory	Motor
480	720	1,000	1,000
Sum myelinated 1,200		Sum unmyelinated 2,000	
Sum all fibers 3,200			

example for the difference between spinal and cranial nerves is that the trigeminal nerve has a lower proportion of unmyelinated fibers.

2.5 Muscle Receptors Other Than Nociceptors

In addition to nociceptors, there are other muscle receptors whose function is essential for the understanding of muscle pain. The most important ones and the nerve fibers supplying them are described below.

Muscle spindles are complex receptive structures that consist of several specialized muscle fibers (the so-called intrafusal muscle fibers; the name is derived from their location inside the spindle-shaped connective tissue sheath. Accordingly, all the "normal" muscle fibers outside the spindle are "extrafusal" fibers). Muscle spindles measure the length and the rate of length changes of the muscle, i.e., their discharge rate increases with increasing muscle length and with increasing velocity of the length change. Their discharge frequency decreases during contraction of the muscle, because they are arranged in parallel to the extrafusal muscle fibers and are relaxed by the contraction. The receptive endings of the spindle form loops around the central portion of the intrafusal muscle fibers. Stretching of that portion is the adequate stimulus for the endings. When the muscle is stretched the loops are deformed, and action potentials are evoked in the fibers connecting the spindle to the central nervous system. These fibers are of three types: the Ia fiber arises from the primary ending that responds to both static length and dynamic length changes and exhibits impulse activity at all muscle lengths. The fiber has a thick myelin sheath and is among the fastest conducting fibers of our body (around 100 m/s; Table 2.1). Group II fibers arise from the secondary ending of the muscle spindle; this is mainly sensitive to length changes (Kandel et al. 2000), and most Group II fibers are not active in a relaxed muscle. In some cases, the secondary endings are supplied by thin myelinated group III fibers. The muscle spindle is the only mechanoreceptor whose sensitivity can be changed by the CNS. To this end, the spindle has motor fibers (Aγ or fusimotor fibers) which cause a contraction of the peripheral parts of the intrafusal fibers and thus stretch the central parts. This "prestretch" increases the sensitivity of the ending to external stretch. The activity of many muscle spindles is used by the CNS to determine the angle of the joint the muscle acts upon. The main central effect of the muscle spindle Ia fiber is excitation of the homonymous muscle (the muscle that harbors the spindle). The Ia fiber has monosynaptic connections with the α-motoneuron; the function of these connections can be tested with one of the tendon jerks, for instance the patellar reflex.

Golgi (tendon) organs measure the tension of the muscle. They are arranged in series with the extrafusal muscle fibers; their location is the transition zone between muscle and tendon. The supplying fiber is the Ib afferent, whose structure is identical to the Ia fiber (thick myelin sheath and high conduction velocity). The receptor has a much simpler structure than the muscle spindle; it consists of receptive endings

that are interwoven between the collagen fiber bundles of the tendon. When the tension of the muscle increases, the endings are compressed and produce an electrical signal. Golgi organs are excited by both muscle contraction and muscle stretch, i.e., during all situations that increase the tension of the muscle. They do not possess a CNS control of their sensitivity. The main central action of the Golgi organ is inhibition of the homonymous muscle. Contrary to the traditional assumption, tendon organs are quite sensitive to stretch: The contraction of a few muscle fibers is sufficient for their activation (Crago et al. 1982). Therefore, the assumption that tendon organs require strong forces for their activation, and prevent the muscle from overload by inhibiting the homonymous α -motoneurons, is questionable.

Muscle spindles and Golgi organs are proprioceptors, i.e., they measure the internal state of the body.

Not all muscles contain muscle spindles and Golgi tendon organs: some of the external muscles of the eye bulb lack spindles and tendon organs (Büttner-Ennever 2007).

Pacinian corpuscles (PC) and paciniform corpuscles. These receptors do not respond to static pressure; they require dynamically changing mechanical stimuli, and are best excited by vibrations of relatively high frequency (close to 300 Hz; Kandel et al. 2000). The receptive ending is formed like a rod, and covered by several concentric membranes which give the receptor an onion-like appearance in cross-sections. Between the membranes, a viscous fluid is present that determines the receptive properties of the ending: a constant pressure stimulus does not excite the receptors, because the fluid moves away and the central rod is under static pressure. Alternating pressure stimuli with a fast onset and offset – such as vibrations – are transmitted to the core of the ending and excite it, because the fluid between the membranes is too viscous to move away quickly. Under these conditions, the receptor behaves like a solid structure that has a rigid connection between the concentric membranes and the receptive ending in the core of the corpuscle.

2.6 Free Nerve Endings in Tendon

The reconstruction of free endings in the calcaneal tendon of the cat at the electron microscopic level yielded various morphological types of free nerve ending connected to group III and IV afferent fibers (Andres et al. 1985). Based on morphological criteria or the location in the tissue, the authors distinguished five types of free nerve ending supplied by group III fibers. One terminated in venous vessels; it had the special feature of a flattened profile in cross-sections, and possessed exposed receptive areas on its edges. Type 2 ended in the wall of lymphatic vessels. Type 3 and 4 supplied the connective tissue around blood vessels, and one of these types had contacts to collagen fiber bundles. The collagen bundles were assumed to transfer mechanical forces to the receptive ending and, therefore, the endings were viewed as mechanoreceptors. The fifth type of group III ending innervated the endoneural connective tissues of small nerve fiber bundles.

In the same study, two types of free nerve endings of group IV fibers were described; both were located in the connective tissue of blood vessels, and some of the fibers contained granulated vesicles. The contents of the vesicles is unknown; they probably contained neuropeptides.

2.7 Free Nerve Endings in Fascia

At present, little information is available about the innervation of fascia. This is an important gap in our knowledge, because fascia is an important component of the musculoskeletal system and likely to contribute to many forms of pain that are subsumed under the label "muscle" pain. One example is low back pain: The thoracolumbar fascia (TF) plays an essential role in body posture and trunk movements (Bogduk and Macintosh 1984). It is not only a passive transmitter of mechanical forces of the low back and abdominal muscles but also contractile by itself (Schleip et al. 2005).

The available data on the innervation of the TF are scarce and partly conflicting. One of the earlier studies even suggested that the TF may not be pain-sensitive (Kuslich et al. 1991). Bednar et al. (1995) studied specimens from the TF of patients with low back pain in the light and electron microscope and found no evidence for specific end organs. They concluded that the TF was deficiently innervated in these patients. One of the reasons for this conclusion was that a few years earlier another group studying human specimens had reported the presence of encapsulated and free nerve endings in the TF (Yahia et al. 1992).

In our group, we have obtained the first – and still preliminary – immunohistochemical data on the innervation of the TF in the rat. In the connective tissue around the superficial lamina of the TF we found many CGRP- and SP-containing free nerve endings. The majority of the fibers were located in the subcutaneous layer, as well as between the fascia and the surface of the multifidus muscle (Fig. 2.8). The SP-positive endings are of particular interest, because they are thought to be nociceptors. The thick collagen fiber bundles of the fascia proper were not richly supplied with free nerve endings. The loose connective tissue around the TF is probably deformed during any trunk movement, and therefore the free nerve endings are strategically situated to sense any disorders in these movements. It is conceivable that overload of the fascia puts mechanical stress and irritation on the endings, and thus may contribute to low back pain.

2.8 Efferent Functions of Nociceptors

2.8.1 Release of Neuropeptides from the Nociceptive Ending

Neuropeptides (e.g., SP, CGRP, VIP, SOM) are stored in vesicles in the varicosities of the peripheral terminal. Whenever a nociceptor is excited, it releases the

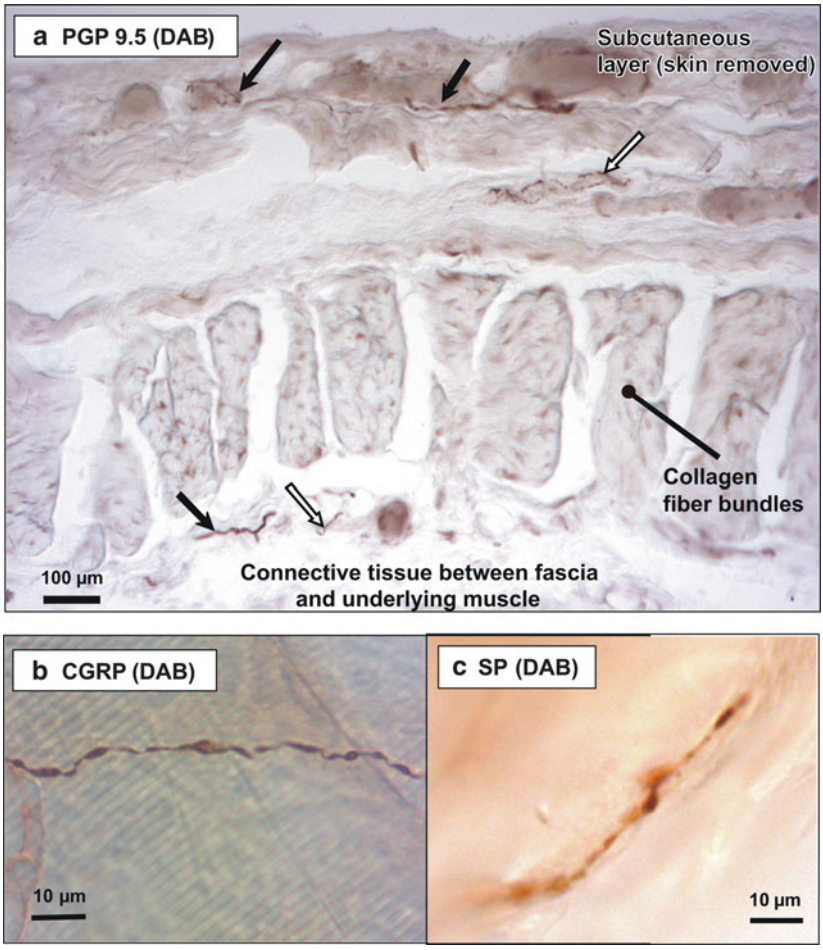

Fig. 2.8 Small-diameter nerve fibers and free nerve endings in the thoracolumbar fascia of the rat. **a** Cross-section in the coronal plane through the fascia at the level of vertebral body L5. The dense collagen fiber bundles that form the fascia proper are cross-sectioned and visible as brick-like structures in the middle layer; on both sides, loose connective tissue connects the collagen bundles to the skin and underlying muscle, respectively. Nerve fibers are mainly present in the loose connective tissue. The receptive free nerve endings are marked by *open arrows* and can be recognized by just visible widenings (varicosities). The *filled arrows* indicate small-diameter fibers of passage. Immunohistochemical fiber staining with antibodies to protein gene product (PGP) 9.5. PGP 9.5 stains all fibers, irrespective of their afferent or efferent nature. The antigen–antibody complex was made visible using the diaminobenzidine (DAB) reaction. **b** Single free nerve ending stained with antibodies to calcitonin gene-related peptide (*CGRP*). CGRP is a neuropeptide that is mainly present in afferent (sensory) nerve fibers, only, but it does not distinguish between nociceptive and non-nociceptive nerve endings. The varicosities are clearly visible. **c** Single nerve ending stained with antibodies to substance P (*SP*). The neuropeptide SP is assumed to be present predominantly in nociceptive fibers

neuropeptides into the interstitial tissue. SP then releases histamine from mast cells, and together with CGRP these agents cause vasodilatation and an increase in vascular permeability of the blood vessels around the active ending. The result is a shift of blood plasma from the intravascular to the interstitial space. Outside the blood vessel, BKN is cleaved from the plasma protein kallidin, serotonin (5-HT) is set free from platelets, and PGs (particularly PGE_2) from endothelial and other tissue cells. All these substances sensitize nociceptors. Thus, the main tissue alteration induced by a nondestructive noxious mechanical stimulus is a localized region of vasodilatation, edema, and sensitized nociceptors.

2.8.2 The Axon Reflex

The release of neuropeptides from an activated nociceptor is an essential aspect of its function. A nociceptor is not a passive sensor of tissue-threatening stimuli; it actively influences the microcirculation and chemical composition of the interstitial space around it. The morphological basis of the axon reflex is that the branches of a single nociceptive ending can extend over a relatively large area (several 100 μm; Fig. 2.9). If a noxious stimulus activates only one part of the ending, the action potentials originating in that region of the ending can invade antidromically (against the normal direction of propagation) those branches of the ending that were not excited by the stimulus. These antidromic action potentials release neuropeptides from the unstimulated branches. The whole process is called the *axon reflex*. It is assumed to be the reason for the visible wheal and flare around a cutaneous lesion. The vascular permeability is increased mainly by SP (and by the neurokinins A and B; Gamse and Saria 1985), whereas CGRP is assumed to act primarily as a vasodilator. There is evidence showing that CGRP enhances the plasma extravasation induced by SP and neurokinins A and B, but reduces the vasodilatory action of SP by desensitizing muscle arterioles to the peptide (Öhlén et al. 1988).

The area of wheal and flare after a localized damage to the skin – for instance around a needle prick – could be an indicator of the extent of the excited nociceptive ending. Of course, this applies only if a single ending is stimulated and if the distance covered by diffusion of the neuropeptides is constant.

The size of the receptive fields (RFs) of cutaneous polymodal nociceptors was found to be less than 2 mm in cat (Bessou and Perl 1969) and 6–32 mm in rabbit (Kenins 1988). A receptive field is that region of the body from which a receptive ending (or a central sensory neuron) can be excited. The above figures are larger than the reported length of the branches of a nociceptor ending (a few hundred μm; Stacey 1969). The difference may be due to the fact that nociceptors can be excited from a certain distance, particularly when coarse probes are used. For a muscle nociceptor, the size of the RF can be determined only with limitations, particularly if it is located deep within the muscle. The reported sizes of superficially located fields or the projections of deep RFs on the muscle surface range from spot-like to

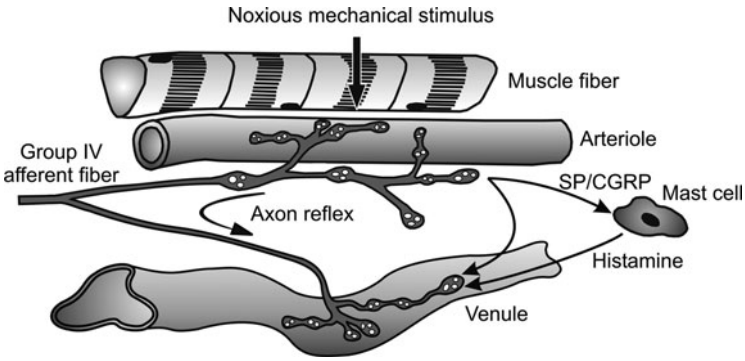

Fig. 2.9 Events occurring around a muscle nociceptor during noxious mechanical stimulation. The nociceptor has two branches, one in the connective tissue around an arteriole, another one close to a venule. The noxious stimulus (*filled straight arrow*) excites the branch on the arteriole; this leads to the release of neuropeptides from the ending such as SP and CGRP. These peptides have a direct action on the small blood vessels in the vicinity of the ending, namely vasodilation and increase in permeability. SP also degranulates mast cells; the released histamine likewise is a vasodilator. Action potentials that are generated in the fiber branch on the arteriole can retrogradely (against the normal direction of propagation) enter the branch on the venule and release neuropeptides. This process is called axon reflex; it is assumed to be responsible for the reddening and swelling of the skin around a localized lesion. The release of neuropeptides from nociceptive endings by retrograde action potentials can also occur in neuropathy or radiculopathy, when action potentials originate in sensory fibers at the site of a nerve compression and are propagated both anterogradely (to the CNS) and retrogradely (to the receptive ending; neurogenic inflammation). The increase in blood vessel permeability by SP is followed by plasma extravasation, which leads to the formation of bradykinin and other agents that sensitize nociceptors. The result of both axon reflex and neurogenic inflammation is a local edema with sensitized nociceptors

several cm^2 in the gastrocnemius muscle of the cat and dog (Kumazawa and Mizumura 1977; Mense and Meyer 1985).

2.8.3 Neurogenic Inflammation

The release of SP, CGRP, neurokinin A, and other agents from nociceptors is the central factor in the cascade of events that lead to neurogenic inflammation in the periphery (Lembeck and Holzer 1979). Neurogenic inflammation is characterized by tissue edema and infiltration by immune cells, i.e., it exhibits the major histological signs of a (sterile) inflammation. It develops whenever action potentials are generated not at the receptive ending but somewhere along the course of primary afferent units (spinal nerve or dorsal root). The action potentials propagate both to the CNS (causing pain) and to the peripheral ending (causing release of neuropeptides and neurogenic inflammation). The published data indicate that vasodilatation can be elicited by antidromic stimulation of both Aδ- and C fibers, but increase in vascular permeability and plasma extravasation by stimulation of C fibers only.

Neuropathies and radiculopathies and other pathological conditions that are associated with antidromic activity in sensory nerve fibers are examples of such events (Marchand et al. 2005). Neurogenic inflammation is likely to increase the dysesthesia and pain of patients suffering from neuropathies.

Neuropeptides also influence immune cells (for a review, see Morley et al. 1987) and synoviocytes. These actions may be of particular importance for the development and maintenance of chronic arthritis and other inflammatory disorders of deep somatic tissues.

Inflammatory disorders are usually accompanied by sensitization of peripheral nociceptors, which is one source of inflammatory pain (for details, see Chap. 3).

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Chapter 3
Peripheral Mechanisms of Muscle Pain: Response Behavior of Muscle Nociceptors and Factors Eliciting Local Muscle Pain

S. Mense

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Abstract This chapter deals with peripheral mechanisms that lead to local muscle pain and describes diseases that exhibit this type of pain. Local muscle pain is due to excitation of muscle nociceptors (so-called nociceptive pain; other forms of

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muscle pain such as radiculopathic pain or pain due to CNS lesions can occur without activation of muscle nociceptors). Nociceptors in muscle are sensitive to strong mechanical stimuli and pain-producing substances, some of which are released from muscle tissue during pathological alterations. Substances such as bradykinin and prostaglandin E_2 have a sensitizing rather than excitatory action and increase the sensitivity of nociceptors to other stimuli. This sensitization of muscle nociceptors is assumed to be the peripheral mechanism of the tenderness of lesioned muscle (there are also CNS mechanisms causing tenderness).

Clinical examples of local muscle pain include trauma, acute inflammation, and intermittent claudication. ATP, protons (H^+ ions), bradykinin, and other substances are known to be released from inflamed tissue. Ischemic contractions elicit strong muscle pain but excite just a small subpopulation of nociceptive free nerve endings. Non-nociceptive free nerve endings in muscle are likely to have an important function in the adjustment of respiration and circulation during muscular exercise.

3.1 Methods Used for Studying the Response Behavior of Single Group III and IV Muscle Afferent Units

In animal experiments, recordings of the impulse activity of single thin myelinated or unmyelinated afferent fibers are made by splitting thin nerve filaments from a dorsal root or a muscle nerve (Fig. 3.1a, b). In humans, the technique of microneurography has been and is being used (Ørstavik et al. 2006). The technique uses fine metal wire electrodes that are advanced through the skin into a nerve. The method has mainly been applied to cutaneous afferents. One of the few exceptions is a study by Marchettini et al. (1996) who recorded the activity of single slowly conducting afferent fibers from the gastrocnemius-soleus (GS) muscle.

In animal experiments, the dissection technique is performed with sharpened watchmaker's forceps under an operation microscope. The nerve-splitting procedure is continued until, during electrical stimulation of the muscle nerve with single shocks, a single action potential can be identified on the screen of an oscilloscope. When the conduction velocity of the action potential is below approximately 20 m/s one can be sure to record from a group III or group IV fiber. To exclude postganglionic sympathetic efferent fibers – which are unmyelinated and have a conduction velocity around 1 m/s – mechanical and chemical stimuli can be applied to the muscle (in microneurography, arousal stimuli such as loud shouting are used for this purpose). Afferent fibers respond to graded mechanical stimuli with a train of action potentials, whereas sympathetic efferents fire just one or two action potentials, when the stimulus damages the nerve. Chemical stimulation with biological agents does not normally excite sympathetic fibers.

To obtain a quantitative estimate of the response magnitude, the action potentials have to be counted. Nowadays, this is done by a computer software that recognizes the shape of the action potential and can monitor the action potentials of a given

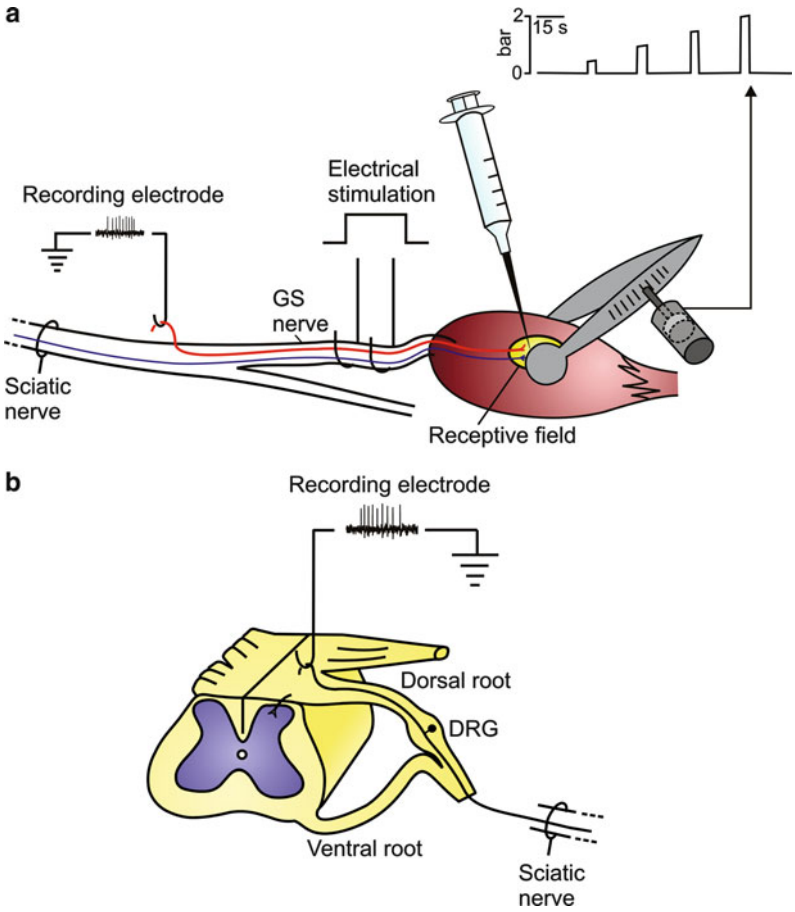

Fig. 3.1 Experimental set-up used for recording of the impulse activity of single muscle nociceptors in anesthetized cats and rats. Small filaments of the muscle nerve (**a**) or a dorsal root (**b**) were dissected by hand under the microscope and put over wire electrodes for the recording of unitary action potentials. The afferent unit under study was characterized by electrical stimulation of the muscle nerve for determining the fiber's conduction velocity, and by natural (mechanical, chemical) stimulation of the receptive ending in the muscle for determining the receptive properties of the unit. In most experiments described in this book, the location, threshold and receptive field of a given unit was first determined with mechanical stimuli applied with a modified anatomic forceps; then, various test substances were injected into the mechanosensitive receptive field (A receptive field of a neuron is that body region from which a neuron can be excited or inhibited by external stimuli). This method ensured that the receptive ending was reached by the chemical. In some experiments, the threshold of the mechanosensitive receptive field was tested with a pneumatic forceps that could be closed with a predetermined pressure. The intensity of the rectangular pressure stimuli is given in the physical unit "bar" in **a**

fiber in a strand of fibers in which several fibers are active (Fig. 3.2b). The activity of the fiber is then transformed into a peri-stimulus time histogram which shows the impulses per counting interval (1 s in most cases) on the ordinate (*y*-axis) against

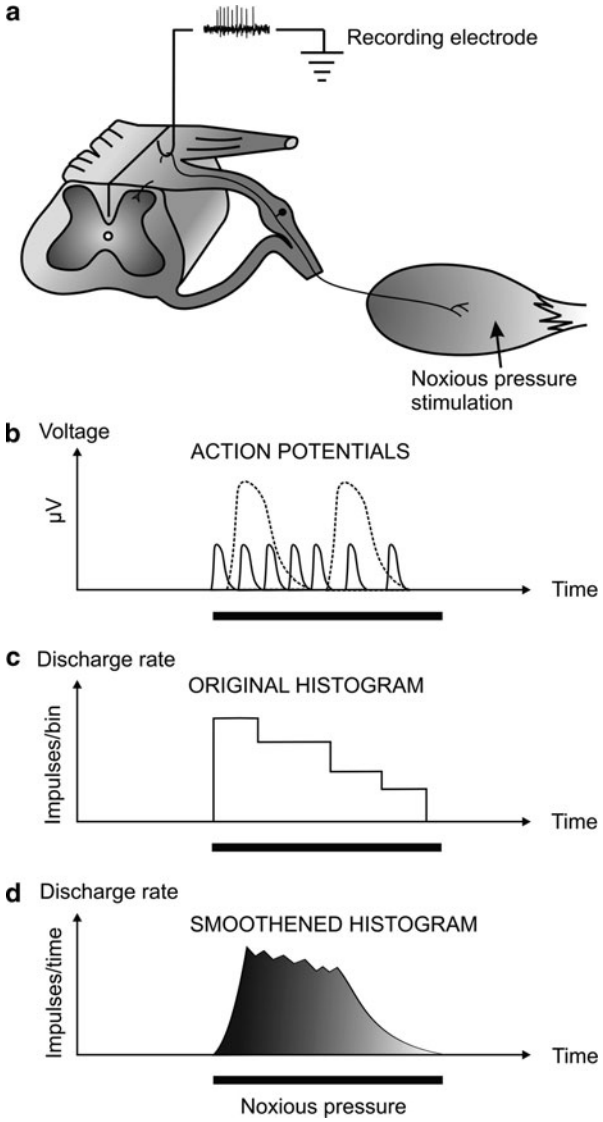

Fig. 3.2 Method used for constructing the smoothed histograms of the receptor activity that are used throughout the book for depicting neuronal activity. **a** Set-up for dorsal root recordings. The impulse activity of the receptive ending was recorded from its central branch close to the spinal cord. **b** Schematic reproduction of an original registration during noxious pressure stimulation of two receptive endings that were present in the same small dorsal root filament. The stimulus duration is indicated by the *filled bar* underneath the abscissa (*x*-axis). The registration shows action potentials from two fibers (the small one drawn in *solid lines*, the large one in *dotted lines*). The action potentials of the two fibers can be separated and counted by special software that distinguishes electric potentials by their shape. **c** Schematic reproduction of the histogram of the unit shown in *solid lines*. The histogram was constructed by a computer that sampled the impulses for a given time (the bin width) and displayed the sum of the impulses per bin on the ordinate (*y*-axis). On the ordinate the discharge rate of the ending is plotted against time on the abscissa. **d** The smoothed histogram was constructed by smoothing the steps of the original histogram

time on the abscissa (*x*-axis; Fig. 3.2c). In this book, the time-course of fiber activity is shown as a smoothed histogram as in Fig. 3.2d.

3.1.1 General Response Properties of Muscle Nociceptors

Cuts, burns, and bruises of the skin are always painful. In skeletal muscle, however, not every lesion elicits pain. Examples are movements of an EMG needle inside a muscle or dissecting procedures during open muscle biopsies, many of which are not perceived as painful. This phenomenon may be due to the fact that the innervation density of that part of the muscle is so low that small lesions can occur without exciting sensory receptors to a sufficient degree. Another possible explanation is that the central connections of the nociceptive muscle afferent fibers are relatively ineffective, so that not enough dorsal horn neurons are activated. (This subject is dealt with in Chap. 4). However, moving the EMG needle in muscle will eventually hit some nociceptors (or a nerve fiber bundle containing nociceptive afferents) and thus elicit pain.

Viscera, too, can be lesioned by knife cuts or burning without causing subjective pain, if the stimulated area is kept small. One possible explanation for this finding is that cuts and burns excite visceral receptors, but as the innervation density of viscera is low, the afferent activity generated by the few activated receptors is not sufficient to elicit subjective sensations. Again, an alternative explanation is that the synaptic efficacy in the CNS of the nociceptive afferents inputs from viscera is not high enough.

In animal experiments, nociceptive units were found that had two receptive fields, i.e., they could be activated from two separate areas in the muscle. In the deep tissues of the cat tail, some units had one receptive field in deep tissues (muscle or joint) and another one in the skin distal to the deep receptive field (Mense et al. 1981). The anatomical basis of this feature is probably branching of the afferent fiber close to the area of termination. This extensive branching differs from the common terminal branching of all free nerve endings in or close to the tissue they innervate. Afferent units with dividing long peripheral axons are probably relatively rare, but they may be functionally relevant, since they reduce the spatial resolution of the nociceptive system and thus could contribute to the diffuse nature of muscle pain.

In tissues other than muscle (joint, skin, viscera) so-called silent, unresponsive, or "sleeping" nociceptors have been described (Grigg et al. 1986; Häbler et al. 1988; Handwerker et al. 1991). In these experiments, the receptor activity was recorded from dorsal root fibers or filaments of the peripheral nerve. These receptors could not be activated by mechanical stimuli under normal conditions, but in inflamed tissue the endings responded readily to local stimuli, such as pressure stimulation, joint movement, or urinary bladder distension. The additional input from the newly recruited receptors probably has an enhancing effect on pain sensations, since it leads to spatial summation in dorsal horn neurons. Whether or not such receptors are present in skeletal muscle is unexplored.

3.2 Stimuli Exciting Muscle Nociceptors

3.2.1 Mechanical Stimuli

Mechanical stimuli of high intensity such as squeezing or pinching the muscle are effective stimuli for muscle nociceptors. In intact tissue, these receptors are silent in the absence of intentional stimulation (i.e., they do not have any resting activity) and do not respond to physiological muscle stretch, contractions, and weak pressure stimuli such as touching the muscle or weak deformation of the tissue (moderate pressure; Mense and Meyer 1985; Mense 1997). The stimulus intensity required for activating a muscle nociceptor is usually lower than that for causing persistent tissue damage. In an animal experiment, a muscle nociceptor can be excited repeatedly, e.g., by squeezing the muscle, without producing a hematoma. This aspect is important for understanding the role of nociceptors as a warning system. The receptors are not supposed to signal the presence of tissue damage but to prevent damage by alerting the CNS when the tissue in which they are situated is approaching its structural or functional limits.

However, for a clear response, muscle nociceptors require noxious (tissue-threatening, subjectively painful) pressure (Fig. 3.3a). The maximal discharge frequency reached by a single nociceptor (20–40 Hz) is much lower than that of a muscle spindle. In this book, nociceptors with a high mechanical threshold are called high-threshold mechanosensitive (HTM) receptors (Hoheisel et al. 2005); they resemble the mechano-nociceptors in the skin (Djouhri and Lawson 2004). The discharges of muscle nociceptors elicited by noxious mechanical stimulation often outlast the duration of the stimulus, i.e., the receptors exhibit afterdischarges (see Fig. 3.3a). The afterdischarges have a duration of a few seconds to several minutes depending on the intensity of stimulation; these discharges might be the reason for the subjective aftersensations following strong noxious stimulation. The mechanism underlying the generation of afterdischarges is unknown; possible explanations are mechanical damage to the axon membrane of the receptive ending, or release of endogenous excitatory substances from tissue cells or the nerve ending by the stimulus (see below).

A study on mechanosensitive group IV endings in the rat GS muscle showed that approximately 60% of these units were HTM receptors (Hoheisel et al. 2005). Among the mechanosensitive group III muscle units, the proportion of HTM endings was smaller. The high mechanical threshold of HTM receptors is surprising considering the structure of a free nerve ending, which is a fragile structure with a semifluid membrane. A recent study demonstrated an ion channel that is mechanosensitive and has a high mechanical threshold, the TRPV4 channel (Liedtke 2005). Possibly, the membrane of HTM units is equipped with these receptor molecules.

Some of the group IV units recorded from cat and rat GS muscle nerve have a low mechanical threshold and can be excited by moderate pressure (weak deformation of muscle tissue; Fig. 3.3c). They are called low-threshold mechanosensitive (LTM) receptors in this book. These units can be distinguished from

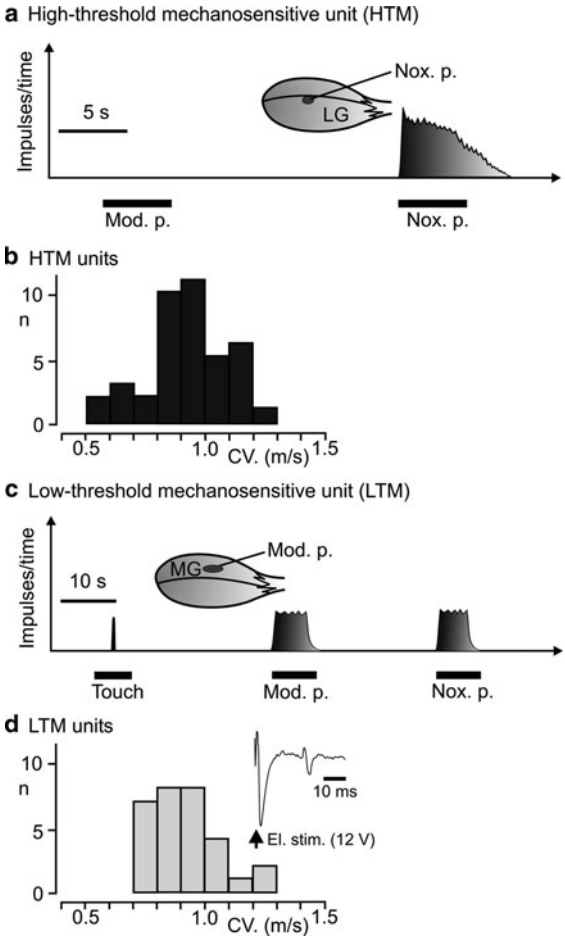

Fig. 3.3 High-threshold mechanosensitive (HTM) and low-threshold mechanosensitive (LTM) unmyelinated units in the rat gastrocnemius-soleus (GS) muscle. HTM receptors are assumed to be (mechano-) nociceptors; LTM units are presumably non-nociceptive receptors (mechanoreceptors). The *filled bars* underneath the abscissa mark the duration of the stimuli applied to the receptive field (RF, *dark gray area* in inset). *Touch*, touching the RF repeatedly with an artist's brush; *Mod.p.*, moderate pressure, innocuous local deformation of the RF; *Nox.p.*, noxious pressure, squeezing the RF with the forceps at a painful intensity. **a** Response of an HTM unit situated in the lateral head of the left GS muscle (LG). It responded only to painful squeezing of the RF. Note that the discharge continued after the stimulus had been terminated. **b** Distribution of the conduction velocities of the afferent fibers of HTM units. The velocities ranged from 0.5 to 1.3 m/s. **c** Response of an LTM unit that had an RF in the medial head of the gastrocnemius muscle. It responded minimally to touching the surface of the muscle. Its response magnitude was identical to the Mod.p. and Nox. p. stimulus. Thus, the ending cannot distinguish between an innocuous and noxious stimulus. Therefore, it unlikely to be a nociceptor. **d** Distribution of the conduction velocities of LTM units. The distribution was similar to that of HTM units, except that fibers conducting between 0.5 and 0.7 m/s were missing. The *inset* shows the original recording of a single unmyelinated fiber

sensitized nociceptors, which also have a low mechanical threshold, because LTM receptors do not exhibit resting activity (see below). The conduction velocities of HTM and LTM receptors are similar but not identical: the conduction velocity of HTM units extended down to 0.5 m/s, whereas the lowest conduction velocity of LTM units was 0.7 m/s (Fig. 3.3b, d). When the mechanical threshold of a larger number of group IV units is quantitatively determined with a pneumatic forceps and the number of units plotted against threshold, two separate populations emerge (Fig. 3.4a, b). These data support the assumption that the HTM and LTM units constitute two functionally distinct receptor populations, with the LTM units probably mediating innocuous pressure sensations from muscle (Light and Perl 2003; Graven-Nielsen et al. 2004). The LTM receptors probably have a LTM receptor in their membrane, for instance the TRPA1 molecule (Zhang et al. 2008).

Teleologically, the existence of non-nociceptive group IV units in muscle was to be expected, because a subpopulation of these fibers has long been known to mediate the adjustment of respiration and circulation during physical exercise (Kalia et al. 1981; McCloskey and Mitchell 1972). They are activated either by

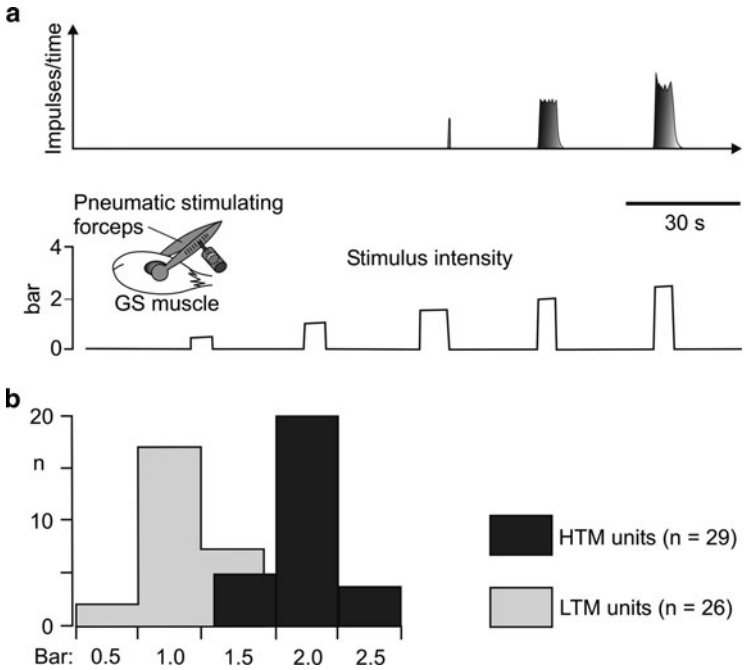

Fig. 3.4 Mechanical thresholds of group IV afferent units from the GS muscle of the rat. The thresholds were determined with a pneumatic forceps. **a** The *upper panel* shows the responses of a single unit to the pressure stimuli indicated in the *lower panel*. **b** Distribution of pressure thresholds of 55 group IV units. The distribution shows two separate populations with little overlap at 1.5 bar. This pressure is the dividing line between LTM (non-nociceptive) and HTM (nociceptive) group IV units

physiological contractions and strong stretch or by muscle metabolites, and have been called *ergoreceptors*.

Collectively, the data indicate that the group IV afferent units from muscle (free nerve endings with unmyelinated fibers) comprise at least three receptor types:

1. Nociceptors
2. Low-threshold mechanoreceptors, and
3. Ergoreceptors

3.2.2 Chemical Stimuli

3.2.2.1 General Considerations

The effects of most chemical stimulants on nerve endings are mediated by specific molecular receptors that are located on the surface of the nerve membrane. Binding of the stimulant to the receptor molecule results either in the opening of an ion channel for small cations (Na^+, Ca^{++}) or in changes in the state of activation of intracellular second messenger systems such as cyclic adenosine monophosphate (cAMP) and protein kinases. The influx of positive ions depolarizes the membrane of the receptive ending (makes its inside less negative). The activation of the second messenger cascade may cause the phosphorylation of (coupling of a phosphate residue to) channel molecules. Phosphorylated channel proteins have a higher opening probability or opening time; therefore, they are better permeable to ions. Collectively, these events may lead to direct excitation of the ending or to a modulation of the reaction of the nerve ending to external stimuli.

Some muscle receptors with small-caliber afferent fibers respond to algesic agents but not to mechanical stimuli such as stretch or local pressure. This type of nociceptor could fulfill the function of a pure chemo-nociceptor. However, even in animal experiments it is difficult to exclude with certainty a HTM-receptive field located deep inside the muscle and/or close to a bone. Another practical problem is that a thorough search of the whole muscle with strong mechanical stimuli is likely to sensitize (increase the excitability of) the nociceptors (see Sect. 3.3.1). Receptors that are strongly excited by ischemic contractions but not (or only weakly) by contractions under physiological conditions (Kaufman et al. 1984) are considered pure chemo-nociceptors by some, but are sensitized by the ischemia to the mechanical forces of the contractions (see below).

Some groups who record the activity of single muscle afferents take a different approach: first, they look for mechanosensitive receptors with group III or IV afferent fibers, then they inject the test substances into the mechanosensitive receptive field or into the muscle artery. With that approach one finds endings that respond to mechanical but not to chemical stimuli, i.e., they appear to be mechano-nociceptors. Again, however, it is impossible to test all possible substances at all concentrations on each mechanosensitive receptor. Therefore, the question as to the existence of pure

mechano- or chemo-nociceptors in skeletal muscle has to be left open. From a general point of view, however, it is unlikely that all muscle nociceptors express all genes for receptor molecules. Therefore, the nociceptive endings probably possess a certain combination of receptor molecules in their membrane which causes a preferred susceptibility to a certain combination of mechanical and chemical stimuli.

The following results were obtained with intra-arterial or intramuscular administration of algesic agents, either alone or in combination with mechanical stimuli. There are two chemical stimuli that appear to be particularly important for muscle pain, namely ATP and an acidic tissue pH.

3.2.2.2 ATP

Adenosine triphosphate (ATP) binds to the purinergic membrane receptor P2X3 and opens an ion channel that is permeable for small cations, mainly Na^+ (Burnstock 2000; Cook and McCleskey 2002). In addition to its function as a neurotransmitter, ATP is an important energy-rich molecule that drives many energy-dependent processes in all cells of the body. The ATP concentration in muscle cells is particularly high, in the millimolar range. Muscle cells require a lot of ATP, not only for contraction but also as an energy source for the calcium pump that transports the Ca^{++} ions back into the sarcoplasmic reticulum after contraction. The normal ATP concentration of a muscle cell is sufficient to excite muscle nociceptors in rat GS muscle when injected intramuscularly close to the receptive ending (Reinöhl et al. 2003; Fig. 3.5). ATP is released from muscle cells when the cell or its membrane is damaged, for instance during trauma and inflammation. When injected intramuscularly in humans, ATP causes pain (Mörk et al. 2003). Since it occurs in all body cells, ATP has been considered a general pain signal by some.

3.2.2.3 Protons

Protons (H^+ ions) are among the most important chemical stimuli for muscle nociceptors, because almost all pathological alterations of a muscle are associated with a drop in tissue pH. A pH value of around 6 is known to occur in inflamed or ischemic tissue. Besides acid-sensing ion channels (e.g., ASIC1 and 3), the vanilloid receptor TRPV1 (formerly called VR1 receptor; Caterina and David 1999; Caterina and Julius 2001) has been found in DRG cells supplying receptive endings in skeletal muscle (Hoheisel et al. 2004). The membrane of the receptive endings is generally assumed to possess the same receptor molecules as the membrane of the DRG cells. Small increases in H^+ concentration such as those found in inflammation and heavy muscle work are sufficient to excite muscle group IV endings. Figure 3.6 shows the responses of a muscle HTM unit to i.m. injections of buffer solutions of various pH (6, 5, 7.4). The receptor reacted in a graded way to

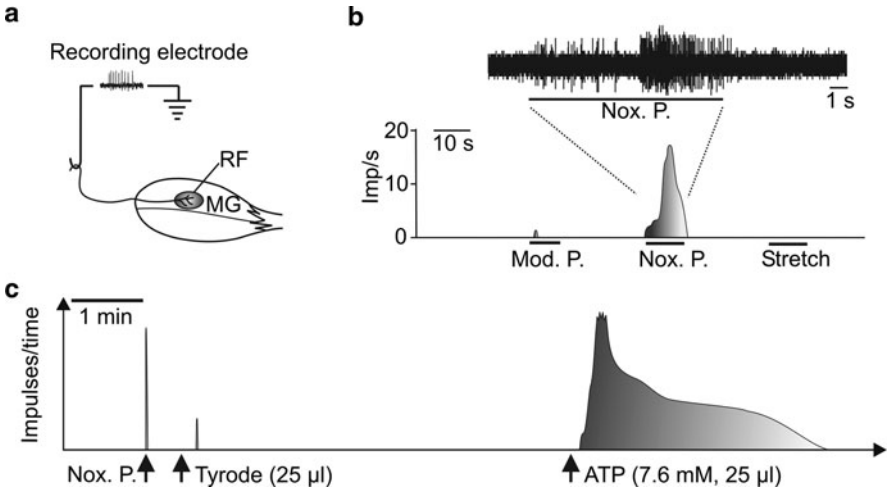

Fig. 3.5 Polymodal group IV unit ("polymodal" indicates that the unit is sensitive to both mechanical and chemical - and possibly also thermal - stimuli). The unit was recorded from the GS nerve (**a**) and required noxious mechanical stimuli for excitation (*Nox.P.*) (**b**). Strong muscle stretch was without effect. The response to Nox.P. is shown as an original registration above the histogram. **c** Response to adenosine triphosphate (*ATP*) injected into the unit's mechanosensitive RF. ATP was injected at a concentration found in muscle cells. Prior to the ATP injection, tyrode solution was injected as a control, without any effect. This shows that the intramuscular injection procedure itself was no stimulus. Many group IV units responded to both noxious mechanical and painful chemical stimuli, but not all units responded to the same pain-producing substances

the degree of acidity, the pH 5 solution eliciting the largest response. The (physiological) pH 7.4 had no effect. In this experiment, we do not know which proton-sensitive receptor molecule(s) mediated the response (one of the ASICS or TRPV1).

Capsaicin is the specific ligand of the TRPV1 receptor. Microneurographic recordings from human muscle nerves demonstrated muscle nociceptors that could be activated by i.m. injections of capsaicin (Marchettini et al. 1996). The capsaicin injections were associated with strong muscle pain. Since capsaicin is the specific stimulant for the TRPV1 receptor, these data show that human muscle nociceptors are equipped with this receptor.

The proton-sensitive receptors are probably activated during exhaustive muscle work, ischemia, and inflammation, which are all conditions with a low tissue pH. The pain during teeth-clenching and bruxism could also be mediated by proton-sensitive receptor molecules, because head muscles are overloaded and probably have a low pH. The proton-sensitive nociceptors may be of particular importance for the induction of chronic muscle pain, because repeated intramuscular injections of acidic solutions have been reported to induce a long-lasting bilateral hyperalgesia (Sluka et al. 2001).

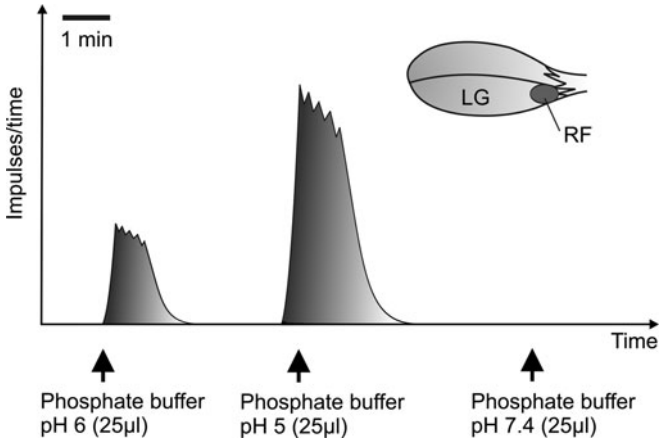

Fig. 3.6 Stimulating effect of acidic buffer solutions on a single group IV muscle receptor. Almost all pathologic muscle alterations are associated with a drop in tissue pH; therefore, the sensitivity of muscle nociceptors to acidic pH values is an important feature. The unit shown was tested with intramuscular injections of buffer solutions, two acidic ones (pH 6 and 5) and one at a neutral pH (7.4). The unit responded with a larger response to pH 5 than to pH 6; apparently, it was capable of "measuring" the degree of acidity. The buffer solution at a neutral pH had no effect

3.2.2.4 Endogenous Inflammatory Substances

The classic inflammatory substances are bradykinin (BKN) cleaved from blood plasma proteins, serotonin (5-hydroxytryptamine, 5-HT) released from blood platelets and chromaffine cells of the gut, and prostaglandin E2 (PGE2) synthesized in endothelial and other tissue cells (e.g., mast cells). Because of their origin in the circulatory system these substances are ubiquitously present in the body. The three substances have long been known to sensitize and excite muscle group IV receptors (Kumazawa and Mizumura 1977; Mense and Meyer 1985)**.** The effects of BK and PG E2 on nerve endings are mediated by specific molecular receptors that are located on the surface of the nerve membrane. Binding of the stimulant to the receptor molecule changes the activity state of the intracellular second messenger systems. Receptor molecules for BKN are the B1 and B2 receptor and for PGE2, the prostanoid (EP2) receptor. In intact tissue, BKN influences the ending through the B2 receptor. However, when the tissue is inflamed, a signal molecule is generated in the altered tissue [probably nerve growth factor (NGF)] which is transported intra-axonally to the DRG cells where it changes the gene expression. One sequel of the changed gene expression is the synthesis of B1 (instead of B2) receptors. The B2 receptors are transported back to the nerve ending in muscle and built into the membrane of the nociceptor. Now the effects of BKN are mediated by the B2 receptor molecule (Perkins and Kelly 1993). This finding demonstrates that the combination of receptor molecules in the nociceptor membrane can change depending on the state of the tissue. The inflammation-induced change in

membrane receptors is an example of a neuroplastic change in the nociceptive ending; it shows that neuroplasticity is not restricted to the CNS. In contrast to the receptor molecules for BKN and PG E2, which influence the intracellular second messenger system, the molecular membrane receptor for 5-HT (mainly the 5-HT3 receptor) controls an ion channel.

Under pathophysiological circumstances, BKN is probably released in amounts that are sufficient for exciting muscle nociceptors, whereas the main function of 5-HT and PGE2 appears to be sensitization rather than excitation of the nociceptive ending.

3.2.2.5 Hypertonic Saline

In animal experiments, hypertonic saline (5 or 6%) injected intramuscularly is an effective and reliable stimulus for muscle group IV units. When injected into the mechanosensitive receptive field of an HTM unit, the responses are usually of high frequency and often long-lasting (Fig. 3.7). Interestingly, hypertonic saline proved to be the only chemical stimulus that excited all free nerve endings tested, including presumably non-nociceptive ones (Hoheisel et al. 2005). This finding speaks in favor of a relatively unspecific mechanism of action of hypertonic saline as an excitatory stimulus, i.e., the excitation is probably not mediated by a particular membrane receptor. It also shows that the injections made into the mechanosensitive receptive fields reached the endings. (If an injected chemical did not elicit a response, a possible reason is that it was not placed close enough to the ending.)

At present, the exact mechanism(s) by which muscle nociceptors are excited by hypertonic saline is/are obscure. Since this stimulus is extensively used in clinical studies on muscle pain, some of the factors that are possibly involved in its

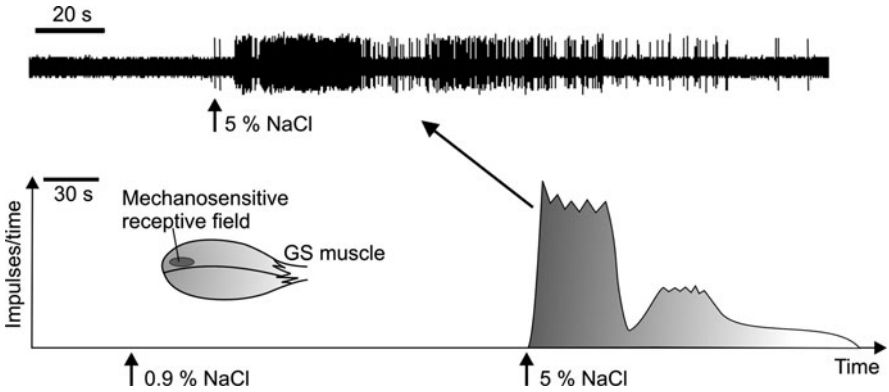

Fig. 3.7 Response of a mechanosensitive muscle group IV fiber to hypertonic saline (5%). Physiologic saline (0.9%) was injected as a control. The vigorous and long-lasting response is quite typical for the stimulating effect of hypertonic saline

excitatory action are discussed below (for an overview, see Kress and Reeh 1996; Mense 2007):

1. Increased tonicity in the interstitial space around the nociceptor. The receptive ending might shrink in the hypertonic environment, and stretch-sensitive Na^+-channels (for instance, the TRPA1 receptor) could open. However, nothing is known about the water permeability of nociceptive endings, and the high mechanical stimulation threshold of muscle nociceptors speaks against this mechanism which requires a high mechanosensitivity of the membrane. If shrinkage of the ending occurs, the intra-axonal ion concentrations may increase, which might also influence the excitability of the ending.
2. High Na^+ concentration around the nociceptor. The high sodium concentration outside the membrane changes the ion gradient across the membrane and could depolarize the ending by a Na^+ influx through Na^+ channels. However, a high Na^+ concentration in the interstitial fluid should have only little influence on the membrane potential of the nociceptive ending, because the Na^+ conductance (the permeability of the membrane) of a resting axon — when no action potentials are generated — is normally low. However, there is evidence indicating that the Na^+ conductance of receptive endings — as opposed to axons — is higher, and therefore the high extracellular Na^+ concentration could cause an effective depolarization with ensuing excitation of the ending. At present, the high Na^+ concentration on the outside of the membrane is the most likely factor for hypertonic saline-induced muscle pain. In contrast, the high Cl^- concentration induced by hypertonic saline appears not to be a stimulus, because Cl^- channels are rare in peripheral nerve fibers and endings.
3. Indirect activation of the nociceptor by other algesic agents released from muscle tissue or the nociceptive ending itself. The injection of hypertonic saline has been reported to release glutamate from muscle tissue (Tegeder et al. 2002). This does not mean that the pain-producing effect of hypertonic saline is solely due to the release of glutamate, because there is evidence indicating that the excitatory action of hypertonic saline on muscle afferents cannot be blocked by NMDA antagonists (Cairns et al. 2003). There can be no doubt that glutamate excites muscle nociceptors and causes muscle pain in humans (Svensson et al. 2003), but to what extent NMDA receptors are involved in the excitatory hypertonic saline effects has to be left open.

In clinical studies on patients and healthy normal subjects, hypertonic saline has long been known to induce pain in muscle, joints, and ligaments (Kellgren 1937; for review, see Graven-Nielsen 2006). However, hypertonic saline is an artificial stimulus, because there are few conditions in which the tissue hypertonicity is raised. Abscess formation is one of them (Schade 1924), but an increase to pain-inducing levels is unlikely. One of the first clinical scientists who used hypertonic saline systematically and extensively to elicit pain in human subjects was Kellgren (1937–38). He induced pain in muscles and ligaments of volunteers by injecting 0.1–0.3 ml of 6% NaCl. At present, several research groups inject or infuse hypertonic NaCl (5–10%) into muscles in healthy subjects and patients to study

the mechanisms of muscle pain in humans. With this method, muscle pain of moderate intensity (values around 7 on a VAS with a range from 1 to 10) can be reliably evoked. The injected volume is of importance, because the innervation density of muscle with nociceptors is low. Therefore, small injection volumes are likely to yield variable or ill-reproducible pain responses. The results obtained with intramuscular injections of hypertonic saline suggest that the receptor population mediating ischemia-induced muscle pain is distinct from that mediating hypertonic saline-induced pain (Graven-Nielsen et al. 2003). In human subjects hypertonic saline appears to excite predominantly group IV muscle afferent units (as opposed to group III units).

An overview of the effectiveness of the stimulating substances ATP, capsaicin, acidic buffer solution, and hypertonic saline (5%) on mechanosensitive muscle group IV afferent units is given in Fig. 3.8. Note that all agents excite HTM (presumably nociceptive) and LTM (presumably mechanoreceptive) endings in almost identical proportions. The response magnitude to the various stimulants was likewise similar in HTM and LTM units. This means that all the agents shown

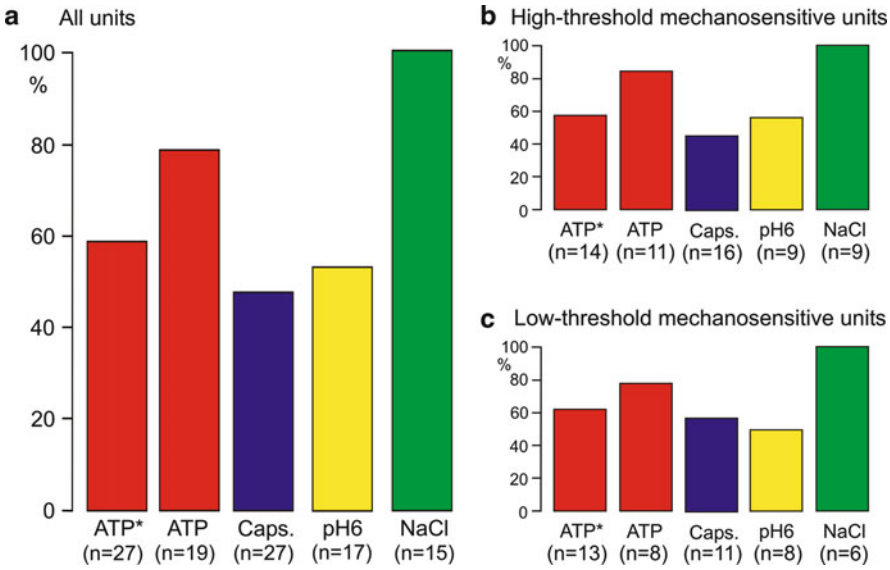

Fig. 3.8 Effectivity of various pain-producing chemicals in terms of the proportion of muscle group IV afferent units activated. **a** All mechanosensitive units irrespective of their mechanical threshold. ATP was injected in two forms: (1) as the original solution with the pH not adjusted (*ATP**). This solution had a pH of 5.5. (2) as a solution with the pH adjusted to 7.4 (*ATP*). Hypertonic saline excited each unit tested. This result was important, because it showed that the injections had reached the endings. Otherwise, a lack of response could mean that the fiber under study was sensitive to the chemical but was not reached by a sufficient concentration. **b**, **c** Separate evaluation of HTM and LTM group IV units. Note that the substances tested were all highly effective, but did not distinguish between HTM and LTM receptors. The proportions of activated HTM and LTM receptors were almost identical for each agent. No substance was a specific stimulus for nociceptors

in Fig. 3.8 are by no means specific stimulants for nociceptive endings, although they are very effective in eliciting pain.

3.2.2.6 Cytokines and Neurotrophins

Cytokines: Interleukins (ILs) and tumor necrosis factor-α (TNF-α). Among the many ILs, IL-1 and IL-6 are assumed to have a pronociceptive action, whereas IL-10 is thought to be anti-nociceptive. In our group, we tested the action of intramuscularly injected IL-6 on muscle group IV afferent units. At the doses used (25 μl at a concentration of 1 μM), the cytokine excited only LTM receptors, i.e., the non-nociceptive subtype of group IV afferent units (Hoheisel et al. 2005). In contrast to the agents shown in Fig. 3.8, this cytokine had a specific action on a subpopulation of the group IV afferents, but not on the nociceptive ones. Because of its selective action on LTM group IV units, IL-6 is unlikely to be involved in muscle pain, at least not at the concentration used.

ILs have been reported to have increased levels in delayed onset muscle soreness (DOMS; Tegeder et al. 2002) and in myofascial trigger points (IL-1β, Shah et al. 2005).

TNF−α at the dosage applied (25 μl at a concentration of 0.6 μM) had no excitatory action on group IV muscle afferent units. This concentration is described in the literature as inducing hyperalgesia in muscle (Schäfers et al. 2003), but there are no data pointing to an immediate excitatory action.

Nerve growth factor. During perinatal development, NGF is known to control the formation of the nociceptive and sympathetic nervous system. In the adult, NGF has a sensitizing action on nociceptors in the body periphery and on central nervous neurons. It has a close relationship to skeletal muscle, because it occurs in free nerve endings in muscle (Reinert et al. 1998), and is synthesized in muscle tissue. Its synthesis increases when the muscle is inflamed (Menetrey et al. 2000; Pezet and McMahon 2006). NGF is a highly interesting stimulus for muscle pain research, because it excites exclusively HTM (presumably nociceptive) receptors (Hoheisel et al. 2005; Fig. 3.9). Actually, it is the first and only substance encountered in many years of muscle pain research that has this property. With intramuscular injections of NGF it is possible to elicit a pure nociceptive input to the spinal cord.

Surprisingly, despite its strong excitatory action on presumable muscle nociceptors, intramuscular injection of NGF in humans is not painful (Svensson et al. 2003), and behaving rats likewise do not show pain-related behavior when NGF is injected into the GS muscle (Hoheisel et al. 2007). The lack of pain during and directly after NGF injection can be explained by the finding that, at the spinal level, the activity evoked by NGF in the muscle nociceptors elicits almost exclusively subthreshold potentials (Hoheisel et al. 2007) and not action potentials. Subthreshold potentials are not transmitted to higher centers, and therefore do not evoke subjective sensations. These findings show that a pure nociceptive input to the spinal cord is not necessarily effective in inducing pain. Apparently, the input pattern that reaches the spinal cord is decisive for eliciting pain. However, the input elicited by NGF is

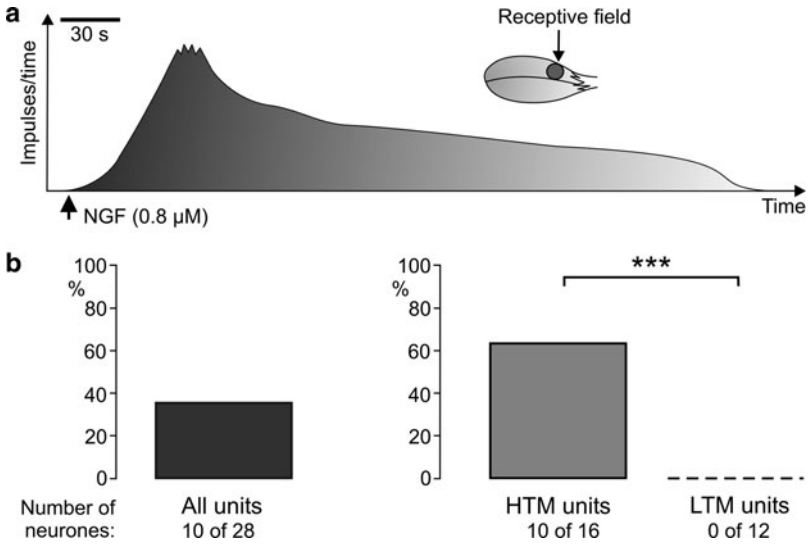

Fig. 3.9 Stimulating effect of nerve growth factor (NGF). **a** A single injection of NGF elicited a response with a large magnitude and long duration. **b** The overall effectivity of NGF as a stimulating agent was smaller than that of the substances shown in Fig. 3.8 (**b**), but NGF was unique in that it stimulated exclusively HTM units (**c**). Actually, NGF was the only substance encountered in many years of muscle pain research which appeared to be a specific stimulus for muscle nociceptors. This finding is surprising, because NGF injected intramuscularly at a similar concentration in humans did not elicit pain

particularly effective for inducing central sensitization. This aspect will be dealt with in Chap. 4.

The membrane receptor for NGF is the tyrosine kinase receptor, subtype A (TrkA). These receptors have been identified on DRG cells supplying the rat GS muscle (U. Hoheisel and S. Mense, unpublished; cf. Fig. 3.11). With regard to the pain-producing property of i.m. injection of NGF, differences between muscles were found: in behavioral experiments on rats, NGF at a concentration of 0.8 μM did not evoke pain when injected into the GS muscle in awake, behaving rats, but when it was injected into the multifidus muscle — one of the deep paraspinal low back muscles —it elicited a medium level of pain-related behavior (U. Hoheisel and S. Mense, unpublished).

It is unknown at present if this finding can be generalized, i.e., if there are systematic differences in pain sensitivity between different muscles. In the case of the paraspinal low back muscles vs extremity muscles, one may argue that low back muscles are special in that they are mainly composed of red muscle fibers and fulfill postural functions, whereas extremity muscles contain mainly white fibers and have a locomotor function. However, also muscles situated in the same body region and belonging to the same functional group have been shown to exhibit differences in pain sensitivity: in the study by Svensson et al. (2003) on

the sensitizing action of NGF in human masticatory muscles, the temporalis muscle was much less sensitized to mechanical stimuli than was the masseter muscle.

3.2.2.7 Glutamate

Nociceptive afferent units from muscle use glutamate as the main transmitter in the spinal cord to drive dorsal horn neurons, and since a transmitter used by a neuron is distributed over all parts of the cell, glutamate also occurs in the peripheral nociceptive ending. When a muscle nociceptor is excited by a local stimulus or antidromic impulses (see above), it releases glutamate in the interstitial space through the axon reflex (Rees et al. 1994; Lawand et al. 2000). Glutamate is also a stimulant for muscle nociceptors, i.e., the nociceptive ending can influence its own excitability by releasing glutamate. In the rat, glutamate has been shown to activate slowly-conducting muscle afferents from masticatory muscles (Cairns et al. 2003; Svensson et al. 2005) and evokes pain-related behavior in animals after injection into the masseter muscle (Ro 2003). In these experiments, glutamate acted on peripheral NMDA receptors that were also found on masseter ganglion cells (Cairns et al. 2003; Dong et al. 2007). Masticatory ganglion cells are likewise depolarised by glutamate through activation of NMDA receptors (Pelkey and Marshall 1998). Discharges evoked by glutamate can be attenuated by ketamine, an uncompetitive NMDA receptor blocker (Dong et al. 2006).

In many conditions of muscle pain, glutamate is elevated in muscle tissue (Rosendal et al. 2004); this has also been shown in DOMS (Tegeder et al. 2002). When an experimental inflammation is induced in a masticatory muscle, the peripheral NMDA receptors appear to be activated because treatment of myositis rats with AP5 — a competitive NMDA antagonist — attenuates the myositis-induced reduction in bite force (Ro et al. 2005). Since AP5 does not penetrate easily into the CNS across the blood brain barrier (Wong and Kemp 1991), this treatment effect is probably due to an action of AP5 on the peripheral NMDA receptors.

In humans, injection of glutamate into skeletal muscle elicits pain (Ge et al. 2005; Svensson et al. 2005). Interestingly, glutamate evokes greater pain responses in women than in men (Cairns et al. 2001), and muscle receptors with slowly conducting afferent fibers respond with larger activations to glutamate i.m. in female rats than in males (Cairns et al. 2001, 2003). This finding shows that the difference in pain sensitivity between females and males is not a (purely) central nervous phenomenon, but manifests itself already at the nociceptor level. It may also explain the higher prevalence of some chronic pain syndromes in women than men (e.g., fibromyalgia syndrome, painful temporomandibular disorder; Rollman and Lautenbacher 2001; LeResche et al. 2003).

Several sets of data underpin the importance of female hormones in the function of the nociceptive system. An increased estrogen level in women is associated with an elevated risk of developing low back pain (Wijnhoven et al. 2006).

In ovariectomized female rats, NMDA-evoked discharges are increased by administration of high doses of estrogens (Dong et al. 2007).

The estrogen action on the NMDA receptor probably includes a modification (upregulation) of the NMDA receptor protein, which increases open time and opening probability of the NMDA ion channel. This results in enhanced NMDA receptor-mediated ion currents (Kalia et al. 2004). Neurons in the nociceptive subnuclei of the trigeminal nucleus in the brainstem express estrogen receptors; therefore, estrogen acting at this site could influence pain sensations originating in the masticatory muscles (Bereiter et al. 2005).

Collectively, the above data suggest that glutamate is an essential stimulus for the excitation of muscle nociceptors and possibly also for the sensitization of dorsal horn neurons. Therefore, i.m. injections of MK- 801 (a non-competitive blocker of NMDA receptors) have been proposed for the treatment of central hyperactivity and excitability, which contribute to muscle allodynia and hyperalgesia (Ushida et al. 1999).

3.2.2.8 General Considerations Concerning the Chemical Excitability of Free Nerve Endings in Muscle

Direct or indirect excitation by chemical stimuli? Theoretically, all substances mentioned above could excite the free nerve endings, directly by binding to specific receptor molecules, or indirectly through the release of other endogenous substances. Therefore, it is important to know if the appropriate receptor molecules are present in the membrane of the endings. Because of the small size of a free nerve ending, the receptors cannot be visualized at the level of the endings. However, since in DRG and trigeminal ganglion cells the same receptor molecules occur as in the ending, the receptors can be visualized in the ganglion cells. In our group, DRG cells supplying nerve endings in the GS muscle were first identified by injecting a retrogradely transported dye into the muscle. Then, antibodies were used to visualize the receptor molecules in the DRG cells. Figure 3.10 describes the method. The experiments showed that the DRG L5 somata supplying the GS muscle expressed TRPV1, ASIC1, P2X3, and TrkA receptors (Hoheisel et al. 2004; Fig. 3.11). The receptor molecules were found particularly in small cell bodies that probably have slowly-conducting afferent fibers. Therefore, the stimulating action of protons, ATP and NGF on free nerve endings in muscle may be due to a direct effect mediated through binding of the stimulants to their specific membrane receptors. However, these data do not exclude the possibility that other substances released from the muscle tissue are included in the response to a given chemical stimulus.

Often, several of the receptor molecules were found in the same cell, and individual cells exhibited quite different combinations of the various receptor molecules. These data show that the DRG cells do not form a homogeneous population but consist of many different types with specific combinations of receptor molecules and probably different functional properties.

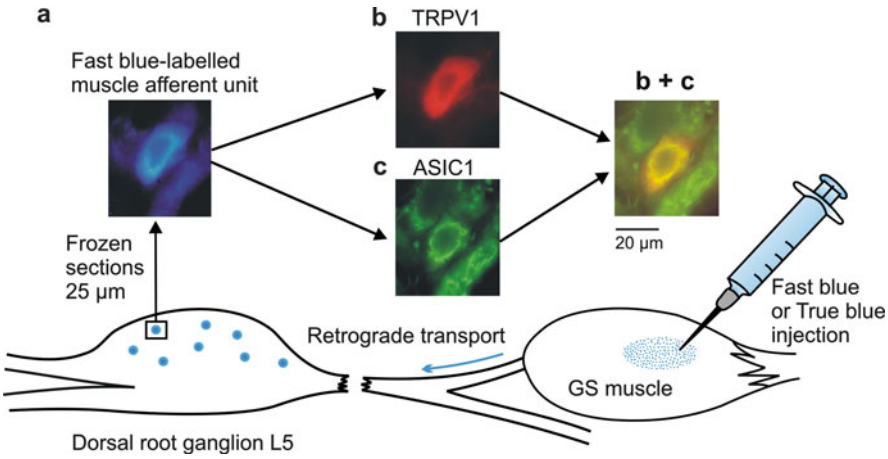

Fig. 3.10 Method for visualizing molecular receptors in the membrane of dorsal root ganglion (DRG) cells supplying the GS muscle. First, a retrogradely transported fluorescent marker (fast blue or true blue) was injected into the GS muscle. The marker was taken up by the receptive endings in the GS, and transported within the afferent fibers to the DRG. Ganglion cells having sensory endings in the GS muscle could be identified by their blue fluorescence (**a**). The labeled cells were treated with antibodies to various molecular receptors relevant for pain, e.g., TRPV1 and/or ASIC1 (**b**, **c**). In some experiments, the same cell was tested with two antibodies to study the combination of molecular receptors present in the cell

3.2.3 Polymodal Nociceptors

In animal experiments on the cat or rat GS muscle, polymodal nociceptors can be recognized by their responses to both high-intensity pressure stimulation and algesic substances (Fig. 3.12). Microneurographic recordings demonstrated that receptors that respond to both noxious squeezing and injection of algesic substances (e.g., capsaicin; Marchettini et al. 1996) also occur in human muscle. Some groups consider all muscle nociceptors to be polymodal (Kumazawa and Mizumura 1976; Kumazawa 1996).

In the skin, polymodal nociceptors can also be excited by noxious temperatures (Djouhri and Lawson 2004), but in muscle noxious heat is a stimulus that cannot be tested regularly. In some experiments, the whole GS muscle was heated to 50°C and a few group IV muscle receptors were found that responded to this stimulus with a high threshold of approximately 43°C (S. Mense, unpublished), but after one or two heating cycles the muscle tissue was irreversibly damaged. When hot solutions (48°C) were injected into the anterior tibial muscle in humans, the subjects reported heat sensations and dull pressure (Graven-Nielsen et al. 2002). These data indicate that thermosensitive receptive endings are present in skeletal muscle, but the number is probably small and the sensations they evoke are less intense than those elicited by the same stimulus from the skin. In an attempt to classify the nociceptive free nerve endings in muscle, they were tested with defined sets of

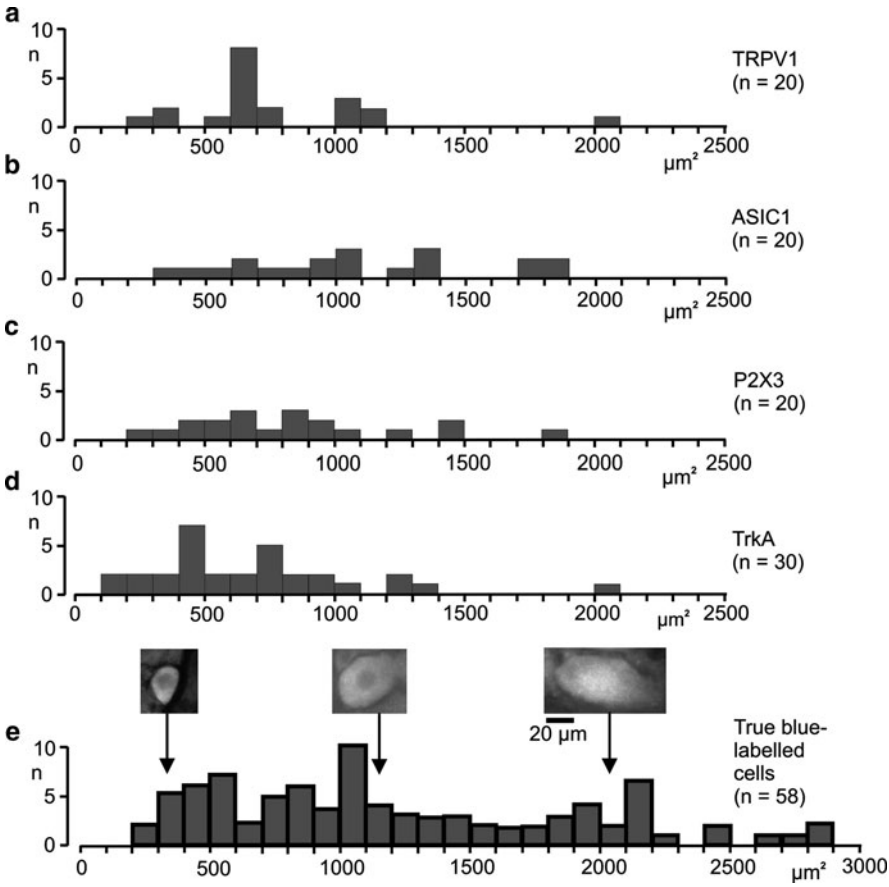

Fig. 3.11 Expression of receptor molecules in DRG cells supplying receptive endings in the GS muscle. Each panel shows the distribution of cell sizes (*x*-axis) with the number of cells on the *y*-axis. **a** Cells expressing TRPV1 receptors, the receptor for capsaicin, H^+, and heat. **b** Cells expressing the ASIC1 receptor, one of several ASIC receptors for H^+. **c** Cells expressing the P2X3 receptor, the receptor for ATP. **d** Cells expressing the TrkA receptor, the receptor for NGF. A comparison with all cells labeled retrogradely with true blue from the GS (**e**) shows that the cells expressing the above receptor molecules belong to the smallest in the ganglion, which probably have unmyelinated afferent fibers

mechanical and chemical stimuli (Kniffki et al. 1978). In these experiments, all possible response combinations were found. The data from this study showed that many group IV receptors respond to all kinds of noxious stimuli and, therefore, might function as polymodal nociceptors (Kumazawa and Mizumura 1976). This does not mean, however, that all muscle group IV units have the same functional properties. Among the nociceptive endings, some appear to respond to mechanical stimuli only, and cannot be excited by chemical stimuli, i.e., they behave like specific mechano-nociceptors.

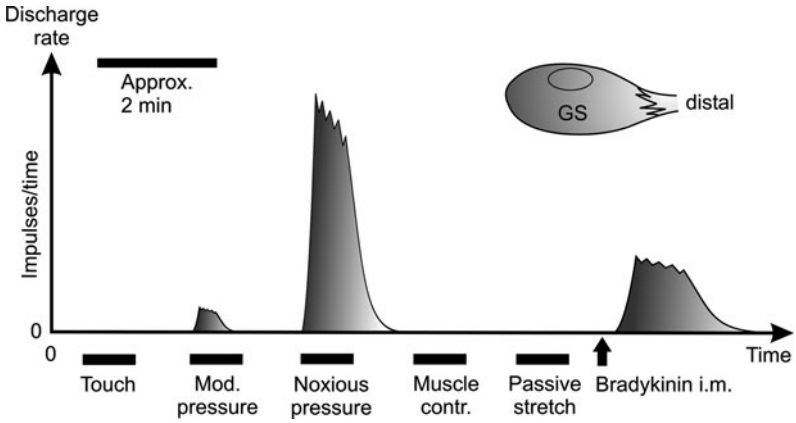

Fig. 3.12 A polymodal nociceptor that has a direction sensitivity to mechanical stimuli. The receptor responded marginally to moderate pressure (*Mod. pressure*) and with a high-frequency discharge to noxious pressure. The response to noxious pressure was much larger; therefore, the receptor can distinguish between innocuous and noxious stimuli and thus fulfils one of the main criteria of a nociceptor. Forces in the direction of the long axis of the muscle, namely active contractions (*Muscle contr.*) and passive stretch were without effect. Apparently, the receptive ending was only sensitive to forces perpendicular to the long axis of the muscle. The additional response to bradykinin demonstrates the polymodal nature of the receptor

As mentioned above, a response to algesic agents does not prove the nociceptive nature of an ending, because non-nociceptive endings are also excited by algesic agents. An in vitro preparation might help to solve all these problems, because here one can apply all possible stimuli in a graded way. In such experiments, however, the open questions are whether we really know all algesic agents (which is not true), and whether all stimulants have the same capacity to penetrate into the tissue.

The doses of pain-producing substances required for the activation of muscle nociceptors in animal experiments are similar to those eliciting pain in humans upon intra-arterial or intra- and subcutaneous injection (Lindahl 1961). The same applies to the time course of activation (latency and duration) which closely resembles the time course of painful sensations in humans. These findings support the assumption that chemically induced pain in humans is due to activation of that subset of free nerve endings which were classified as nociceptors in animal experiments.

3.3 Acute Sensitization of Nociceptors

3.3.1 General Features of Peripheral Sensitization

Sensitization of nociceptors results in an increased excitability. A sensitized muscle nociceptor has a lowered mechanical threshold, an increased response magnitude to noxious stimuli, and often background (or resting) activity, i.e.,

discharges in the absence of intentional stimulation. Such a peripheral sensitization is the neurophysiological basis of tenderness, pain during movements, and hyperalgesia. The resting discharge of nociceptors, which are normally silent, is assumed to be the correlate of spontaneous pain. The increased activity in sensitized muscle nociceptors probably leads to excitability changes in nociceptive neurons in the spinal cord, brainstem, and higher centers. Therefore, sensitization of peripheral nociceptors is usually accompanied by sensitization of central nociceptive neurons.

After experimental sensitization (by injecting sensitizing stimulants or inducing a muscle inflammation), muscle nociceptors do not necessarily show all of the signs of sensitization mentioned above. Some units responded clearly to the stimulant without exhibiting any detectable decrease in mechanical stimulation threshold; others had a decreased (or increased) stimulation threshold, without responding to the chemical stimulus (Hoheisel et al. 2005). This finding clearly demonstrates that activation and sensitization of a receptive ending are independent of each other. A nociceptor can be activated without being sensitized (this situation may lead to subjective pain without tenderness) or can be sensitized without being activated (this may lead to tenderness without spontaneous pain). Group IV receptors with a decreased mechanical sensitivity in the absence of any response were likewise found (Hoheisel et al. 2005; cf. Fig. 3.15).

3.3.2 Mechanical Sensitization by Endogenous Substances

Many substances that are released from pathologically altered tissue increase the *mechanical* sensitivity of nociceptors. For instance, in inflamed tissue there is plasma extravasation and BKN is cleaved from a high-molecular-weight kininogen in the blood plasma and sensitizes muscle nociceptors to mechanical stimuli. The sensitization is associated with a decreased mechanical threshold of the nociceptor, which now responds to weak pressure stimuli. The sensitized muscle receptor is still connected to nociceptive central nervous neurons and, therefore, elicits subjective pain when stimulated by weak mechanical stimuli. This sensitization of muscle nociceptors is the best established peripheral mechanism explaining local tenderness (allodynia). An example of a BKN-induced mechanical sensitization of a polymodal muscle nociceptor is shown in Fig. 3.13. Before injection of BKN, the receptor behaved like a typical nociceptor, in that it only responded to noxious squeezing (noxious pressure). It was also excited by BKN injection into the receptive field of the receptor, and a few minutes after BKN the nociceptor responded to touching the surface of the muscle and to moderate pressure stimulation (weak deformation of the muscle). In this state, the nociceptor would have been classified as a low-threshold mechanoreceptor that was also sensitive to BKN.

Not all endogenous substances released in inflamed or otherwise damaged tissue sensitize muscle nociceptors. For instance, after intramuscular injection of NGF at a

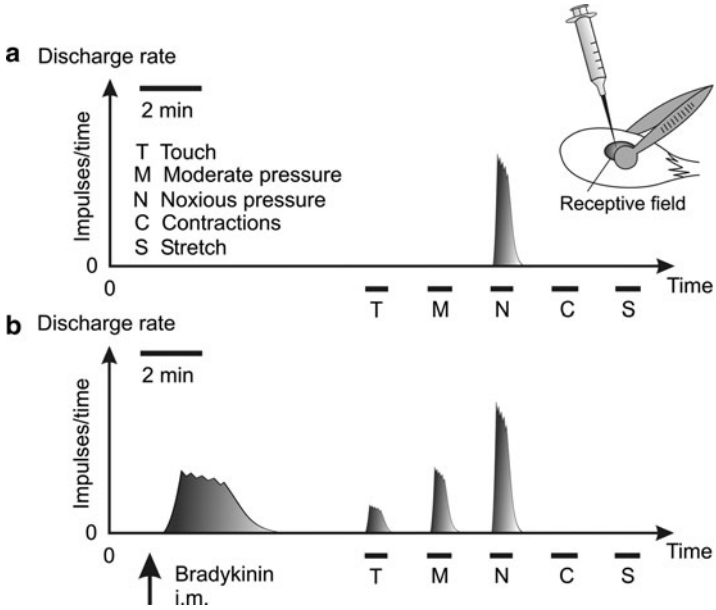

Fig. 3.13 Bradykinin-induced sensitization of a muscle nociceptor to mechanical stimuli. When the receptor was first tested (**a**) it responded only to painful pressure (N). **b** Bradykinin was injected intramuscularly (*i.m.*) into the receptive field of the ending. Approximately 5 min after the bradykinin injection, the receptor behaved like a low-threshold mechanosensitive ending in that it responded also to touch (*T*) and moderate pressure (*M*). These stimuli were completely ineffective before application of bradykinin. Note that the receptor was sensitized to pressure stimuli but not to muscle contractions (*C*) and stretch (*S*)

concentration sufficient to excite the muscle nociceptors, the mechanical threshold of the receptors did not change (at least not in a period of up to 30 min after NGF injection). The first significant signs of an NGF-induced mechanical sensitization of muscle nociceptors, namely increased mechanical responsiveness and lowered threshold, were found 5 days after intramuscular injection (V. John, U. Hoheisel, S. Mense, unpublished; Fig. 3.14). Note in Fig. 3.14b that 5 days after NGF all units tested had a low mechanical threshold, i.e., apparently all former HTM units were sensitized. These experiments were performed with human recombinant NGF on group IV endings in the rat GS muscle. Recently, Mann et al. (2006) reported that NGF-induced sensitization occurred in afferent fibers of the rat masseter muscle. The apparently higher NGF sensitivity of the receptive endings in the masseter muscle may be one factor contributing to the high prevalence of chronic pain in orofacial muscles.

Like NGF, the pro-inflammatory interleukin-6 (concentration 1 μM) and hypertonic saline (5%) had no acute sensitizing effect (up to 30 min after intramuscular injection) on the mechanical responsiveness of muscle nociceptors (Hoheisel et al. 2005). The findings obtained with hypertonic saline may be of interest for studies in

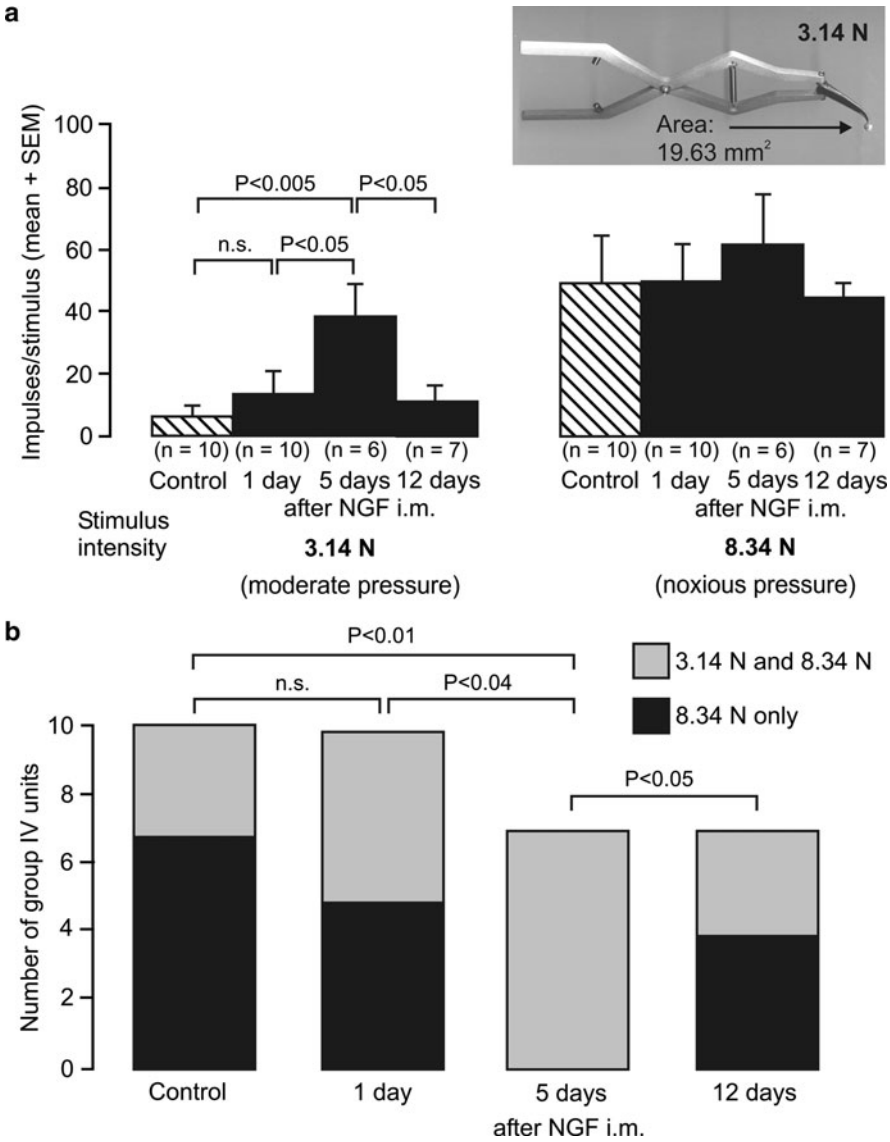

Fig. 3.14 Delayed sensitization of group IV muscle receptors to mechanical stimuli by i.m. injection of nerve growth factor (*NGF*). A single injection of NGF at a concentration of 0.8 μM was given into the GS muscle, and single group IV units were recorded 1–12 days after the injection. **a** The units are sorted according to their response magnitude to two defined mechanical stimuli (3.14 and 8.34 N) applied with a calibrated forceps (*see inset*). The 3.14 stimulus was perceived as moderate, innocuous pressure when applied to the experimenters' hypothenar muscle, the 8.34 N stimulus as painful. *Left panel* in **a**: the response magnitude to the 3.14 N stimulus showed a significant increase at day 5 after the NGF injection and had returned to normal at day 12. *Right panel* in **a**: the response magnitude to the 8.34 N stimulus never showed a significant increase. **b** Proportion of group IV units responding to the two stimuli. Units requiring the noxious

which this solution is injected repeatedly in human subjects. However, a few hours after NaCl 5% i.m. there were clear signs of allodynia and hyperalgesia in behavioral experiments on rats (Chap. 4).

A surprising finding was that several of those substances that are released in pathologically altered tissue had a *desensitizing* action on the mechanical responsiveness of muscle nociceptors, i.e., directly after intramuscular injection the response magnitude to noxious pressure was decreased. An example studied long ago is leukotriene D_4 (LT D_4). Leukotrienes are lipid mediators, which are assumed to be involved in the effects of an inflammatory response. They are produced in the body from arachidonic acid by the enzyme 5-lipoxygenase. Some such as LT B_4 have a chemotactic effect on migrating neutrophils, i.e., they attract the leukocytes to the damaged tissue. They have been shown to induce hyperalgesia in behavioral experiments (Samuelsson 1983). Leukotriene D4 appears to be the only LT whose influence on single muscle receptors has been tested so far (Mense and Hoheisel 1990). The desensitization after infiltration of the RFs with 0.1–1 μg of LT D4 expressed itself in a reduction of the response magnitude to mechanical stimulation. Whether or not this effect is associated with subjective hypoalgesia in humans is unknown. The increased synthesis of LTs by lipoxygenase following a drug-induced block of cyclooxygenase (COX-1 and COX-2) has been discussed as a mechanism that may contribute to the analgesic action of cyclooxygenase blockers such as ASA (Schweizer et al. 1984).

The cytokine TNF-α and the neurotrophine brain-derived neurotrophic factor (BDNF) likewise had a desensitizing effect on the mechanosensitivity of muscle nociceptors. The time course of the desensitization was similar for both agents with the minimum response occurring 6 min after intramuscular injection and complete recovery 8–10 min after injection (Fig. 3.15a, b; Hoheisel et al. 2005). At the concentrations used (TNF- α, 0.6 μM; BDNF, 1 μM), neither substance excited the endings.

Collectively, the findings that some inflammatory substances increase and some decrease the mechanical responsiveness of muscle nociceptors suggests that even in the very body periphery — at the nociceptive ending — a balance exists between pain-promoting and pain-inhibiting factors and processes. The data also show that caution has to be exercised when increased levels of inflammatory substances have been found in the tissue of patients with muscle pain. The increase does not necessarily mean that the pain problem of the patient is due to these substances.

Fig. 3.14 (continued) stimulus (8.34 N) for activation are shown in *black*, those responding to both stimuli, in *gray*. Note that 5 days after the NGF injection, all units responded to the moderate, innocuous stimulus. This indicates that at this time all high-threshold units had been sensitized and had lowered their stimulation threshold into the innocuous range. Up to 30 min after NGF i.m., the responsiveness of group IV muscle receptors was not significantly increased (not shown)

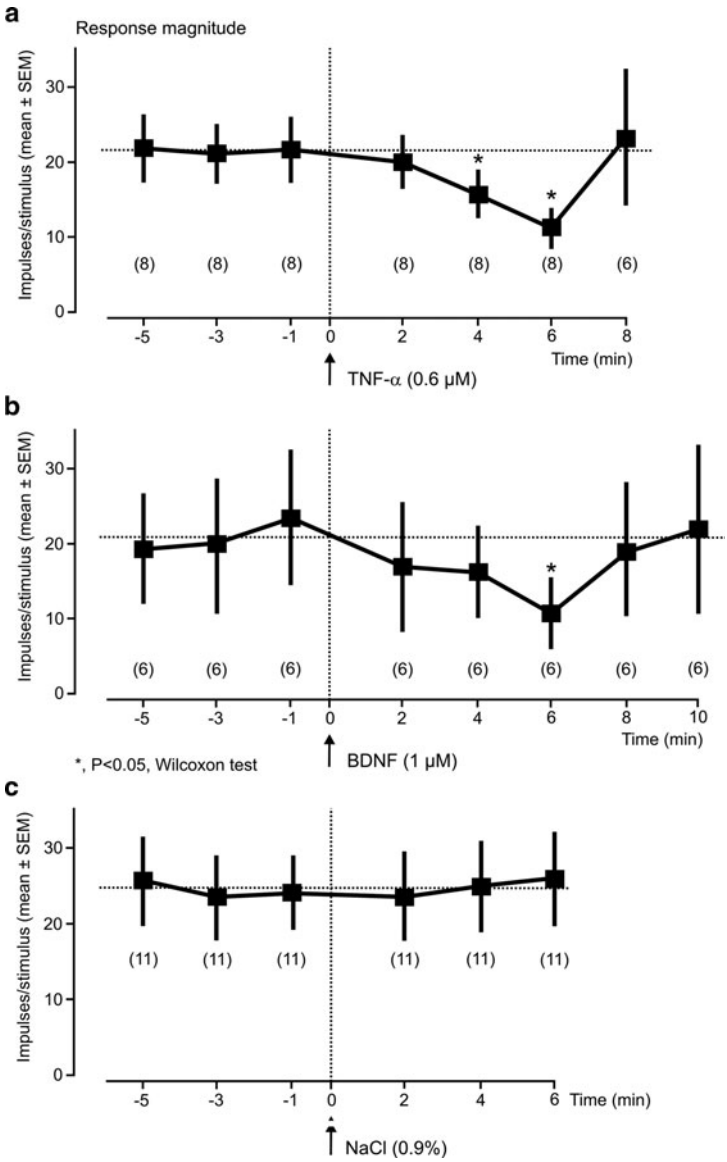

Fig. 3.15 Short-lasting desensitization of muscle group IV receptors by TNF-α and BDNF. Repeated noxious pressure stimuli were applied to the units' receptive field at 2-min intervals and the response magnitude measured (the number of tested units is given in brackets). After three stimuli, the test substances were injected into the receptive field of the unit under study, and the mechanical stimulation continued. **a**,**b** TNF-α and BDNF led to a short-lasting significant reduction of the response magnitude 4–8 min after intramuscular injection. Panel **c** shows that this effect was not due to the injection procedure as such, because physiologic saline had no effect on the response magnitude

3.3.3 Interactions Between Chemical Stimuli at the Receptive Nerve Ending

Many endogenous substances increase the responsiveness of muscle nociceptors to other chemical stimulants. These interactions between endogenous substances are of great practical importance, because in pathologically altered tissue various stimulating and sensitizing substances are released together. The pain elicited in human subjects by injection of a combination of BKN and 5-HT into the temporalis muscle is likewise stronger than that caused by each stimulant alone (Jensen et al. 1990).

PGE2 and 5-HT have long been known to enhance the excitatory action of BKN on slowly conducting muscle afferent units (Fig. 3.16; Mense 1981). On the other hand, BKN is known to increase the synthesis and release of PGE2 from various types of tissue (Jose et al. 1981). By this mechanism, BKN is capable of potentiating its own action, i.e., in the presence of PGE2 the action of BK is enhanced in a more than additive way. From the above data it has to be concluded that in the BKN-induced activations of muscle nociceptors there is a prostaglandin component. Consequently, it should be possible to decrease the BKN action on group IV muscle receptors by blocking the PG synthesis with non-steroidal anti-inflammatory drugs such as acetylsalicylic acid (ASA; Vane 1971; Ferreira 1972). Single fiber recordings in anesthetized cats have shown that this is the case: systemic administration of ASA strongly reduced the stimulating effects of BKN on muscle group IV receptors (Fig. 3.17; Mense 1982). These experiments demonstrate unequivocally a peripheral site of action of ASA. It is important to note that ASA also has a central action and inhibits the transmission of nociceptive information in the CNS (Burian and Geisslinger 2005).

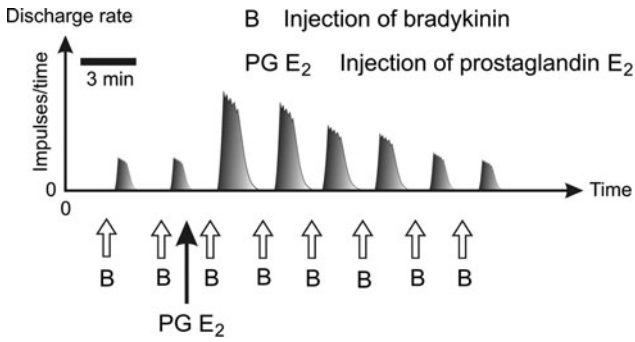

Fig. 3.16 Sensitization by prostaglandin E2 (*PG E_2*) of a group IV muscle receptor to bradykinin (*B*). Every 3 min, injections of a painful dose of B (26 μg in 0.3 ml saline) were given into the artery of the GS muscle, and the responses of the muscle receptor recorded. After the second response, an intervening injection of PG E_2 (30 μg) was given via the intra-arterial route. Note that PG E_2 in the dose applied did not excite the receptor but sensitized it to following injections of B. Apparently, the dose (or concentration) of PG E_2 required for sensitizing the group IV receptor is smaller than that for exciting it. The sensitizing PG E_2 effect lasted for approximately 15 min

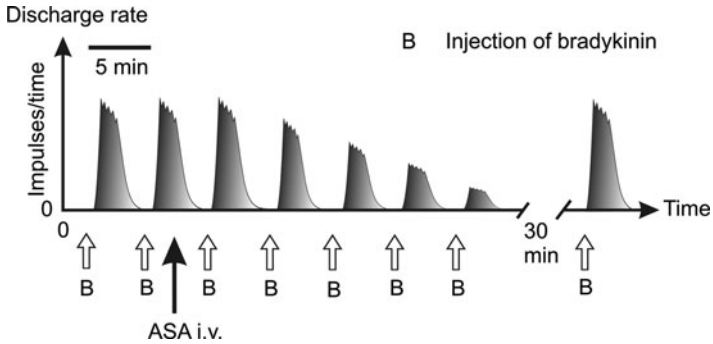

Fig. 3.17 Reduction of the responses to bradykinin (*B*) by an intravenous injection of acetylsalicylic acid (*ASA*). Experimental procedure and labeling as in Fig. 3.16. ASA was injected at a dose of 50 mg/kg bodyweight. The first ASA-induced reduction in the responsiveness to bradykinin occurred approximately 15 min after injection. One hour after administration of ASA, the magnitude of the response to bradykinin had returned to normal

Data from animal experiments show that the concentration of PGE2 and 5-HT required for potentiating the BK action on muscle receptors is lower than that for exciting the receptive ending. At the beginning of a pathological tissue alteration, when the concentrations of sensitizing agents are increasing, the receptive endings will probably be first sensitized and then excited. This assumption is consistent with the clinical observation that in the course of a pathological alteration the patient first experiences tenderness (due to nociceptor sensitization) and then spontaneous pain (due to nociceptor excitation).

3.3.4 Responses of Free Nerve Endings in Muscle to Ischemia and Ischemic Contractions

3.3.4.1 Effects of Ischemia Without Contractions

Generally, ischemia alone (without muscle contractions) does not elicit pain in humans and is not an effective stimulus for muscle nociceptors in animal experiments. In studies where a tourniquet is used to induce ischemia in a limb, pain usually occurs after approximately half an hour. However, the pain appears to be mostly due to the pressure exerted on the nerve by the tourniquet and not by the ischemia. Most experiments employing interruption of the blood supply to a resting extremity were carried out several decades ago (Lewis et al. 1931). The main result of these studies was that complete ischemia for periods up to 20 min is not painful and does not evoke cardiovascular reflexes (Staunton et al. 1964).

In animal experiments, when muscle group III and IV receptors are tested with ischemia alone, they do not respond to ligation of the muscle artery for 5 min (Mense and Stahnke 1983). Following a longer-lasting complete interruption of the

blood supply (experimentally induced by circulatory arrest), most of the slowly conducting muscle afferent units started to fire action potentials 15–60 min after the onset of ischemia. The discharge had a bursting pattern (high frequency discharges separated by silence) with an increasing mean frequency. The activity lasted for periods of several minutes up to half an hour, then the units fell silent and could no longer be activated by mechanical stimulation of the muscle or electrical stimulation of the muscle nerve (S. Mense, unpublished). Probably, the lack of energy during prolonged ischemia caused a progressive depolarization of the axonal membrane, because the molecular ion pumps — which normally contribute to the maintenance of the resting membrane potential — can no longer work. When the membrane potential approached threshold potential, the nerve fibers fired action potentials until the membrane was depolarized completely, i.e., there was no longer an ion gradient across the axonal membrane and the nerve fibers were blocked.

The mechanism(s) involved in ischemic muscle pain is/are still obscure. Candidate substances are high interstitial concentrations of potassium ions (Hnik et al. 1976, which depolarize the nerve membrane, and lactate, which could stimulate muscle nociceptors through a low pH. Another important substance is BKN. The kinin is released from plasma proteins during ischemia (Sicuteri et al. 1964; Nakahara 1971) and, because of its strong action on nociceptors, is likely to contribute to ischemic pain.

A clinical example of muscle pain caused by ischemia in a resting muscle is severe peripheral arterial disease (PAD) e.g., stage III after Fontaine's classification (Meru et al. 2006), which is characterized by ischemic pain at rest. Other examples are acute cases of compartment syndrome caused by increased pressure (e.g., due to inflammation or hematoma) in a muscle ensheathed by a tight fascia such as the anterior tibial muscle. The high intrafascial pressure leads to occlusion of blood vessels in the muscle. In this case, an additional painful factor may be the mechanical stimulation of nociceptors sensitized by the hypoxia and/or the release of BKN and other endogenous substances.

3.3.4.2 Ischemic Contractions

Interestingly, even at moderate levels of exercise during cycle ergometry, muscle pain can develop within a few minutes (O'Connor and Cook 2001). It has been shown that intramuscular pressures exceeding 20–40 mmHg (depending on the size of the muscle) may partially or completely arrest blood flow in the muscle. This pressure corresponds to approximately 10–20% of maximal voluntary contraction (Sjögaard et al. 2000). If muscles contract under ischemic conditions, pain develops within about 1 min (Lewis et al. 1931). Bessou and Laporte (1958) were the first to show that muscle group IV afferent units are activated during ischemic contractions. They did not record the activity of single muscle afferent fibers but measured the compound action potential of many group IV fibers of the GS muscle nerves in animal experiments and found that a large proportion of these units became active during tetanic muscle contractions under ischemia.

Single fiber recordings from group III and IV muscle receptors showed that a relatively small population of units (approximately 10%) reacted in a way that suggested an involvement in the mediation of ischemic pain (Mense and Stahnke 1983). The receptors did not react to contractions without arterial occlusion but reached high discharge frequencies when the same amount of muscle work was repeated under ischemic conditions (Fig. 3.18). The time course of the activation during ischemic contractions was similar to that of the pain induced in humans performing ischemic work contractions (Lewis et al. 1931): after the onset of the contractions there was a delay of approximately 1 min before the receptor activity rose, and the frequency stayed at an elevated level after the contractions had been discontinued but the ischemia maintained. All the receptors that reacted with a high response magnitude to ischemic contractions were group IV units; group III receptors were only minimally affected (see also Kaufman et al. 1984). Therefore, intermittent claudication may be an example of muscle pain that is due to activity in non-myelinated (as opposed to thin myelinated) nociceptive fibers. This interpretation fits with the dull and cramping nature of the pain of intermittent claudication, whereas group III fiber-mediated pain is generally felt as a relatively sharp and tearing pain.

Recently, an in vitro preparation of the mouse plantar muscles was used to record from single group III and IV muscle afferents during ischemic contractions (Wenk and McCleskey 2007). The authors found 8 out of 42 slowly conducting muscle afferent units to respond to ischemic contractions. Four out of 8 units tested for acid sensitivity were also excited by a reduced pH in the organ bath. This may

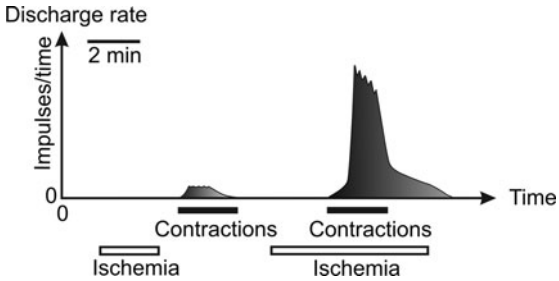

Fig. 3.18 Response of a muscle nociceptor to ischemic contractions. The periods of contractions are indicated by *filled boxes*, those of ischemia by *open boxes*. The contraction was elicited by electrical stimulation of the muscle nerve (contraction force approximately 50% of maximal force). Ischemia was induced by occlusion of the muscle artery. Ischemia alone caused no activation. The first period of contraction was performed in the absence of ischemia; the receptor showed a small activation during the contraction. The second period of contraction was performed during ischemia. After about 1 min of ischemic contraction, the impulse activity of the receptor rose steeply and reached a relatively high frequency of discharge. The ischemia was maintained for about 1.5 min after the end of the contractions. When the contraction was discontinued, the discharge frequency dropped markedly, but remained at an elevated level as long as the ischemia was maintained. The activity returned to zero only after the blood supply of the muscle had been restored

indicate that the low tissue pH during ischemic work is an important factor for the pain. As in our study, none of these receptors was activated by ischemia alone.

Most of the group III and IV receptors tested with ischemic contractions by our group did not react at all, although the contractions were continued until the muscle was completely exhausted. The receptor shown in Fig. 3.19 had a thin myelinated afferent fiber; its discharge frequency rose in a graded fashion with increasing forces of contraction (not shown). This type of ending was assumed to be a non-nociceptive contraction-sensitive receptor. It behaved similarly to a Golgi tendon organ, in that it was quite sensitive to low forces of contraction and also could be excited by strong stretch of the muscle. However, there is no evidence in the literature that tendon organs can be supplied by group III afferent fibers; therefore, the ending was probably a free nerve ending. The receptor might mediate subjective force sensations, or alternatively could function as a mechanosensitive ergoreceptor. In support of the assumption that the receptor was not a nocieptor, its responses to contractions were not changed when the contractions were repeated under ischemic (noxious) conditions. The receptor was unable to distinguish between a physiological (non-painful) and noxious (painful) stimulus. This is one of the most important requirements for a nociceptive function.

The mechanisms underlying the pain of intermittent claudication are still a matter of controversy. The situation is rather complex because in a muscle that performs ischemic contractions an unknown but presumably large number of chemical and physical factors are continuously changing. In 1931, Lewis and coworkers rejected the theory that lack of oxygen elicits the pain of intermittent claudication, and proposed a physicochemical mechanism ("factor P") as the cause of ischemic muscle pain. In subsequent clinical studies, a multitude of factors have been discussed as causing the pain, e.g., chemical metabolites,

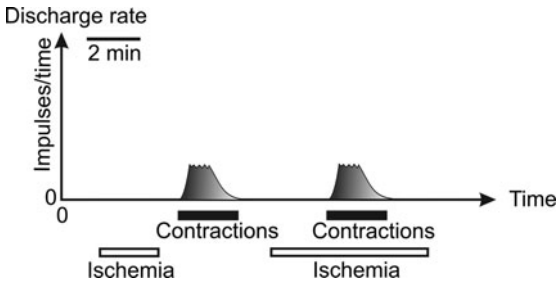

Fig. 3.19 Responses of a contraction-sensitive group III receptor during normal and ischemic contraction. The labeling is the same as that used for testing the nociceptor in Fig. 3.18. The receptor was not excited by ischemia alone, but responded clearly to contraction without ischemia. The ischemic contraction did not elicit a greater response than that without ischemia, i.e., in its response behavior the receptor could not distinguish between normal and ischemic contraction. A comparison between Figs. 3.18 and 3.19 demonstrates that ischemic contractions are not an effective stimulus for all muscle receptors with slowly-conducting afferent fibers. Ischemic contractions appear to be a rather specific stimulus that excites only a relatively small subgroup of these receptors

accumulation of potassium ions (K^+), and reduced pH due to release of lactic acid. Reduction of tissue pH is one of the most likely factors, because during exhausting exercise it has been reported to drop from 6.6 to 6, a value sufficient for excitation of muscle nociceptors (Sahlin et al. 1976; see above). Lactic acid was soon ruled out, because patients with McArdle's disease — who are unable to produce lactic acid due to a gene defect — often present with pain of intermittent claudication or angina pectoris. Another candidate substance is the nonapeptide BKN. The importance of BKN for the pain of intermittent claudication was supported by the finding that administration of a proteinase inhibitor in claudication patients extended the distance the patients were able to walk without pain (Digiesi et al. 1975). Electron microscopic investigations of bioptic material of claudication patients showed that the muscle exhibited signs of inflammation with infiltration by inflammatory cells and muscle fiber necrosis (Sutherland et al. 2000). The necrosis adds ATP to the list of candidate substances, because muscle cells contain high concentrations of ATP which are released into the interstitial space when a muscle fiber is damaged.

In conclusion, a possible mechanism for the activation of nociceptors in a muscle contracting under ischemic conditions is that, first, BKN or low pH sensitizes the nociceptors, and the sensitized nociceptors are then activated by the mechanical force of the contractions. Such a mechanism is suggested by the time course of activation of the single group IV unit shown in Fig. 3.18: The unit was not excited by ischemia or contractions alone, but gave a strong response during ischemic contractions. Moreover, the activity dropped markedly when the contractions were discontinued and the ischemia maintained. However, as long as the muscle was ischemic, a basal level of receptor activation (and also pain) persisted because of the high intramuscular concentration of chemical stimulants.

The intensity of ischemic muscle pain of patients was found to depend on three factors, namely frequency of contraction, force of contraction, and the duration of time during which the contractions continue (Mills et al. 1982). Of these, contraction frequency was the most important factor, whereas contraction force was of minor importance.

3.3.5 Effects of Inflammatory Tissue Changes on the Activity of Muscle Group IV Units

Most of the data on the discharge behavior of free nerve endings in inflamed muscle are available from the rat. An experimental myositis was induced by infiltrating the triceps surae or other muscles with carrageenan, a sulphated polysaccharide extracted from red seaweeds, or complete Freund's adjuvant (CFA), which is composed of inactivated and dried mycobacteria. A few hours after the induction of experimental inflammation, the muscle exhibited every sign of a myositis (hyperemia, edema, infiltration by polymorphonuclear leukocytes; Berberich et al. 1988). These changes are known to be associated with the release of pro-inflammatory substances which

appear in the rat paw in a temporal order, namely 5-HT and histamine first (up to 1.5 h after the carrageenan injection), then BK, and finally PGs (more than 2.5 h after carrageenan; DiRosa et al. 1971). The main effects of an inflammation on Group III and IV muscle receptors were an increase in resting activity and a lowering in mechanical stimulation threshold as described below.

3.3.5.1 Resting Discharge

The terms "resting", "background" or "ongoing" discharge are used for receptor activity that occurs in the absence of intentional stimulation (by the experimenter). Of course, in inflamed muscle many chemical stimulants are released that could excite the receptive endings. Therefore, "spontaneous discharge" is not appropriate.

An inflammation-induced resting discharge is characterized by its irregular, often intermittent nature, with phases of bursting activity alternating with long periods of silence (Fig. 3.20). As shown in Fig. 3.20, the bursts can reach peak frequencies similar to those evoked by mechanical stimuli of moderate intensity. Bursts in afferent fibers are known to be effectively transmitted at spinal synapses, because the synaptic potentials elicited in dorsal horn neurons occur at short intervals and can superpose (temporal summation). The bursts are likely to cause (spontaneous) pain if the discharge frequency and number of active fibers are high enough. An increased resting discharge is not only present in HTM (presumably nociceptive) units but also in LTM receptors that respond to innocuous pressure and probably do not have a nociceptive function. In inflamed tissue, the latter probably comprise both true LTM receptors and sensitized (originally high-threshold) units (see below).

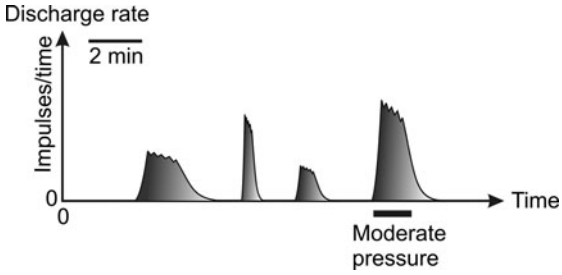

Fig. 3.20 Resting discharge of a group III ending in inflamed muscle. The recording was obtained from a unit whose receptive ending was situated in an inflamed GS muscle (acute inflammation induced by infiltration with carrageenan several hours ago). A high proportion of the units recorded in inflamed muscle exhibited intermittent ongoing discharges as shown in the *left part of the figure*. At the end of the recording, the unit was tested with moderate pressure stimulation. The mechanically induced response had a peak frequency that was about equal to the background discharge. Such an ongoing activity is likely to elicit the spontaneous pain of myositis if it occurs in nociceptive units, or dysesthesia if it occurs in non-nociceptive receptors

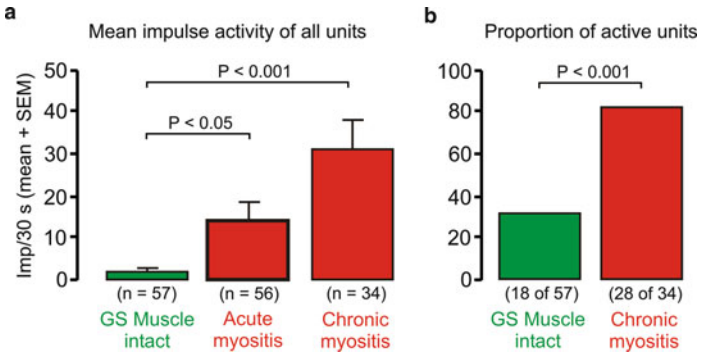

Fig. 3.21 Comparison of ongoing (resting) discharge of mechanosensitive group IV receptors in intact, acutely inflamed, and chronically inflamed gastrocnemius muscle of the rat. The acute inflammation was experimentally induced by infiltrating the muscle with carrageenan and had a duration of 2–8 h; the chronic inflammation was induced by infiltration with Complete Freund's Adjuvant, and lasted 12 days. **a** Mean discharge rate under the three conditions of the study. Note that — although the increase in fiber activity in inflamed muscle was significant — the mean frequency reached at the end of a 12-day period of inflammation did not exceed 1 Hz (30 impulses/30 s). This finding is important for interpreting the neuroplastic changes elicited in spinal neurons by an acute and chronic inflammation (see Chap. 4). **b** Proportion of units showing ongoing activity in acutely and chronically inflamed muscle. The increase was likewise significant

In muscle group IV afferent fibers of myositis animals, both the mean discharge frequency and the proportion of units exhibiting resting discharge were found to be higher in inflamed muscle (Fig. 3.21; Diehl et al. 1993). Note that in Fig. 3.21a the mean frequency does not exceed 1 Hz, even in chronically inflamed muscle. Despite this rather low frequency, the neuroplastic changes in the circuitry of the spinal cord of myositis rats can be very marked (see Chap. 4 for details). Apparently, a low-frequency input from muscle nociceptors is sufficient for inducing spinal neuroplastic changes if it lasts long enough. The chronic myositis had a duration of 12 days; considering the short life expectancy of approximately 2 years of a laboratory rat, the myositis was assumed to be chronic.

3.3.5.2 Inflammation-Induced Mechanical Sensitization

The other inflammation-induced change in the discharge behavior of group IV receptors is an increase in mechanical sensitivity. Figure 3.22a shows a HTM (presumably nociceptive) unit that responded exclusively to noxious pressure before induction of the inflammation with carrageenan i.m. It was also excited by the inflammation-inducing agent. Two hours later, the receptor had a lowered mechanical threshold and now responded to weak deformation of the muscle (moderate pressure). The receptor was still connected to nociceptive spinal pathways; therefore, its activation by the innocuous mechanical stimulus could probably elicit pain. The proportion of receptors responding to weak mechanical stimuli

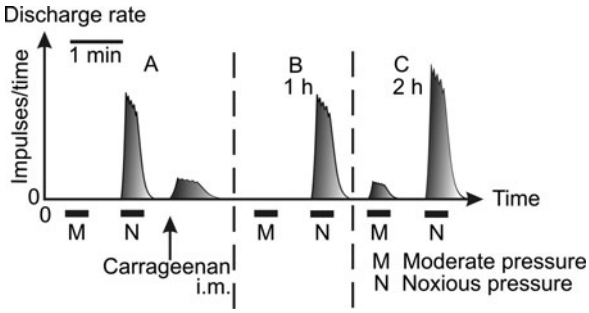

Fig. 3.22 Sensitization to mechanical stimuli of a single nociceptor during development of an acute inflammation. **a** Intact muscle before induction of the inflammation. The unit responded to noxious pressure only, and was also weakly excited by the intramuscular injection of carrageenan which was used to induce the inflammation. **b** One h after injection of carrageenan. The receptor still had a high mechanical threshold and was not excited by the moderate pressure stimulus. **c** Two h after injection of carrageenan. The receptor had lowered its mechanical threshold into the innocuous range and responded also to moderate pressure. The activation of a nociceptive ending by innocuous stimuli (e.g., weak local pressure) may lead to the tenderness of an inflamed muscle. Non-nociceptive (LTM) group IV receptors in inflamed muscle behaved similar to nociceptive ones (not shown). The increased responsiveness and ongoing discharges of non-nociceptive endings in an inflamed muscle may be responsible for the dysesthesias that are one of the common symptoms of myositis

likewise increased in the inflamed muscle. This change was reflected in a higher proportion of LTM units in animals with acute (2–8 h duration) and chronic (duration 12 days) myositis. The proportion rose from 40% in intact muscle up to more than 80% in chronically inflamed muscle (Fig. 3.23). A possible explanation for this finding is a sensitization of nociceptive (originally HTM) units which have a lowered mechanical threshold in inflamed muscle and respond to innocuous stimuli. In patients, this mechanism may explain the tenderness of inflamed muscle (and probably also the pain during movements). According to our data from animal experiments, the tenderness is mainly due to a sensitization of group IV receptors, because the mechanical threshold of group III units did not change significantly.

The sensitization of slowly conducting muscle afferent units is probably caused by the release of inflammatory substances and/or neuropeptides from the inflamed tissue. Prostaglandins are one of these factors: intravenous administration of ASA, a blocker of the cyclooxygenase 1 and 2, abolished the resting discharge and largely restored the normal pressure sensitivity of group IV units in inflamed muscle (Diehl et al. 1993). Figure 3.24 shows a receptor in inflamed muscle that had a low mechanical threshold and a relatively high level of resting activity. Under these conditions, we could not tell if the receptor originally was an LTM unit or a sensitized HTM ending. Approximately 30 min after injection of ASA i.v., the resting activity of the receptor was gone and it responded only to noxious pressure. In this case, ASA restored the typical properties of a nociceptor, namely a lack of

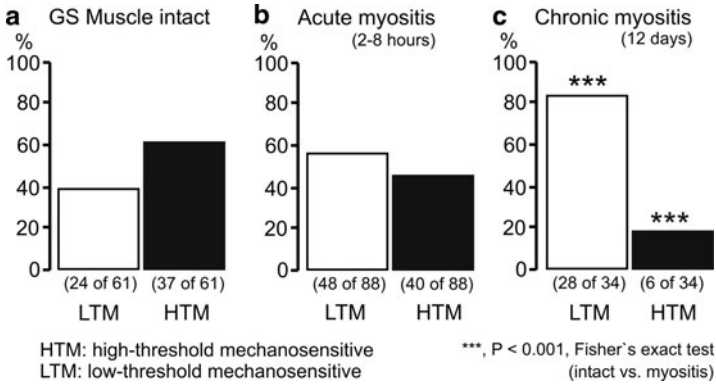

Fig. 3.23 Changed mechanical responsiveness of mechanosensitive group IV muscle receptors in intact, acutely inflamed, and chronically inflamed gastrocnemius muscle of the rat. In **a**, **b**, and **c**, the proportion of LTM units relative to HTM units is shown. **a** In intact muscle, the proportion of HTM (presumably nociceptive) endings is close to 60%, and that of LTM (presumable non-nociceptive) units 40%. **b** In acutely inflamed muscle (2–8 h duration) the proportion of HTM receptors was (nonsignificantly) decreased, presumably due to a beginning sensitization of the nociceptors. **c** In chronically inflamed muscle, the proportion of HTM receptors had dropped to less than 20%, and that of LTM units was increased to more than 80%. The data show that in inflamed muscle the mechanical threshold of a group IV unit is no indication of its nociceptive or non-nociceptive function

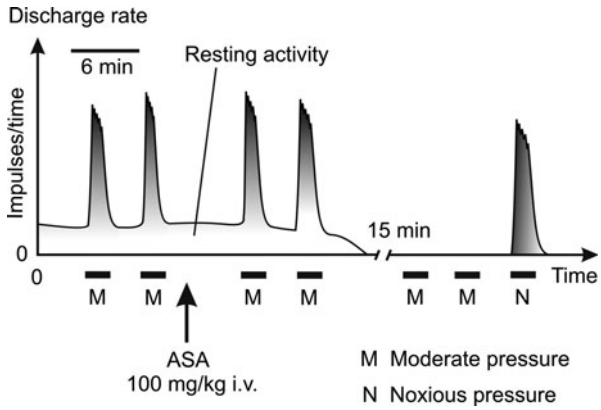

Fig. 3.24 Effect of acetylsalicylic acid (ASA) on the inflammation-induced ongoing activity and increased mechanical responsiveness of a single group IV ending. In the beginning of the recording, the receptor had ongoing activity, and responded twice to moderate (innocuous) pressure stimulation. Approximately 5 min after intravenous injection of ASA the background activity started to decrease, but at this time the mechanical threshold was unchanged. Approximately 30 min later, the ongoing activity was gone, and the receptor had a high mechanical threshold. It no longer responded to moderate pressure, but required noxious pressure stimulation for activation. The ending had regained two typical properties of a mechano-nociceptor (no ongoing activity and high mechanical threshold). By abolishing the ongoing activity and increased mechanical excitability of nociceptors, ASA may alleviate the spontaneous pain and tenderness of inflamed muscle

resting discharge and a high mechanical threshold. In other receptors the effect of ASA was not so clearcut. This may be due to the fact that in inflamed tissue many sensitizing substances are acting simultaneously on the receptors, whereas ASA blocks only the synthesis of PGs.

PGs are by no means the only substances that may be involved in the induction and maintenance of inflammatory processes. Further candidates are SP, CGRP, and neurokinin A (Wallengren and Hakanson 1987; Holzer 1988) as well as IL-1β, IL-6, TNF-α, nitric oxide (NO), and ATP (Marchand et al. 2005). Also NGF is discussed as a pro-inflammatory substance in muscle. With the exception of TNF-α (Reid and Li 2001) and NGF (Stuerenburg and Kunze 1998), these substances have not yet been shown to occur in skeletal muscle and have an increased concentration in flamed tissue.

For inflammatory pain there are endogenous processes inhibiting the pain. A recent report showed that delta-opioid receptors are particularly effective in this regard. Delta receptor knock-out mice exhibited enhanced mechanical and thermal hyperalgesia following CFA-induced inflammation (Gavériaux-Ruff et al. 2008). Conversely, treatment with a selective delta-receptor agonist produced antihyperalgesia in wild-type mice, but this effect was abolished in delta knock-out mice. The delta-opioid receptor may be a promising target for treating chronic pain conditions that have a strong inflammatory component.

3.3.5.3 Effectiveness of Chemical Stimulants in Chronically Inflamed Muscle

Surprisingly, inflammation-induced mechanical sensitization is not accompanied by higher sensitivity to chemical stimulants, at least not to all of them. Examples are shown in Fig. 3.25: in chronically inflamed GS muscle of the rat, ATP i.m. — which was one of the most effective chemical stimuli for group IV receptors in intact muscle — was found to be less effective when the muscle was inflamed. The same applied to NGF (Fig. 3.25b), although the difference did not reach significance for either agent. Of the substances tested, only hypertonic saline (NaCl 5%) showed no change (Fig. 3.25c). One possible explanation for this finding is that in inflamed muscle ATP and NGF are released, so that an additional dose of the same stimulant has less effect. If this assumption is true, it should be possible to "titrate" the concentration of chemical stimulants in a muscle by injecting the same agent at various concentrations. The result of such a test is shown in Fig. 3.26: buffer solutions at a pH of 7.4, 6, and 5 were injected in intact and chronically inflamed GS muscle and the discharges of group IV afferent units recorded. The greatest difference between intact and inflamed tissue was obtained with the pH 6 solution (Fig. 3.26, middle panel). This may indicate that the pH of the inflamed muscle tissue was close to pH 6, and the muscle nociceptors were already under the influence of an increased proton concentration. Therefore, adding a solution of about the same pH was not an effective stimulus. If this interpretation is true, the lack of effect with the pH 7.4 solution in inflamed

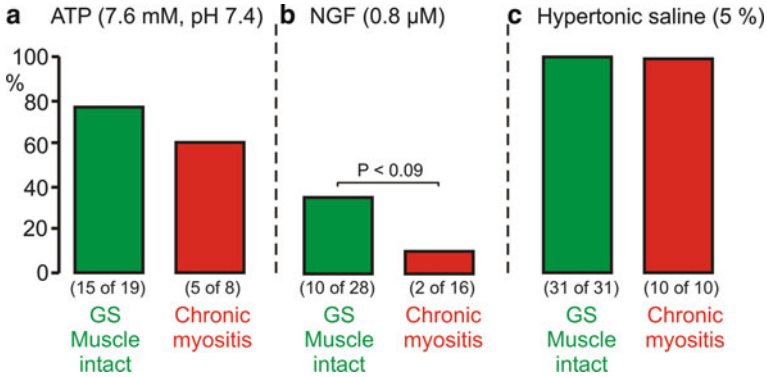

Fig. 3.25 Reduced excitatory action of ATP and NGF on group IV units in inflamed muscle. **a**, **b** Compared with intact muscle, for the units in chronically inflamed muscle (12 days after induction of the myositis) the proportion of endings excited by ATP and NGF was nonsignificantly reduced. With the conservative statistical evaluation used (nonparametric test, two-sided) the effect was close to significance for NGF. **c** The excitatory action of hypertonic saline was unchanged in inflamed muscle. A possible explanation for this result is that both ATP and NGF are released in inflamed muscle tissue. Therefore, the endings are already under the influence of the two substances, and additional amounts of ATP and NGF are less effective stimuli

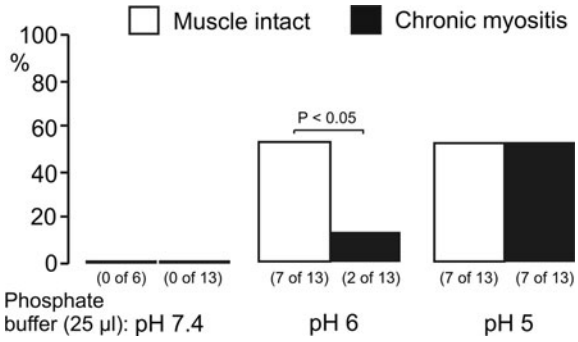

Fig. 3.26 Effectiveness of buffer solutions at various pH as stimulants for group IV endings in intact and chronically inflamed muscle. *Left panel*; a buffer solution at a neutral pH (7.4) had no excitatory effect. *Middle panel*; a solution at pH 6 excited significantly less units in inflamed muscle. *Right panel*; a solution at pH 5 was equally effective in intact and inflamed muscle, and excited approximately 50% of the units. A possible interpretation is that the pH in the chronically inflamed muscle was close to 6; therefore, a solution at pH 6 is not an effective stimulus

muscle – which has a lowered pH of 5 to 6 – could mean that muscle group IV units do not have receptor molecules for a low pH (reduced proton concentration) in their membrane.

3.4 How Do Muscle Spindle Afferents Behave in Inflamed Muscle?

This question is clinically relevant, because changed responsiveness of muscle spindles might contribute to the motor symptoms of myositis patients. The available literature on this issue is scarce. A histological study of the paravertebral muscles of patients undergoing surgery for recurrent lumboischiadic discogenic pain (Rozhold et al. 1990) reported that the capsule of muscle spindles was thickened and the intrafusal muscle fibers atrophied. More recent basic science data show that the monosynaptic reflex of both flexor and extensor muscles in the decerebrate cat is enhanced when the GS muscle is acutely inflamed (Schomburg et al. 2007). The reflex increase was maximal approximately 2 h after induction of the inflammation.

In our group, we recorded the impulse activity of single afferent fibers of muscle spindle primary endings (Ia fibers) in rats. A comparison was made between spindles in intact and chronically inflamed GS muscle. In intact muscle, the Ia fibers usually have a resting activity of approximately 40 Hz; this activity was not significantly changed in animals in which the GS muscle was inflamed (Fig. 3.27a).

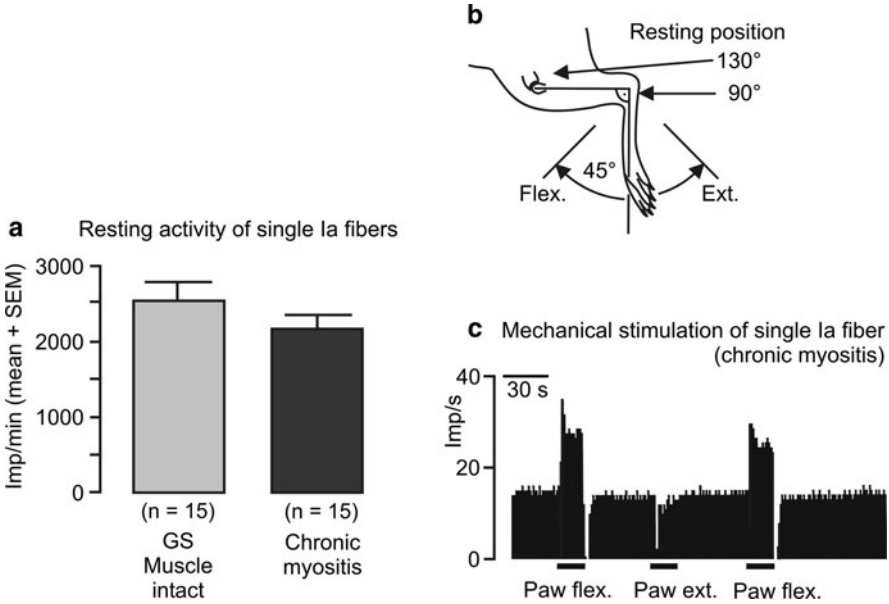

Fig. 3.27 Data showing that the response behavior of primary endings of muscle spindles (supplied by Ia fibers) was not changed by a chronic myositis. **a** In intact muscle, the Ia fibers had a relatively constant resting discharge of approximately 2,500 impulses/min. This discharge was not affected by the myositis. **b** Position of the left hindlimb of a rat in which the responses of Ia fibers to movements of the knee joint were studied. The knee joint was fixed at an angle of 130°, the ankle joint at 90°. Flexion and extension movements of the ankle joint were made to 45° from resting position. The preliminary data indicate that the response behavior of the primary endings was not changed by the myositis. An example of the largely normal responses of a single Ia fiber in inflamed muscle to the movements is shown in **c**

The resting activity was measured with the hindlimb in approximate middle position (knee joint 130°, ankle joint 90°; Fig. 3.27b). For testing the sensitivity of the spindles to movement, the ankle joint was passively extended or flexed by 45° and kept in this position for 15 s. The typical response of a spindle primary ending to the movements is shown in Fig. 3.27c. During paw flexion (stretching of GS muscle) the spindle showed a differential–proportional receptor behavior with an overshoot at the beginning of the flexion and a plateau phase when the paw was kept in the flexed position. At the end of the flexion, when the paw returned to the initial position, the normal resting discharge was interrupted for 1–2 s. During extension of the paw (passive shortening of the GS muscle), the spindle fell silent for approximately 1 s. This normal receptor behavior was not altered by a chronic inflammation of the GS muscle.

Our interpretation of this finding is that the primary spindle endings are protected by the fibrous capsule of the spindle, and therefore are not directly influenced by the massive inflammation induced by Freund's adjuvant. The more or less constant resting discharge in inflamed muscle is surprising, because in a former study we had found that the γ-motor neurons supplying the GS muscles are inhibited during an *acute* myositis (Mense and Skeppar 1991). This should decrease the resting discharge of muscle spindles. Unfortunately, no data on the behavior of γ-motor neurons in *chronically* inflamed muscle or on group II muscle spindle afferents are available. In conclusion, the resting discharge and response behavior of muscle spindle primary endings in chronically inflamed muscle was largely unaltered in anesthetized animals with intact neuraxis. Apparently, the Ia receptor is not sensitive to chronic pathological changes in muscle, and is therefore unlikely to contribute to the symptoms of patients with chronic muscle pain.

3.5 Effects of a Chronic Muscle Lesion on the Innervation of Skeletal Muscle

Longer-lasting pathological alterations of muscle tissue not only sensitize nociceptors but also increase the innervation density of muscle tissue with neuropeptide-containing nerve endings. Experiments on the rat GS muscle showed that an inflammation of 12 days' duration — which can be considered chronic for a rat — is associated with an increase in innervation density of neuropeptide-expressing fibers. The neuropeptides were visualized in histological sections with antibodies coupled to a marker that was visible under the light microscope. The increased innervation density was particularly marked in endings that contained SP; the density of these SP-immunoreactive endings increased by a factor of about 2 (Reinert et al. 1998). Since SP is assumed to occur predominantly in nociceptors, the increased innervation density may be one factor contributing to enhanced pain sensations from an inflamed muscle (hyperalgesia). The reason for this hyperalgesia could be as follows: when a painful stimulus acts on a muscle that has an increased density of nociceptors, the stimulus will excite more nociceptors and, therefore, elicit more pain.

3.6 Response Properties and Possible Functions of Nonnociceptive Free Nerve Endings in Muscle

Many muscle receptors with group III and IV afferent fibers (free nerve endings) can be activated by weak deformations of the muscle, by physiological stretch, or by contractions. Testing with a variety of stimuli in animal experiments excluded an origin of these nerve fibers in muscle spindles, pacinian corpuscles, or tendon organs. A relatively high proportion of group III and IV muscle afferent units appear to comprise LTM receptors (Fig. 3.3c,d; Hoheisel et al. 2005; Light and Perl 2003).

In this book, the HTM (presumably nociceptive) and LTM (presumably non-nociceptive) units are presented as two distinct populations. However, not all experimental observations fit in this distinction. For instance, the discharge of LTM endings should saturate when the stimulus intensity reaches noxious levels, whereas a typical nociceptive HTM receptor should increase its discharge frequency into noxious stimulus intensities. However, the response of LTM units to noxious local pressure stimulation (squeezing) is greater than that to innocuous deformation. In our group, we nevertheless do not classify the LTM units as nociceptors, since their responses to innocuous stimuli reached a considerable percentage of the maximum discharge rate. Moreover, these endings have a low threshold to local pressure, and therefore probably elicit strong central nervous effects during normal muscle activity. Such a behavior is atypical for nociceptors. When a muscle is tested with pressure stimuli of increasing intensity, even muscle spindles behave similarly to LTM receptors, in that they exhibit maximum responses to noxious mechanical stimuli. The reason for the increasing response of LTM units to noxious mechanical stimuli is probably the three-dimensional structure of a muscle. Mechanical stimuli spread within the tissue, so only part of the stimulus energy may reach the ending.

An interesting subtype of non-nociceptive Group III and IV muscle receptors were endings that were described long ago (Kaufman et al. 1983; Mense and Stahnke 1983). They were special in that they responded in a sensitive way to graded active contractions and showed an almost linear characteristic between muscle force and discharge rate. This response behavior resembles that of the hypothetical "ergoreceptors" postulated by Kao et al. (1963); they are supposed to mediate respiratory and circulatory adjustments during physical work. Later, McCloskey and Mitchell (1972) showed by indirect evidence that the receptors were supplied by unmyelinated afferent fibers, and therefore were distinct from muscle spindles and tendon organs. Besides the LTM units — which best respond to local pressure — chemosensitive ergoreceptors also appear to exist in skeletal muscle (Kao 1963). These receptors are assumed to be sensitive to the substances that are released in a working muscle. According to the results presented above, protons could be such a stimulus.

As to their sensory function, the LTM units could mediate innocuous pressure and force sensations from skeletal muscle. It is an old clinical experience that deep

tissues underneath a completely denervated skin region are still sensitive to light pressure (Head et al. 1905). A recent study on the sensitivity of deep tissue, employing a combination of skin anesthesia and ischemic nerve block, reported that the subjects felt light pressure stimulation through the anesthetized skin after all myelinated fibers had been blocked (Graven-Nielsen et al. 2004).

The presumably non-nociceptive units (the LTM and contraction-sensitive ones) made up about two-thirds of the Group III receptors. Among the endings with Group IV afferent fibers, the HTM (presumably nociceptive) type was the most frequent one (60%; Fig. 3.23a).

In a pathologically altered (inflamed) muscle, irregular activity in LTM receptors might be responsible for the dysesthesias that often accompany a myositis and sometimes are the prominent subjective symptom (see Chap. 8 in the companion volume by Mense and Gerwin (2010)). As noted above, in inflamed muscle a true LTM unit cannot be distinguished from a sensitized HTM receptor that has lowered its mechanical threshold and therefore behaves like an LTM ending.

3.7 Local Causes of Muscle Pain

In this section, types of muscle pain are addressed which are due to pathological changes in the muscle tissue or muscle afferent fibers, as opposed to pain that is felt locally in muscle but has a central origin (e.g., referred muscle pain).

3.7.1 Mechanical Causes

The following disorders are listed under mechanical causes, but it is unlikely that mechanical stimuli are not accompanied by chemical changes. Mechanical traumas to muscle will release sensitizing substances, even in cases of "pure" nerve compression leading to neuropathic pain (Marchand et al. 2005).

3.7.1.1 Blow to Muscle

A forceful impact to the muscle which activates nociceptors is painful. This can happen without causing damage to muscle fibers, if the blow is relatively mild. A stronger blow causes a painful lump at the site of the blow which usually subsides spontaneously within less than 1 h. The cause of the transient swelling has not been clearly resolved. Possible mechanisms are (1) formation of a local tissue edema, or (2) sliding of the actin and myosin filaments which is restricted to the site of impact. The blow may release Ca^{++} ions from the intracellular sarcoplasmic reticulum or

cause leaks in the cell membrane, so that Ca^{++} ions can enter the muscle cell from the outside where the calcium concentration is much higher than intracellularly.

The pain associated with this phenomenon often outlasts the noxious stimulus. This may be due either to afterdischarges in nociceptors following a strong activation (Fig. 3.3a) or to the release of stimulating substances from the damaged tissue (e.g., ATP). Since the pain and swelling is transient, it requires no treatment.

Interestingly, directly after the blow the muscle is weak and cannot develop much force. If for instance the deltoid muscle has been hit, it is difficult to move the arm. The weakness is likewise transient; it may be due to an acute inhibition of the homonymous motor neurons by muscle nociceptors excited by the impact (cf. Chap. 7).

Strong impacts may cause bleeding within the muscle. The result is local swelling, tenderness, and increased warmth that may remain for days. The tenderness is probably due to the release of sensitizing substances such as BKN, 5-HT, and PGs from the injured tissue.

In the acute phase, the treatment includes application of cold to the muscle and elevation of the injured part to reduce the swelling and the release of inflammatory substances. One or 2 days after the acute trauma, gentle use of the muscle and application of warmth to the skin of the affected region facilitates the healing process.

3.7.1.2 Rupture of Muscle and Tendon

Theoretically, rupture or tearing of the muscle or its tendon can occur in all muscles if they are acutely overloaded, but appear to be particularly frequent in the gastrocnemius and biceps (for reviews, see Matava et al. 2005; Blackmore et al. 2006).

The local pain of muscle ruptures has an acute onset; it is immediately followed by circumscribed swelling and tenderness. Several days later, ecchymosis may appear as an indication of bleeding at the site of muscle tear. On manual examination, the deficit in muscle bulk or lack of continuity of the tendon can often be identified. The injured site remains tender for a considerable time. The cause of the tenderness again is probably due to the release of sensitizing substances. In this case, potassium ions (K+) from injured cells may be an additional factor which depolarizes the receptive endings.

Because of the immediate and strong pain, the patient usually remembers when and where the rupture has occurred. However, tendon ruptures may go unnoticed. This applies particularly to partial ruptures restricted to the tendon center. A possible reason is that — as mentioned in Sect. 2.7 of Chap. 2 – the innervation density is low in the center of the Achilles tendon. Therefore, a partial rupture of a tendon may occur without eliciting subjective sensations.

A ruptured muscle is generally treated symptomatically to reduce the sterile inflammatory reaction at the site of the lesion and then to promote healing. It is rarely repaired surgically. However, in the case of a ruptured tendon, especially in

the ankle region, surgical repair may be essential to avoid muscle imbalance and serious disturbance of ambulation.

3.7.1.3 Spontaneous Hematoma

A large spontaneous intramuscular hematoma can occur occasionally as a complication of anticoagulation therapy. A review of 126 cases with hematomas in the rectus abdominis muscle following anticoagulation therapy (Cherry and Mueller 2006) showed that the hematoma causes local swelling, local pain, and tenderness. The diagnosis can be confirmed by ultrasound scanning or computed tomography. Most patients can be treated with symptom management and blood transfusions.

3.7.1.4 Delayed-Onset Muscle Soreness or Postexercise Muscle Soreness

The best-established cause of DOMS are excessive or unaccustomed eccentric (lengthening) muscle contractions. During eccentric contractions, the actin–myosin apparatus is activated (therefore the movement is called contraction), but the muscle does not shorten, because it is lengthened by an external force. Eccentric contractions are nothing special; they occur very often during daily life, namely every time a muscle has to decelerate a joint movement, for instance going down stairs.

DOMS develops when lengthening contractions are performed at high, unaccustomed loads. Therefore, it can occur after any vigorous sport activity, but is particularly common following unaccustomed descent from a mountain climb or lifting weights up and down. The vulnerability of muscles to eccentric work as compared to concentric contractions relates to the well-established difference in the contraction mechanics. During eccentric contractions the muscle develops forces that are much higher than the maximum voluntary concentric contractions (where the muscle shortens; Lieber 1992) and the mechanical efficiency of the muscle sometimes exceeds 100% based on the energy expended and analysis of expired air. Because of the higher forces, the mechanical stress on all structures in muscle and tendon is also higher.

The most prominent symptoms of DOMS are soreness and stiffness. The symptoms do not appear immediately after exercise, but with a delay of between 8 and 24 h following the unusual activity. The soreness has been reported to start at the muscle–tendon junction and then to spread through the entire muscle. The symptoms peak during the first day or two, and usually resolve in 5–7 days. The muscle becomes slightly swollen and tender to palpation, has a restricted stretch range of motion because of pain, and is painful when voluntarily contracted with more than minimal effort. The stiffness, the shortening, and the painfulness of the muscle can not be attributed to muscle spasm. Several studies of resting electromyographic activity after strenuous eccentric exercise showed no increase in average electrical

activity in the exercised muscles through the first 3 days, during the peak of soreness (Bobbert et al. 1986; Jones et al. 1987). Usually, there is no pain or discomfort at rest. Because of its self-limiting nature, DOMS does not require treatment (MacIntyre et al. 1995).

Traditionally, DOMS was assumed to be due to microtraumas of the muscle followed by a sterile inflammation and repair. The inflammatory process releases sensitizing substances which could explain the tenderness and pain during movements, although the relevance of inflammation was questioned quite early (MacIntyre et al. 1995). There was clear histological evidence of mononuclear infiltration, but again this change had a different time course from the tenderness. Moreover, NSAIDs did not affect the DOMS symptoms (Newham 1988). The tenderness and pain during movement were probably due to a sensitization of muscle nociceptors. However, the events leading to the sensitization are still obscure. Two hypotheses have been proposed as possible explanations for the soreness and tenderness of DOMS, the biochemical and the mechanical hypotheses (Pyne 1994). They are based on studies of the blood chemistry and histological changes associated with DOMS.

Blood biochemistry: One of the first substances that could be ruled out as a cause of the soreness and tenderness was lactic acid. It is the product of anaerobic metabolism (Lieber 1992), but after physical work it returned to normal levels before the symptoms of DOMS occurred. Moreover, it was found unchanged following bouts of eccentric exercise. Most blood chemistry changes (e.g., IL-1, total thiobarbituric acid-reactive substances, lactic dehydrogenase, serum creatine phosphokinase, aspartate aminotransferase, and serum glutamic oxaloacetic acid transaminase) peaked within the first 24 h following exercise, generally well before the peak intensity of muscle soreness.

Mechanical factors: Because of the discrepancies in time course between biochemical parameters and clinical symptoms, mechanical factors were discussed (Newham et al. 1983) and histological studies were carried out to find the sequelae of mechanical stress on the muscle structure. At the cellular level, biopsies of human muscles exposed to exhausting eccentric exercise showed no abnormality of fiber organization or regeneration. However, under the electron microscope, characteristic changes were found. Immediately after exercise, a high proportion of the Z bands (which connect one sarcomere to the next) showed generalized broadening and streaming (scattered severe broadening; cf. Yu et al. 2002). These changes persisted for at least 3 days, and only 7 days following exercise, recovery had occurred in most studies. In one study of unusually severe eccentric exercise, myofibrillar necrosis, inflammatory cell infiltration, glycogen depletion, and lack of myofibrillar regeneration persisted for 10 days. This picture resembles that of a sterile inflammation, and the slow time course of the inflammatory process could explain the long delay between physical work and soreness.

In muscle tissue from animals, mostly rats, immunocytological examination for the intermediate filament desmin (a cytoskeletal protein that is located just underneath the muscle cell membrane and stabilizes it) revealed changes in desmin

structure and signs of an increased synthesis of desmin in the region of the Z-bands. These changes peaked at 3 days close to the time of maximum soreness. Also, single fiber recordings obtained from rats in which the extensor digitorum longus (EDL) had performed eccentric contractions 2 days prior to recordings fit in this picture: the slowly conducting afferent units from EDL exhibited lower mechanical thresholds and greater responses to mechanical stimuli. This finding indicates a mechanical sensitization which could explain the tenderness of a DOMS muscle (Taguchi et al. 2005). Interestingly, there was no increased sensitivity to heat and chemical stimulants such as BKN, ATP, and solutions with low pH. This is another example of a sensitization of peripheral receptors which is restricted to one stimulus modality.

Collectively, the animal data seemed to explain the tenderness of DOMS in humans, but later biopsy studies from human muscles could not substantiate many findings known from animal experiments. Histological studies of human muscles showed that the staining for desmin was not or only marginally changed, even though the biopsies were taken at a time when the subjects had developed DOMS. Also, other changes obtained in animal experiments could not be found in humans with DOMS, for instance a marked activation of satellite cells (Yu et al. 2002; Crameri et al. 2007). Yu et al. (2002) concluded that in human DOMS muscles there is no muscle fiber degeneration and no cell necrosis.

One possible explanation for this discrepancy between animal and human data may be that in animal experiments, the eccentric contractions were elicited by electrical stimulation of the muscle nerve. This electrically induced pattern of motor unit activation differs greatly from physiological contractions (Crameri et al. 2007). The electrical stimuli excite all motor units of the muscle simultaneously and the contractions have an abrupt onset, whereas the recruitment of motor units during voluntary exercise is gradual. Apparently, the animal data reflect the events occurring during DOMS only partially, and some additional changes found only in animal muscles are obviously due to the electrical stimulation of the muscle nerve as opposed to voluntary contractions.

To date, the question as to the causes of the tenderness and pain during movement of DOMS cannot be answered. Possibly, the symptoms are due to a combination of biochemical and mechanical factors. A third hypothesis (in addition to the biochemical and the mechanical ones) should be mentioned: it postulates that the induction of eccentric contractions requires a unique pattern of motor commands (Enoka 1996). This makes it even more difficult to develop an animal model of DOMS.

Treatment: The soreness and pain of DOMS is remarkably resistant to any drug treatment. NSAIDs have no great effect (Newham 1988), which indicates that PGs are not involved in the sensitization of nociceptors in a sore muscle. Since PG E_2 may be important in muscle repair, PG blockers may not only be useless, but detrimental to restoration of the damaged contractile elements. Gentle stretching of the muscle toward restoration of its normal stretch range of motion may temporarily ameliorate the degree of soreness. However, in a controlled study, it had no effect on the overall course of muscle soreness (Molea et al. 1987).

3.7.1.5 Local Tenderness Due to Myofascial Trigger Points

Most patients are unaware of the exquisite tenderness to palpation of a trigger point (TrP). The pain for which they seek relief is usually referred from this hyperirritable site in the muscle to a body region remote from the TrP. This confuses the picture for the patient and those practitioners who are not familiar with the symptoms of TrP.

The etiology, pathophysiology, pain, and tenderness of TrPs are dealt with in Chaps. 2–4 in the companion volume by Mense and Gerwin (2010).

3.7.1.6 Chronic Work-Related Muscle Myalgia (Repetitive Strain Injury)

Probably the best description of a patient suffering from chronic work-related muscle pain was given by an Italian colleague in the eighteenth century: "The maladies that afflict the clerks aforesaid arise from three causes: first, constant sitting, secondly the incessant movement of the hand and always in the same direction, thirdly the strain on the mind from the effort not to disfigure the books by errors or cause loss of their employers when they add, subtract, or do other sums in arithmetics" (cited after Arksey 1998). This description already underlines not only the mechanical factors acting on muscle (repetitive strain, cumulative trauma, and overuse), but also the low force level at which the work is done, and the mental stress. As to the conditions under which the muscle works, two factors have to be emphasized. One is holding the muscle in a relatively fixed position, often under load, for prolonged periods. The other is a repetitive movement that gives the muscle incomplete recovery time between movements. There are several possible causes of the incomplete relaxation between contractions: (1) too little time, (2) pain in the muscle (see Chap. 7), and (3) psychological stressors.

Some of the factors involved in chronic work-related myalgia (CWRM; cf. Johansson et al. 2003) are as follows: (1) Muscle ischemia. As stated above, as little as 10–20% of maximal voluntary contraction of a muscle may be sufficient for occluding the microcirculation of that muscle (Sjögaard et al. 2000). (2) Increased activity in the sympathetic nervous system. During muscle work, the sympathetic nervous system is activated and muscle arterioles are under control of the increased sympathetic outflow. However, normally this vasoconstrictor influence is counteracted by metabolic substances released from the muscle. If this balance is disturbed, sympathetic activity could lead to vasoconstriction, even in a working muscle (Saltin et al. 1998). (3) Depletion of energy resources. Chemically bound energy is stored in muscle in the form of glycogen. Large, fast fatigable muscle fibers store more glycogen than the small fibers which do most of the work during prolonged, low-force contractions. Therefore, the glycogen stores of the small fibers are easily exhausted, and if the circulation is impeded, they cannot be replenished. The resulting lack of ATP in small fibers is likely to lead to painful contractures (Sjögaard and Sjögaard 1998). (4) Changed motor unit recruitment. Usually, the small, low-threshold, fatigue-resistant motor units (Type I) are recruited first, and

the large, high-threshold, fatigable units last. During monotonous low-force work the muscle as a whole may not be overloaded, but if the small muscle fibers do all the work, these fibers are prone to be overloaded. This is the main postulate of the "Cinderella hypothesis" (Hägg 2003; Hostens and Ramon 2005). The pain during this kind of monotonous work may be mediated by proton-sensitive membrane receptors, because the small muscle fibers are almost continuously contracted and probably have a low pH. Actually, small fibers that are activated first and deactivated last during low-force work have been identified experimentally (Sjögaard and Sjögaard 1998). (5) Shear forces between active and inactive fibers. During high-force contractions of a muscle, almost all muscle fibers are activated together, but during low-force contractions only the small fibers are contracting, and shearing forces build up between active motor units and adjacent inactive ones. In the long run, the shearing forces may release sensitizing substances from interstitial cells which sensitize muscle nociceptors. Sensitized nociceptors respond to weak stimuli and could be excited by the relative movement between the muscle fibers. Collectively, the data indicate that the Cinderella phenomenon reflects a loss of motor control, because the motor units do not take turns. Moreover, the afferent input from muscle receptors (including not only nociceptors but also muscle spindles and tendon organs) changes, which compromises motor coordination (Johansson et al. 2003).

3.7.1.7 Painful Contractions of Normal Muscle

Voluntary contraction of a completely ischemic muscle becomes extremely painful in about 1 minute. Sustained contraction of a muscle with intact blood supply elicits pain only if the force of contraction is sufficient to occlude blood vessels. The percentage of maximal voluntary contraction required for interrupting blood supply varies between muscles, but sustained contraction of 30% to 40% is likely to impair circulation (Sjögaard et al. 2000). During bicycle exercise maximum blood flow occurs between 50% and 70% (Clausen and Lassen 1971) of maximum work load. Beyond that limit, the muscle develops relative ischemia.

Muscle pain and muscle fatigue are not the same. Fatigue is measured as a progressive reduction in force of maximum voluntary contraction and as a reduction in median frequency of the EMG activity. It takes more effort to activate a fatigued muscle, but this does not make movement painful. However, if a movement becomes painful with continued effort, the pain is likely to be described as fatigued, which it may or may not be, if the muscle is objectively tested for fatigue.

3.8 Metabolic Problems

Reduction or depletion of the energy supply to a muscle can cause muscle fatigue and pain. Usually, metabolic disorders that compromise energy supply contribute to muscle pain indirectly by acting as aggravating and perpetuating factors.

However, a number of metabolic deficiencies are primary causes of muscle pain. A prominent example is McArdle's disease.

3.9 McArdle's Disease

McArdle's disease is caused by a deficiency of the enzyme myophosphorylase; more specifically, it is a glycogen storage disease (glycogen storage disease type V (GSD-V)). The disease is genetically heterogeneous: to date, more than 55 different mutations are known (Nogales-Gadea et al. 2007). The enzyme deficiency compromises glycolytic metabolism, a type of metabolism mainly Type II muscle fibers depend on. The symptoms include exercise intolerance with myalgia, early fatigue, painful cramps, weakness of exercising muscles, and myoglobinuria, i.e., presence of myoglobin in urine. Myoglobinuria may result from necrosis of muscle fibers which send their contents (including myoglobin) into the blood. Usually, the patient's pain is proportional to the amount of exercise.

A distinctive feature of McArdle's disease is the development of muscle contractures (activation of the muscle contractile mechanism without motor unit action potentials). The underlying mechanism is inadequate recovery of calcium by the sarcoplasmic reticulum.

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Chapter 4
Central Nervous Mechanisms of Muscle Pain: Ascending Pathways, Central Sensitization, and Pain-Modulating Systems

S. Mense

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Abstract The afferent fibers from muscle nociceptors make the first synaptic contacts in two regions of the spinal cord, the most superficial layer and the neck of the dorsal horn (lamina I and laminae IV–VI, respectively). The postsynaptic neurons send their axons into several ascending tracts that all mediate muscle pain: the spinothalamic, spinoreticular, and spinomesencephalic tracts. For orofacial muscle pain the first synaptic contacts are located in the subnucleus caudalis (the caudeal part) of the spinal trigeminal nucleus in the brainstem. The next center for the processing of nociceptive information is the thalamus, namely the most caudal parts of the ventral posterolateral nucleus (VPL) for the body and the ventral posteromedial (VPM) nucleus for the head. At the cortical level a center specific for muscle pain does not appear to exist. The nociceptive information is processed in various areas including the primary and secondary somatosensory cortices, prefrontal cortex, insula, and anterior cingulate cortex.

Central sensitization consists of several processes that occur in a temporal order, albeit with great overlap: increased excitability of nociceptive neurons, opening of formerly ineffective or silent synapses, metabolic changes, and changes in gene expression of the postsynaptic neuron. In patients, the increased excitability and resting activity of central nociceptive neurons is reflected in allodynia, hyperalgesia, and spontaneous pain. The final stage involves morphological changes in the wiring of the nociceptive network which perpetuate the chronic hyperexcitability and -activity.

Endogenous pain-modulating systems comprise firstly the afferent or segmental inhibition. The underlying mechanism of this type of pain modulation is the inhibition of the spinal nociceptive transmission by an input in thick myelinated afferent fibers. These fibers supply sensitive (non-nociceptive) receptors in the skin and deeper tissues. The second system is the descending inhibition, which originates in the mesencephalon and has synaptic connections with neurons in the rostral ventral medulla and the spinal cord. The system is tonically active and permanently dampens the excitability of nociceptive neurons at the origin of the spinothalamic tract. The system is tightly connected to a descending pain-facilitating pathway that has the same site of origin (mesencephalon and medulla) and facilitates nociceptive transmission in spinal nociceptive neurons. The final inhibition of spinal neurons is exerted by neurons that use enkephalin, serotonin, or norepinephrine as a transmitter.

The presence of several pain-modulating systems explains why pain can occur in the absence of any noxious stimulus (for instance, in patients who have a dysfunction of the descending pain-inhibiting pathway), or why even strong injuries do not elicit subjective pain (for instance, in injured soldiers in combat).

4.1 Ascending Pathways and Centers for Nociceptive Information

4.1.1 Pain Components

Knowledge of the various components of a pain sensation is essential for the understanding of the following sections, because for some of the components special pathways or centers exist. Figure 4.1 shows the main pain components. Normally, nociceptive activity in lower centers precedes the pain, but there are also cases in which pain occurs without activation of nociceptors and lower nociceptive centers (see below). Panel a comprises all events included in nociception: reception of a tissue-threatening stimulus by a nociceptive nerve ending, conduction of the resulting action potentials in nociceptive fibers and ascending tracts, and the processing of the information in nociceptive centers. Information processing in this context means inhibition, enhancement, or contrasting of the incoming neuronal information. As emphasized below, pain occurs in the cortex (panel b). The subjective pain components are:

1. Sensory-discriminative component. This component helps to recognize the nature, location, intensity, and time course of a painful stimulus.

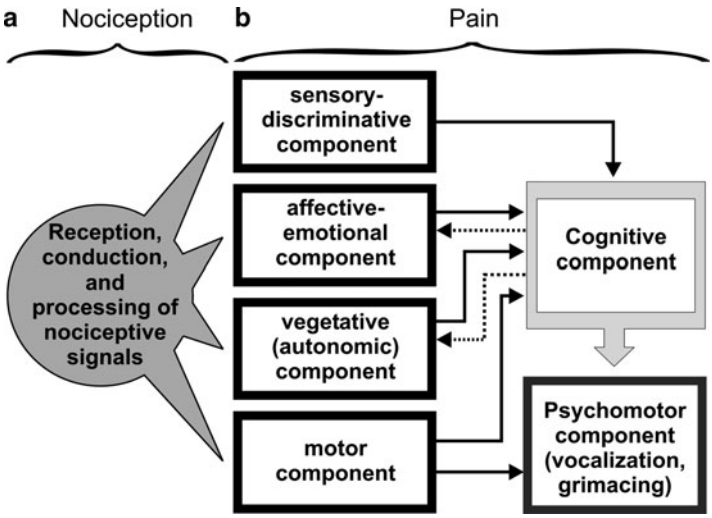

Fig. 4.1 Pain components. **a** Shows the processes that take place caudal to the cortical level, namely reception of a noxious stimulus, conduction of the nociceptive message to higher centers, and processing of the nociceptive information at all centers and nuclei, before it reaches the cortex. **b** The cortex extracts the nociceptive information from the simultaneous afferent activity in various nociceptive and non-nociceptive ascending tracts. The pain components are: (1) sensory-discriminative component, (2) affective-emotional component, (3) vegetative (autonomic) component, (4) motor component, (5) cognitive component, and (6) psycho-motor component

2. Affective-emotional component. This component is responsible for the fact that normally a painful stimulus hurts.
3. Vegetative (autonomic) component. This component includes blood pressure and heart rate changes during strong pain.
4. Motor component. This component consists mainly of motor reflexes (e.g., increased muscle tension).
5. Cognitive component. This component comprises the subjective assessment of the nature of the pain in terms of being dangerous to the patient's life. For instance, cancer pain may be an indication of a life-threatening disease. Under these circumstances, the cognitive component may enhance the pain.
6. Psycho-motor component. This component includes motor expressions as signals to other people showing that one is in pain (e.g., vocalization, grimacing).

4.1.2 Centers and Pathways for the Information from Muscle Nociceptors

4.1.2.1 General Remarks

When a tissue-threatening stimulus acts on muscle tissue, the information about the intensity and nature of the stimulus is encoded in action potentials that enter the spinal cord — or in the case of cranial nerves, the brain stem — via nociceptive muscle afferent fibers. The terminals of these afferents make synaptic contacts with second order neurons, the cell bodies of which are located in the dorsal spinal cord or brain stem. The signal from the muscle nociceptors is transmitted to the second order neurons through neurotransmitters. The nociceptor terminals end in presynaptic boutons (enlargements of the presynaptic terminal) that release the neurotransmitters glutamate or aspartate to activate the postsynaptic cells. This is the end of the pathway that can be considered specific for muscle pain. There is no evidence of the existence of an ascending tract that is specific for muscle pain. In dorsal horn neurons that have synaptic contacts with terminals from muscle nociceptors, the nociceptive information from muscle is mixed with information from other tissues: there are virtually no second order neurons that have an exclusive input from muscle nociceptors. The cells receiving mixed input form the large population of convergent neurons.

4.1.2.2 The Distribution of Nociceptive Information in the Spinal Cord

The afferent impulses from peripheral nociceptors enter the gray matter of the spinal dorsal horn via the dorsal roots (Fig. 4.2). "Gray matter" denotes those areas of the CNS that contain mainly neurons (and glial cells, see below), whereas the white matter consists of myelinated and unmyelinated nerve fibers. The majority of

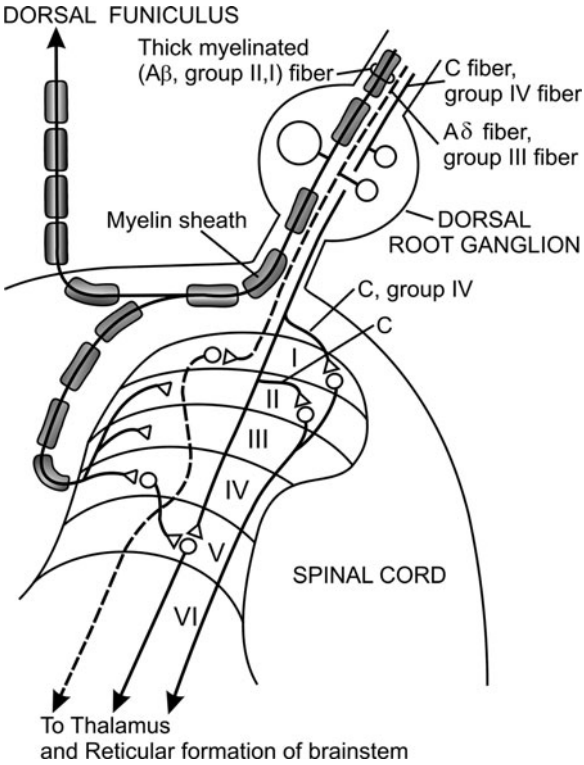

Fig. 4.2 Termination of nociceptive afferent fibers in the dorsal horn. Most nociceptive Aδ or group III fibers (*dashed line*) have synaptic contacts in the most superficial layer of the dorsal horn (lamina I). The cutaneous C fibers terminate in both lamina I and II, the group IV fibers from muscle in lamina I, only. Both unmyelinated fiber groups have an additional site of termination in the neck of the dorsal horn (laminae V, IV, VI). The thick myelinated fibers make synaptic contact in the layers in between (mainly lamina III). The thick muscle spindle afferents (e.g., Ia fibers) are not shown; they descend to the ventral horn and contact the motor neurons

nociceptive afferent fibers are unmyelinated fibers (group IV fibers from muscle and joint, C fibers from skin) and terminate in the superficial dorsal horn [lamina I and II after Rexed (1952)] and in the neck of the dorsal horn (lamina IV to VI; Fig. 4.2). There is a difference between the termination pattern of unmyelinated fibers from the skin and muscle in that muscle group IV fibers do not terminate in lamina II (Mense and Craig 1988). Thin myelinated Aδ-fibers often have their first synapse in Lamina I, the dorsalmost situated layer of the gray matter. In this layer, there are so-called nociceptive specific (NS) neurons that react exclusively to noxious stimuli. In contrast, the neurons in the neck of the dorsal horn exhibit an extensive convergence of nociceptive and non-nociceptive inputs from various tissues of the body. Lamina III is a major termination site for thick myelinated fibers from the skin.

The NS neurons in lamina I could well mediate the sensory-discriminative component of pain, i.e., the information on the nature, location, intensity, and time course of a noxious stimulus.

The reason why the majority of nociceptive fibers converge together with non-nociceptive fibers on the same neurons in the neck of the dorsal horn is unclear. One hypothesis is that the convergent wiring fulfils the function of a filter for nociceptive impulses. In particular, the nociceptive information from deep somatic tissues (muscles and joints) appears to be subject to a strong inhibition by non-nociceptive afferent fibers. This has been shown in experiments with the administration of tetrodotoxin (TTX), the toxin of the buffer fish. TTX blocks the conduction in thick and thin non-nociceptive fibers. When the non-nociceptive fibers in the dorsal roots were blocked with TTX, the synaptic efficacy of activity in unmyelinated fibers from muscle was markedly increased (Lambertz et al. 2008).

4.1.2.3 Normal Function of a Dorsal Horn Neuron

A dorsal horn neuron that has excitatory input from a nociceptive group IV fiber is shown in Fig. 4.3. The neuron is also contacted by an inhibitory synapse and is under the influence of a microglial cell. Figure 4.3 is highly simplified; in reality, the surface of a central neuron is completely covered by synaptic boutons, up to 10,000 boutons per cell. Most of the synapses on the cell body are inhibitory, and on the dendrites, excitatory.

Figure 4.3 shows some of the basic synaptic events that accompany the activation of a dorsal horn neuron. The excitatory synapses – of which only one is shown – evoke depolarizing excitatory postsynaptic potentials (EPSPs) in the membrane of the postsynaptic neuron by opening molecular ion channels that are permeable to small positively charged ions (cations, mainly Na^+ and/or Ca^{++}). Thus, the membrane potential of the neuron — which is normally negative at the inside — becomes more positive, i.e., the potential moves in the direction of the firing threshold. The firing threshold is reached only if several EPSPs are elicited almost simultaneously and superimpose. Then the neuron is excited (i.e., it fires action potentials). Inhibitory transmitters such as glycine or gamma-aminobutyric acid (GABA) likewise open ion channels in the cell membrane by binding to receptor molecules, but in this case the ion flux is carried by an inward movement of negative ions (e.g., Cl^-). Thus, the inside of the cell becomes more negative, the membrane is hyperpolarized, and its potential moves away from firing threshold. The postsynaptic neuron is less excitable because the synaptic potential is inhibitory (inhibitory postsynaptic potential, IPSP). The hyperpolarization counteracts the depolarization. When many inhibitory synapses are active together with excitatory ones, more EPSPs are required to bring the membrane potential to firing threshold.

In addition to receptors associated with ion channels, there are G-protein [guanosine triphosphate (GTP)]-coupled receptors that transfer signals across the postsynaptic membrane by activating a chain of molecules in or close to the

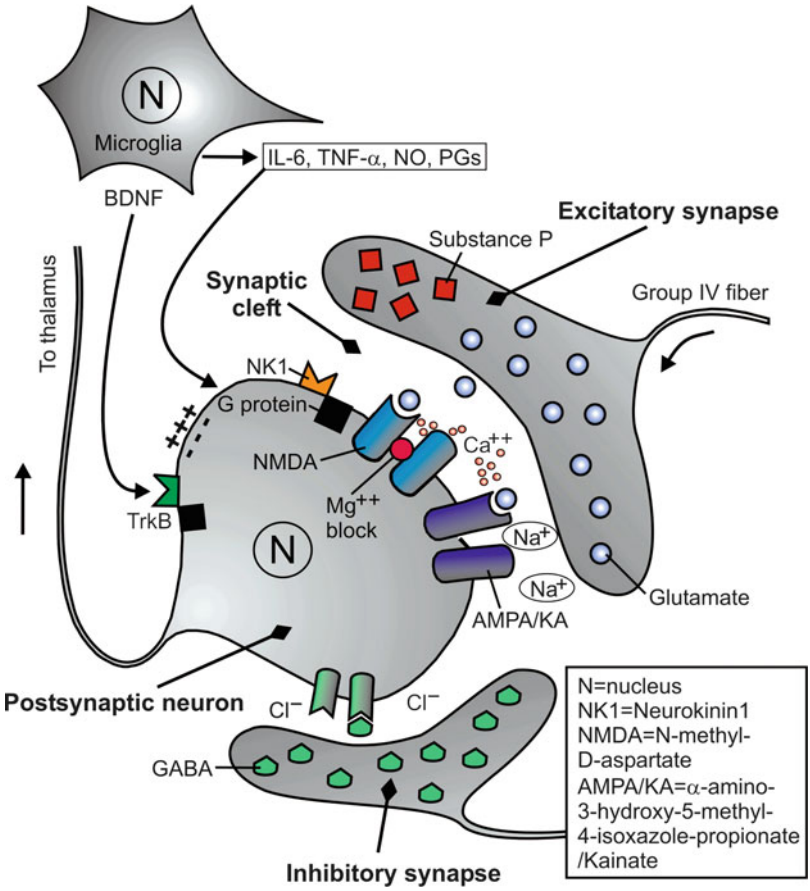

Fig. 4.3 Basic arrangement of the synaptic contacts on a nociceptive dorsal horn neuron. The afferent fiber from a muscle nociceptor (a group IV fiber) forms a broadened spinal terminal (*upper right*). The terminal is the presynaptic part of an excitatory synapse with the postsynaptic neuron, and contains the neurotransmitters glutamate and substance P (SP). Glutamate elicits a transient depolarization in the membrane of the postsynaptic neuron by opening ion channels that are permeable to Na^+ or Ca^{++}. (AMPA and NMDA channels; normally, only the AMPA channel can be opened). It is important to note that most of the AMPA synapses are ineffective (silent or "sleeping," cf. Fig. 4.9). An inhibitory synapse is shown in the lower middle which uses GABA as a transmitter. It opens a Cl^- channel in the membrane of the postsynaptic neuron. If the discharge frequency of the nociceptive group IV fiber is high or persistent, substance P (SP) is also released from the presynaptic terminal. SP binds to a G-protein coupled receptor molecule, the neurokinin 1 (NK1) receptor. The G-protein (guanosine triphosphate (GTP))-coupled receptors transfer synaptic signals across the postsynaptic membrane by activating an intracellular chain of events (not shown). The microglial cell in the *upper left* is activated under pathological circumstances. It then releases many substances that sensitize the postsynaptic nociceptive neurons. Brain-derived neurotrophic factor (*BDNF*) is one of them. It binds to the tyrosin kinase B (*TrkB*) membrane receptor

membrane. These receptors bind a ligand [for instance substance P (SP)] and control intracellular signal cascades which — depending on the type of G protein — activate or deactivate second messengers [second messengers are molecules such as calcium ions or cyclic adenosine monophosphate (cAMP) that influence intracellular enzymes]. If the discharge frequency of the nociceptive fiber is high, SP is also released from the presynaptic terminal. SP does not open an ion channel, it binds to a G-protein coupled receptor molecule. SP is well known for its capacity to cause long-lasting depolarizations in dorsal horn neurons, which is one of the prerequisites of the sensitization of central neurons (Randic and Miletic 1977; Zieglgänsberger and Tulloch 1979; see below).

The nociceptive afferent group IV fiber shown in Fig. 4.3 releases the amino acid glutamate as a transmitter substance (the first or primary messenger). In the CNS, glutamate is the main transmitter used by nociceptive neurons. Glutamate influences the membrane potential of the postsynaptic cell by binding to many specific receptor molecules. In the figure, two membrane receptors are shown that open ion channels, namely one that binds *N*-methyl-D-aspartate (NMDA), the so-called NMDA channel, and a channel binding other excitatory amino acids (the non-NMDA channels). Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate are the main transmitter substances that open the latter type of channel (Choi 1992; Bettler and Mulle 1995). Binding of glutamate to the non-NMDA receptor molecule opens the channel for positively charged small ions (mainly sodium ions) that have a higher concentration outside. When the ion channel opens, the ions enter the cell and depolarize the membrane. During such a normal activation, the NMDA channel is not opened. It is blocked by a magnesium ion (Mg^{++}) that is pushed out of the channel only when the membrane is depolarized to a sufficient degree. Then the greater number of positive charges inside the cell expel the positively charged Mg^{++}. In the open state, calcium ions (Ca^{++}) can enter the cell through the NMDA channel.

The inhibitory synapse in Fig. 4.3 uses gamma-amino-butyric acid (GABA) as a neurotransmitter, but in the spinal cord glycine is another effective inhibitory transmitter to postsynaptic neurons. An important aspect is that most of the AMPA synapses on the surface of a central neuron are ineffective (silent or "sleeping," cf. Fig. 4.9). Action potentials arriving at the presynaptic bouton of an ineffective synapse have very little influence on the postsynaptic neuron; they just elicit a very small EPSP which does not affect the overall excitability of the neuron. The reason for this lack of effectivity is probably that the channels are relatively impermeable to Na^{+} (the opening time of the channel is short and/or the opening probability low). Since activation of AMPA channels is the normal way of exciting dorsal horn neurons, and the NMDA channels are blocked by Mg^{++}, the entire neuron is inexcitable if the AMPA channels are absent or relatively impermeable. The number of ineffective synapses in the CNS is probably much greater than that of the effective (open) synapses. It is generally assumed that normally each peripheral nerve excites dorsal horn neurons in only a few spinal segments. However, the nerve has many ineffective synapses with neurons in adjacent segments. This is clinically relevant, because in a pathologic situation the ineffective synapses can become effective.

At the molecular level the increased effectivity of ion channels can be explained by a conformational change of the channel molecules which renders them more permeable to Na^+. The opening of formerly ineffective synapses (the sleeping synapses are awakened) leads to the formation of new effective connections of the neuron with the periphery. This mechanism appears to be a key feature of central sensitizing processes (Li and Zhuo 1998). If many of the ineffective synapses are opened, the result is a functional reorganization of the spinal dorsal horn (Hoheisel et al. 1994a). The lesion-induced transition from ineffective to effective synapses is likely to underlie pain referral and spread of pain.

A nociceptive synapse has two basically different ways of functioning:

1. When a short-lasting or low-frequency discharge arrives at the presynaptic ending, only glutamate is released. In the absence of SP, glutamate can only open the non-NMDA (AMPA/kainate) channels-. This results in a short-lasting depolarization of the postsynaptic neuron due to an influx of sodium ions. Thereafter, the neuron attains its previous state of excitability.
2. When a long-lasting or high-frequency input arrives at the presynaptic ending, glutamate and SP are released together. By binding to the G protein coupled receptor neurokinin 1 (NK1) SP activates the intracellular cascade, leading to the formation of kinases (see below). Simultaneously, the intracellular accumulation of sodium ions causes a depolarization and the opening of the NMDA channel. In the long run, these events lead to a sensitization of the postsynaptic neuron which is described in more detail in Sect. 4.5 (Baranauskas and Nistri 1998; Sandkühler 2000).

4.1.2.4 Dorsal Horn Cells Responding to Nociceptive Input from Muscle

Location and Morphology. In the first studies dealing with slowly conducting input from muscle to dorsal horn neurons, cells receiving input from muscle group III fibers were found mainly in the neck of the dorsal horn (lamina V; Pomeranz et al. 1968; Hoheisel and Mense 1990). Later studies showed that the superficial dorsal horn (lamina I and II) is also an important region for nociception from deep somatic tissues (Cervero et al. 1976; Fig. 4.2), although primary muscle group III fibers do not terminate in lamina II. Lamina I turned out to be an important site of origin for neurons that (1) could be driven by noxious stimulation of muscle, and (2) had ascending fibers projecting to the thalamus, i.e., they were part of the spinothalamic tract (STT; Craig and Kniffki 1985). As mentioned above, the STT is not the only tract that conducts nociceptive information from muscle to higher centers.

The location of dorsal horn cells that probably mediate muscle pain fits with the spinal termination areas of primary afferent fibers from muscle nociceptors. In the few studies dealing with the spinal terminations of identified single fibers from muscle and other deep tissues, nociceptive afferent fibers have been found to form presynaptic terminals mainly in laminae I and IV/V (Mense et al. 1981; Hoheisel et al. 1989), i.e., in the same laminae in which nociceptive dorsal horn cells are

located. This close spatial arrangement may indicate a monosynaptic connection between primary afferents and dorsal horn neurons but, with the techniques used at the time of the study, this interpretation is somewhat speculative.

The morphology of dorsal horn neurons processing input from muscle nociceptors is heterogeneous, i.e., a neuron driven by nociceptive input from muscle cannot be identified based on the shape of the cell body and the form and extent of its dendritic tree. In cat and rat, they include marginal cells in lamina I whose dendrites are oriented in the transverse plane, stalked cells in lamina II that often project to lamina I, and large multipolar cells in lamina IV–VI. From the work of several groups (for reviews see Brown 1981; Morris et al. 2004) no clear evidence has been obtained indicating that the functional properties of a dorsal horn cell are reflected in its morphology. Usually, general features such as an inhibitory or excitatory function can be correlated with morphology [and some authors even attempted to couple morphological features with certain aspects of pain (Morris et al. 2004)], but generally there is no means of recognizing dorsal horn neurons driven by muscle nociceptors.

Response Types

Neurons having exclusive input from deep somatic tissues. Many dorsal horn neurons with deep input (particularly in the neck of the dorsal horn) have properties of proprioceptive cells, i.e., they are dominated by input from muscle spindles and tendon organs. The main target area of afferents from spindles and tendon organs is in the ventral horn, but the afferent fibers send collaterals to neurons in the neck of the dorsal horn. These cells are mainly involved in locomotor control and therefore are disregarded in this chapter.

Dorsal horn neurons responding exclusively to activation of muscle nociceptors are extremely rare in the cat (Craig and Kniffki 1985). In contrast, among dorsal horn neurons that have nociceptive input from other deep somatic tissues such as joint, ligament, and tendon, approximately 20% were found to be exclusively driven by deep nociceptive input (Schaible et al. 1987; Hoheisel and Mense 1990). These neurons did not respond to innocuous mechanical stimuli of deep tissues but required noxious intensities of stimulation for activation. These units apparently represent a rather specific cell population for nociception from deep tissues similar to the nociceptor-specific cells described in studies on cutaneous nociception. However, in the above studies on cat dorsal horn neurons, all cells had additional additional input from the skin (see below). Therefore, at least in the cat, no sizable spinal pathway specific for deep somatic pain appears to exist.

On the other hand, in a study on rat dorsal horn neurons (Yu and Mense 1990a) the great majority (approximately 80%) of the cells with deep input belonged to the high-threshold mechanosensitive (HTM) type, which means that they responded only to noxious mechanical stimuli ("HTM deep neurons," Fig. 4.4). In studies of cutaneous nociception, these cells are often called NS. Many HTM deep neurons in the rat had receptive fields (RFs) in skeletal muscle, i.e., they could be activated by

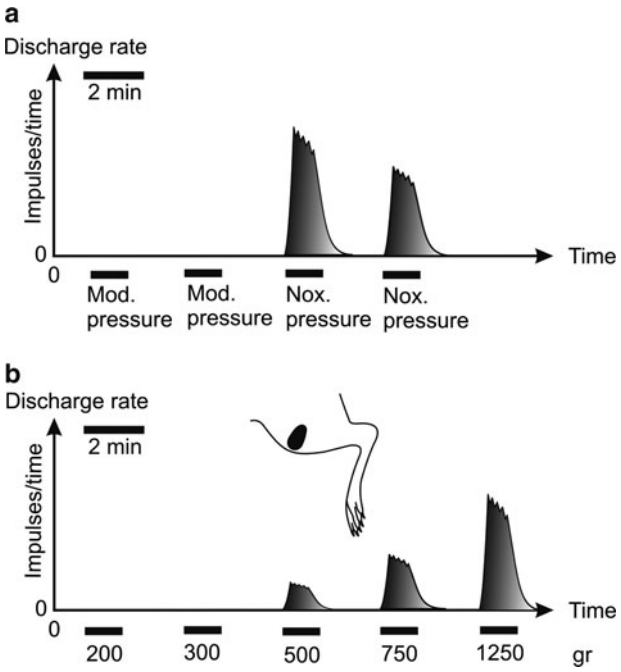

Fig. 4.4 Response behavior of a nociceptive dorsal horn neuron. The neuron had input from muscle nociceptors, and could be excited by high-intensity mechanical stimulation (noxious pressure) of the biceps femoris muscle (**a**). It did not respond to weak deformation (moderate pressure) of the muscle, and therefore was classified as a high-threshold mechanosensitive (putative nociceptive) neuron. Stimulation with a stimulating apparatus that delivered defined mechanical stimuli to the muscle (**b**) confirmed the high mechanical threshold of the neuron. The noxious pressure stimulus in **a** was equivalent to approximately 600 gr

stimulating muscles. These results show that there may be a species difference in the relative number of spinal neurons mediating muscle pain, and nothing is known about human dorsal horn neurons in this regard.

The remaining dorsal horn cells with deep input had a mechanical threshold in the innocuous range and responded strongly to weak deformation of muscle and other deep tissues [“low-threshold mechanosensitive (LTM) deep neurons”]. These cells had response properties similar to those of the peripheral LTM group IV units (see Chap. 2). The HTM deep neurons, many of which had RFs in skeletal muscle, had a stimulus response function that became steeper with increasing intensity of the mechanical stimuli, whereas the response curve of LTM deep cells showed signs of saturation with higher stimulus intensities, i.e., the curve became flatter. The response behavior of the LTM deep neurons indicates that their function is probably not nociceptive. A true nociceptive cell should be able to encode the intensity of a painful stimulus, i.e., it should exhibit increasing activity within the noxious range.

The steep response characteristic of HTM deep neurons at high stimulation intensities may explain why muscle pain usually starts slowly and then becomes intolerable very fast (for instance during ischemic contractions).

Neurons with convergent input from receptors in muscle and other tissues. Many dorsal horn neurons with muscle input have long been known to have additional input from other sources such as cutaneous and other deep receptors (Pomeranz et al. 1968). Because of the convergent input, many of these cells can be excited by mechanical stimulation of both muscle and skin, i.e., they exhibit multiple (mostly two or three) separate RFs in the skin and deep tissues. The activity of muscle nociceptors appears to be processed by dorsal horn neurons that can be also driven by other input sources. The situation is similar to visceral nociception, which likewise is mediated by neurons that have input from both visceral organs and somatic structures (skin, muscle, joints; Foreman et al. 1984; Cervero 1983).

In most studies on dorsal horn cells, the multireceptive or wide-dynamic-range (WDR) cells are assumed to participate in the encoding process by which noxious stimuli are perceived and identified (Dubner et al. 1989). These cells have a low mechanical threshold but continue discharging within the noxious range, i.e., they exhibit a combination of the response features of LTM and HTM neurons. This suggests that they receive input from various receptor classes including low-threshold receptors and nociceptors. Therefore, a low threshold to mechanical stimulation does not necessarily mean that the neuron has nothing to do with nociception.

The marked input convergence of spinal neurons is one possible explanation for the poorly-localized nature of muscle and other forms of deep pain. On the other hand, the convergence makes it difficult to understand how neurons in higher centers extract the information on the activity of muscle nociceptors from the activity of spinal neurons. When a noxious stimulus acts on a peripheral tissue, many different receptors and afferent pathways are activated. Therefore, a complex pattern of activity arrives at the cortex where pain originates. Depending on the state of attention of the individual, the degree of activity in pain-modulating pathways, and other factors, the cortex extracts nociceptive or other information from the input pattern. Therefore, noxious stimuli do not evoke pain in all situations, and innocuous stimuli can evoke pain in others.

A functionally important aspect of the marked convergence at the spinal level is that many of the convergent fibers contacting a given neuron have ineffective or silent synapses. Under pathophysiological circumstances the ineffective synapses can become effective (see below). Thus, new connections between the body periphery and the spinal cord can be formed.

Somatotopy in the dorsal horn. As will be described in Chap. 5, referral of muscle pain is characterized by a mislocalization of pain by the patient, since the referred pain is felt remote from the lesion. Generally, localization of a stimulus depends on a somatotopical arrangement of central nervous neurons, i.e., each cell processes the information from a particular body region (its receptive field, RF). A given neuron responds only if its RF is stimulated. Therefore, the discharge of a neuron always contains information about the site of the stimulus. When the RFs of

all dorsal horn neurons are combined, a (distorted) map of the body periphery will appear. The existence of such a map has been described for the skin, but little information is available on the somatotopy of dorsal horn neurons with deep input.

One of these studies (Yu and Mense 1990b) showed that cells with deep RFs on the distal hindlimb were located medially in the dorsal horn and those with proximal RFs laterally. Assuming that the cells with nociceptive input from deep tissues mediate deep pain, this somatotopy could be the basis for a good localization of the pain, but apparently it is not used for this purpose. Possibly, the somatotopical arrangement is of importance for the control of local motor reflexes.

4.2 Ascending Nociceptive Tracts in the Spinal Cord

The old view that the spinal cord consists mainly of nerve fibers that conduct nociceptive information like an electric cable is obsolete. The spinal cord is the first central nervous center that processes nociceptive information originating in peripheral nerve endings. For instance, inhibitory spinal neurons can block nociceptive information before it reaches higher centers. Blocking nociceptive information at the spinal level is much more effective than at higher levels because before the information has reached the higher centers it has probably left some traces in the lower nociceptive centers.

In the following sections the ascending and descending tracts are treated as though they are small bundles of fibers that convey nothing else than nociceptive information to higher centers (labeled lines). This is a highly simplified view. In reality the pathways are small networks of neurons that have collaterals to other lines and are interrupted by synapses. Each synapse is the site of information processing, so that the information that reaches the higher centers differs from that that has entered the spinal cord or brain stem. Moreover, each natural noxious stimulus excites a certain spectrum of both nociceptive and nonnociceptive afferent fibers. Nevertheless, for reasons of brevity, in the following sections nociceptive tracts will be addressed as such and will be drawn as simple lines. For details of tracts and sensory centers, see Brown (1973).

4.2.1 Spinothalamic Tract (STT, Tr. spinothalamicus)

The *lateral* STT is the main pathway for nociceptive information from peripheral nociceptors to higher nociceptive centers (thalamus and cortex; Fig. 4.5). Please note that the *anterior* STT is not nociceptive but transmits coarse pressure sensations to the thalamus. In the following paragraphs, only the lateral STT will be addressed.

The neurons of origin of the STT are situated in the spinal dorsal horn, mainly in laminae I (and probably also in laminae IV–VI); their axons cross in the same or

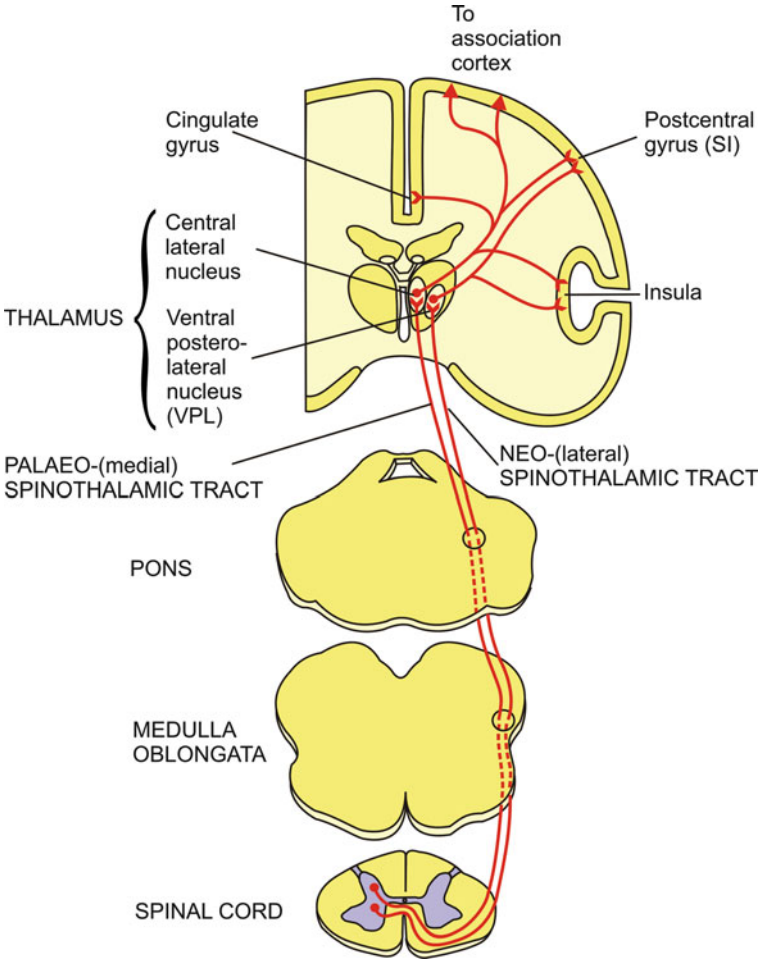

Fig. 4.5 The spinothalamic tract (STT). The STT has two parts, the phylogenetically recent neo-(lateral) spinothalamic and the old palaeo-(medial) spinothalamic tract. The neurons of origin for both parts of the STT are located in the spinal dorsal horn or in the subnucleus caudalis of the trigeminal spinal nucleus. Neurons projecting directly to the thalamus can be found mainly in laminae I; their axons cross to the contralateral side and ascend in the ventrolateral funiculus. The neo-spinothalamic tract terminates in the lateral thalamic nuclei [e.g., ventral posterolateral nucleus (VPL)]. It projects mainly to the postcentral gyrus (the primary somatosensory cortex, SI) of the cortex, and appears to mediate the sensory-discriminative component of pain sensations. The palaeo-spinothalamic tract terminates in medial thalamic nuclei such as the central lateral nucleus and the centromedian nucleus. It has diffuse projections to the anterior cingulate gyrus, the insula and other cortical areas, and is assumed to mediate the affective–emotional component of pain

adjacent segment to the contralateral side and ascend in the ventrolateral funiculus. The tract has two parts, the phylogenetically old palaeospinothalamic tract (palaeo-STT) and the more recent neospinothalamic tract (neo-STT). The former terminates

in medial thalamic nuclei such as the central lateral nucleus and the centromedian nucleus, the latter in the lateral thalamus [e.g., ventral posterolateral nucleus (VPL)]. The neo-STT projects in the cortex mainly to the postcentral gyrus (the primary somatosensory cortex, SI) and appears to mediate the sensory-discriminative component of pain sensations. The palaeo-STT projects in a diffuse way to the anterior cingulate gyrus, the insula, and other cortical areas. The medial STT appears to mediate the affective–emotional component of pain. The STT is not the only ascending nociceptive tract in humans. Further pathways for nociceptive information are the spinoreticular and the spinomesencephalic tract.

4.2.2 Spinoreticular Tract (Tr. spinoreticularis)

The spinoreticular tract (SRT) has the same neurons of origin in the spinal dorsal horn as the lateral STT (Fig. 4.6a). The axons likewise cross to the contralateral side and ascend to higher centers. In contrast to the STT, the SRT is interrupted several times by synapses. The tract gives off collaterals to the reticular formation in the medulla oblongata, and most fibers terminate in the reticular formation of the pons. From here, there is a connection to the medial nuclei of the thalamus. Presumably, the tract mediates the vegetative (autonomic) component of pain sensations. Whether the SRT possesses uncrossed ipsilaterally ascending fibers cannot be answered to date. These uncrossed fibers could explain the recurrence of pain in patients after transection (chordotomy) of the ventrolateral funiculus on the side contralateral to a painful lesion. This intervention is performed mainly as an ultimate therapy in cases of pain in which drug treatment fails. The chordotomy operation aims at interrupting the lateral STT together with the SRT. Usually the pain is gone after the chordotomy, but in some patients it reappears several weeks after the operation. One possible explanation is that during development, the SRT was a bilateral tract of which only the crossed side survived. The synapses of the ipsilateral part became ineffective, and after the chordotomy the ineffective connections of the ipsilateral SRT were reopenend. Then the nociceptive information from the painful lesion ascends ipsilaterally and reaches higher nociceptive centers.

4.2.3 Spinomesencephalic and Spinobrachial Tract (Tr. spinomesencephalicus and Tr. spinoparabrachialis)

These tracts do not transmit the nociceptive information to the thalamus but to the mesencephalon, namely to the reticular formation close to the periaqueductal gray (PAG) in the mesencephalon and to the parabrachial nucleus (PB; Fig. 4.6b) in the pons. The PB is situated close to the superior cerebellar peduncles (also known as “brachia conjunctiva” in Latin). From the PAG and PB there are projections to the

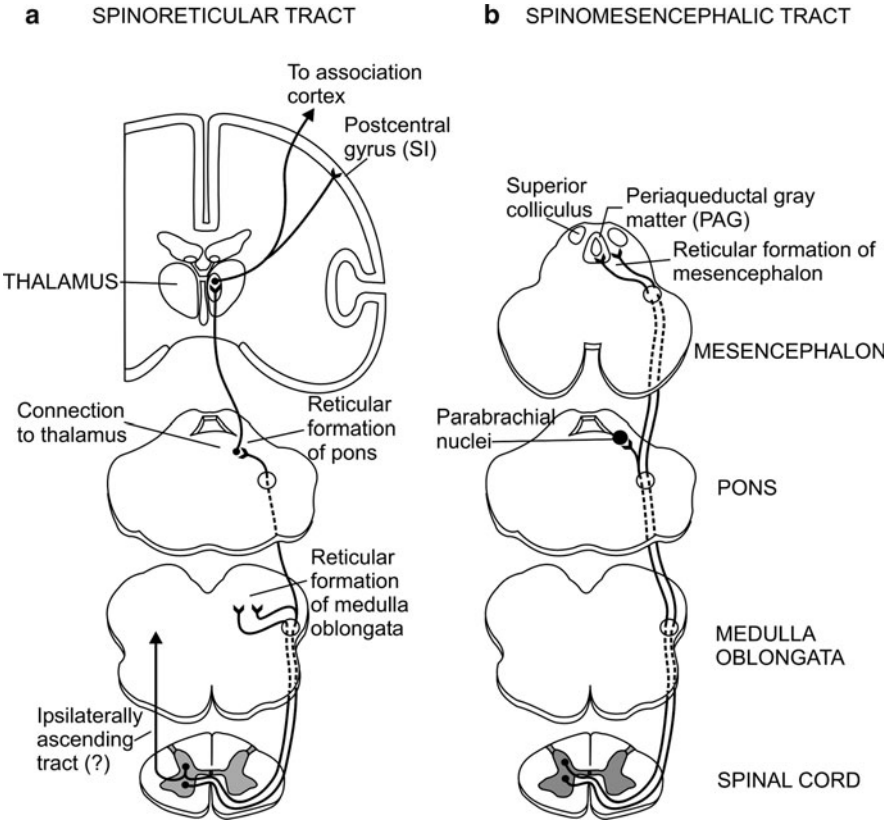

Fig. 4.6 Further ascending nociceptive tracts. **a** The spinoreticular tract (SRT). This tract has the same neurons of origin in the dorsal horn as the STT. The axons likewise cross to the contralateral side, and ascend to higher centers. In contrast to the STT, the SRT is interrupted several times by synapses. The tract gives off collaterals to the reticular formation in the medulla oblongata, and terminates in the reticular formation of the pons. Here, it has a connection to the medial nuclei of the thalamus. Presumably, the tract mediates the autonomic component of pain sensations. Whether the SRT has additional uncrossed (ipsilaterally ascending) fibers is a matter of debate. **b** The spinomesencephalic and spinobrachial tract (Tr. spinomesencephalicus and Tr. spinoparabrachialis). These tracts transmit the nociceptive information to the brainstem, namely to the reticular formation close to the periaqueductal gray (*PAG*) in the mesencephalon and to the parabrachial nucleus (PB) in the pons. From these nuclei there are projections to the corpus amygdaloideum (amygdala), a part of the limbic system. The spinomesencephalic tract may contribute to the affective–emotional component of pain

corpus amygdaloideum (amygdala), a part of the limbic system. The limbic system is responsible for emotions and memory processes and the amygdala is involved in fear and stress reactions. Because of these connections the spinomesencephalic and spinoparabrachial tract may contribute to the affective–emotional component of pain.

4.2.4 The Thalamus: The Last Nociceptive Center Below the Cortex

There are two nociceptive groups of nuclei in the thalamus: the medial nociceptive thalamus includes the nuclei (ncl.) intralaminares (intralaminar nuclei, situated in the thin sheets of myelinated fiber bundles that divide the nuclei), as well as the ncl. centralis lateralis (central lateral nucleus) and the ncl. centromedianus (centromedian nucleus; Fig. 4.7). The lateral nociceptive nuclei include the caudal portions of the VPL for the processing of nociceptive information from the body, and the VPM for nociceptive information from the face. These caudal portions of the VPL and VPM form subnuclei of small cell bodies, the ncl. ventrocaudalis parvocellularis externus and internus, after Hassler (1966). In the Nomina Anatomica they are

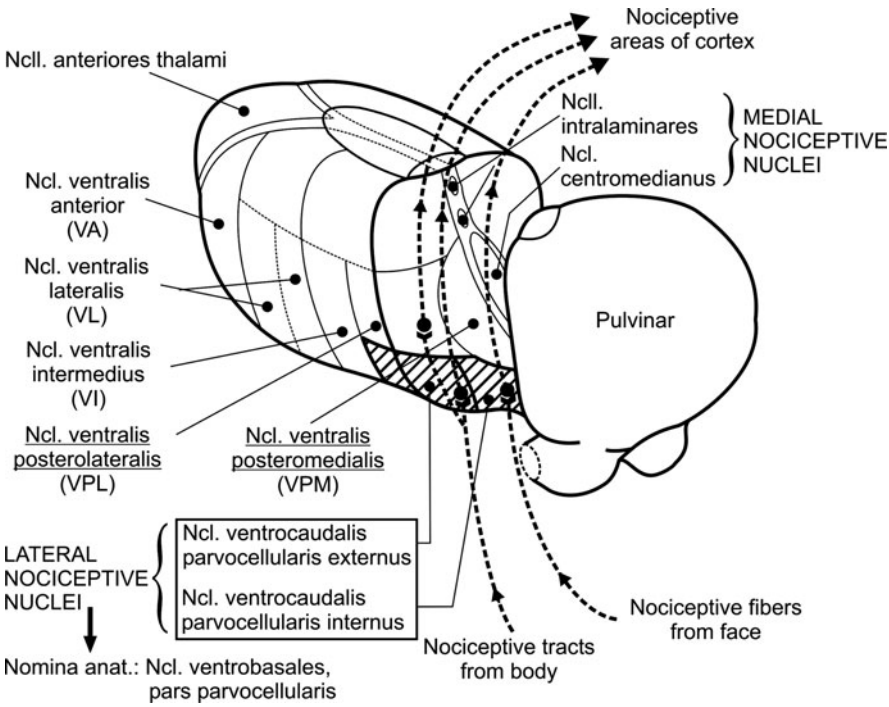

Fig. 4.7 The thalamus. There are two major nociceptive groups of nuclei in the thalamus: the medial nociceptive thalamus includes the nuclei intralaminares (intralaminar nuclei, situated in the thin sheets of myelinated fiber bundles that divide the nuclei) as well as the nuclei centralis lateralis (central lateral nucleus) and centromedianus (centromedian nucleus). The lateral nociceptive nuclei comprise the caudal parts of the *VPL* for the processing of nociceptive information from the body, and the *VPM* for nociceptive information from the face. These caudal portions of the VPL and VPM form subnuclei of small cell bodies, the nuclei ventrocaudalis parvocellularis externus and internus, after Hassler (1966). In the Nomina Anatomica they are called nuclei ventrobasales, pars parvocellularis (ventrobasal complex, parvocellular part)

called Nuclei ventrobasales, pars parvocellularis (ventrobasal complex, parvocellular part). Besides the parvocellular nuclei at the caudal rim of the VPL and VPM there are probably additional sites of nociceptive processing in the main nuclei of VPL and VPM.

To what extent the above nuclei are involved in the processing of information from muscle nociceptors is unknown. A small number of nociceptive neurons with musculotendinous input have been shown to be present in the ventral and dorsolateral periphery of the VPL and in the transitional zone between VPL and ventrolateral nucleus of the cat (the "ventral periphery," Kniffki and Mizumura 1983). The location of nociceptive neurons in the periphery of the VPL appears to be typical for the cat; in the rat, nociceptive cells with articular input have been found intermingled with tactile neurons within the VPL and VPM (Guilbaud 1991). There are also data suggesting that the caudal portion of the ventromedial nucleus is a rather specific nucleus for deep pain in the rat (Floyd et al. 1996). More recent data show that the thalamic nuclei receiving the strongest excitatory input from rat muscle nociceptors are the ventralis lateralis (VL) bilaterally and the VPL contralaterally (Gholami et al. 2006).

In primates, the lateral STT has been shown to terminate mainly in the VPL, nucleus ventroposterior inferior, and centralis lateralis (Gingold et al. 1991). These regions may correspond to the nucleus ventralis caudalis parvocellularis in humans (Hassler 1976).

Data obtained with positron emission tomography (PET) in humans indicate that the posterior thalamus is involved in pain processing (Hsieh et al. 1995). However, in this thalamic region a reduction in regional blood flow (suggestive of a decrease in neuronal activity) of the thalamus was found in pain patients. The clinical significance of these findings is still obscure.

It is possible that other nuclei of the thalamus (e.g., the posterior and medial nuclei) also process information from nociceptive fibers. The posterior nuclei in the cat have been found to contain cells with nociceptive properties (Guilbaud et al. 1977), and some of the units in the medial thalamus responded to noxious stimulation of deep tissues in this species (Dong et al. 1978).

In polyarthritic rats, neurons in thalamic nuclei have unusual response characteristics with long afterdischarges and lowered mechanical thresholds (Gautron and Guilbaud 1982). Cells of the nucleus centralis lateralis of arthritic rats acquire an input from the inflamed joints which is not present in normal animals. These data suggest that under pathological conditions nociceptive pathways to the thalamus may be opened which are silent or ineffective in the intact animal. This neuroplastic change is probably associated with a sensitization of the neurons. Such lesion-induced changes in connectivity of central neurons appear to be a general mechanism under pathological circumstances. Similar changes have been observed also at the spinal level (see below).

Whether cutaneous, muscle, and joint pain are processed in different thalamic nuclei is unknown. There is evidence indicating that at least the proprioceptive information from muscle and joint projects to separate areas near the nucleus ventralis intermedius (Hardy et al. 1980).

Thalamic pain (pain due to thalamic lesions) occurs predominantly after a lesion of the ventroposterior region [the ventral postero-inferior (VPI) nucleus] of the thalamus, a part of the lateral nociceptive thalamus (Bowsher et al. 1998). The reason why a lesion of the lateral thalamus is followed by spontaneous pain is still obscure. There is some clinical evidence that the lateral thalamic nuclei (VPI and reticular nuclei) tonically inhibit the activity of the medial thalamic nuclei. This may be of importance in cases where the lateral thalamus is destroyed or damaged, e.g., by a stroke. Then the medial thalamus is disinhibited (Cesaro et al. 1991), which may result in thalamic pain, i.e., excruciating and diffuse pain in the entire contralateral side of the body. As the medial nuclei mediate the affective–motivational component of pain, the disinhibition of these nuclei is likely to cause a particularly aversive pain.

4.3 Pain Originates in the Cortex

Conscious sensations of pain are not present in centers below the cortex. Subjective pain is the result of the cortical processing of nociceptive information from lower centers (Basbaum and Jessell 2000). Therefore, terms like “pain receptor” or “pain pathway” are misnomers.

Most sensory modalities such as vision or hearing have spatially restricted cortical centers. Pain is the only modality for which there is no specialized center in the cortex. This is surprising, because pain is a vital sensory modality. Patients with insensitivity to pain due to the absence of nociceptive unmyelinated fibers have a reduced life expectancy, because they frequently injure themselves in daily life and suffer from normally painful disease without recognizing it (Fields 1987).

Early work on the nociceptive processing in the cortex has shown that in some areas of the monkey somatosensory cortex (Brodmann areae 3b and 1) there exist neurons that receive input from cutaneous nociceptors (Kenshalo and Isensee 1983). In a study on the rat somatosensory cortex, out of 292 neurons 91 responded to noxious stimulation. Among these, 13 cells were driven from deep tissues (Lamour et al. 1983). The proportion of cortical neurons driven by deep input has been reported to change if pathological alterations occur in the periphery of the body (Guilbaud 1991).

To date, there are only a few reports that specifically address the input from muscle nociceptors to cortical neurons. In one of these studies (Iwamura et al. 1981), noxious stimuli were applied to the gastrocnemius-soleus (GS) muscle in cats during a systematic search for neurons in area 3a responding to these stimuli. Only approximately 10% of the cells with deep input from the contralateral hindlimb were found to respond to nociceptive input from muscle.

In studies using fMRI (functional magnetic resonance imaging) or PET in humans, the following cortical areas consistently respond to acute pain stimuli: primary somatosensory cortex (SI), secondary somatosensory cortex (SII), prefrontal

cortex (PFC), anterior cingulate cortex (ACC), and insular cortex (IC). Figure 4.8 shows the location of these areas. It is worth noting that the areas relevant for pain are distributed over large parts of the lateral and medial cortex. In Fig. 4.8, a specific component of the pain sensation is attributed to each area, although this separation is somewhat speculative.

The relevance of the SI for the sensory-discriminative pain component is well established. For the other areas correlation to a specific pain component is less well proven. The PFC is assumed to mediate mainly the cognitive and affective pain component. The latter function is well known from patients with lesions of the frontal cortex. Often these patients can recognize painful stimuli, but the stimuli do not hurt because the affective component is missing. To what extent the ACC (a part of the cingulate gyrus that is visible in the medial view directly above the

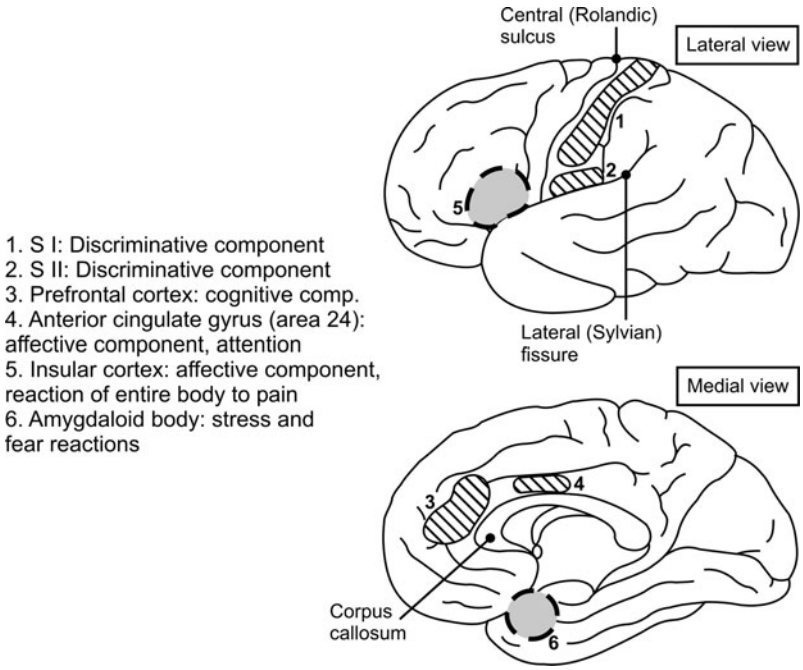

Fig. 4.8 Nociceptive areas of cortex. In the figure, a specific component of the pain sensation is attributed to each area, but for some areas this functional relationship is speculative. The *post-central gyrus* (the primary somatosensory cortex, SI) appears to be the main site of processing of the sensory-discriminative pain component. The *secondary somatosensory cortex* (SII) has a bilateral input, and is likewise a center for the sensory-discriminative pain component. The *prefrontal cortex* is assumed to mediate the cognitive and affective pain component. To what extent the *anterior cingulate cortex* really mediates pain sensations, or is activated as part of an attentional or arousal reaction, is unclear at present. The *insular cortex* (the insula) has recently been acknowledged to be a major center for pain sensations. The amygdaloid body (amygdala) is not a part of the cortex, but because of its relevance for pain sensations in stress situations, it is included in the figure

corpus callosum) really mediates pain sensations, or is activated as part of an attentional or arousal reaction, is unclear at present. On the other hand, the IC (the insula) has attracted growing interest recently, because data are accumulating that this area is essential for many aspects of pain (Zhuo 2008). The function of the IC was unknown for a long period of time, because it is hidden under the so-called opercula, parts of the frontal and parietal cortex close to the lateral (Sylvian) fissure of the brain.

The IC appears to receive direct connections from the thalamus (Craig 2003) and plays a key role in decision making and pain behavior. Together with the ACC, it is thought to be mainly important for the affective component of pain, i.e., the unpleasantness of pain. Pain is still perceived when the IC is damaged, but it does not cause suffering, i.e., it has lost its affective component (Greenspan et al. 1999). In a recent study, the anterior IC showed a particularly strong activation during acute muscle pain (elicited with i.m. injection of hypertonic saline) as opposed to cutaneous pain following subcutaneous injection (Henderson et al. 2007).

Brain imaging data from chronic pain patients show that in neuropathic pain the discriminative tactile capabilities were reduced, whereas pain-related activity in the brain matrix (those areas that are activated when painful stimuli are applied) is enhanced (Hofbauer et al. 2006). Sustained high intensities of spontaneous pain have been found to be accompanied by increased activity in the medial PFC (mPFC) and the ACC. In studies using electroencephalogram (EEG) recordings, evidence was found that in neuropathic pain patients there is an ongoing over-excitation in these and other brain areas (Stern et al. 2006). In chronic phantom pain a change in cortical representation has been found which might contribute to the pain (Flor et al. 2006).

It is worth noting that a cortical activation in the fMRI can be due to increased discharges in excitatory or inhibitory neurons. Activity in excitatory nociceptive neurons may be correlated with pain, whereas increased activity in pain-inhibiting circuits is accompanied by decreased pain.

Recent data show that one of the key mechanisms of central sensitization [long-term potentiation (LTP)] induced by nociceptive input takes place not only at the spinal but also at the cortical level (Zhuo 2008).

4.4 General Remarks on Pain Concepts

An important point to consider is how we can distinguish between different types of pain (e.g., muscle, joint, cutaneous, visceral pain), when we know that nociceptive information from different sources uses the same neurons at the spinal level. One possibility is that the pattern of impulses in a given pathway and/or a certain combination of input sources are essential for the recognition of a particular type of pain (Perl 1998).

In chronic pain the situation is even more complex, because under these conditions the nociceptive pathways and centers exhibit marked neuroplastic changes. As outlined below, these changes affect different aspects of the neurons and glial cells (including functional, metabolic, and structural) and have different time-courses. The neuroplastic changes do not take long to develop — the first changes occur shortly after an unusually strong or long-lasting activation of nociceptive pathways (Coderre et al. 1993; Hoheisel et al. 1994a; Woolf and Salter 2000).

4.4.1 Pain Memory

The mechanism of opening or strengthening of ineffective synapses is assumed to play a role in learning processes at higher levels of the CNS. For example, neurons in the striatum of male singing birds have been shown to acquire new connections this way in the process of learning their species-specific song (Mooney 1992). Similar events appear to occur in cortical neurons in mammals during associative learning (Desimone 1992, Sandkühler 2000). In fact, the similarities between chronic pain and learning processes are striking: in a recent report, two patients have been described who no longer experienced chronic pain after they had become amnesic following a stroke or seizures (Choi et al. 2007).

It is easy to imagine that each injury or nociceptive input leaves traces in the central nervous system (the pain memory). The traces may consist of an increased excitability of central neurons (which probably is easily reversible), of metabolic changes in nociceptive neurons (which take longer to reverse), or formation of new connections in the CNS in the sense of a reorganization of the spinal cord or higher centers. The changes in cortical representation found in amputees are a prominent example for a persistent pain memory (Flor 2008). Some of these latter changes are possibly irreversible. Chronic migraine patients who experienced pain as newborns are one example of a pain memory that is not extinguished in years (Maneyapanda and Venkatasubramanian 2005).

Therefore, we have to assume that in chronic pain patients the nociceptive pathways look different from what has been presented above. The treatment of these patients is also difficult because the neuroplastic changes need time to reverse.

4.5 Mechanisms of Central Sensitization

4.5.1 Introduction

Many chronic muscle pain patients show signs of a sensitization such as allodynia, hyperalgesia, spread of pain, and pain referral. During patient examination, the two basic forms of sensitization (peripheral and central) are difficult to distinguish.

Mechanisms of peripheral sensitization have been addressed in Chap. 3. This section focuses on mechanisms of central sensitization, i.e., mechanisms that lead to increased excitability of nociceptive neurons at the spinal (and higher) levels. From many basic science and clinical studies, we know that every long-lasting or strong input from muscle nociceptors to the spinal cord or to neurons in the trigeminal subnucleus caudalis of the brain stem changes the excitability of these neurons. The resulting neuroplastic changes are clinically important because they mark the beginning of the transition from acute to chronic pain. Contrary to former beliefs, these changes do not take long to develop; a few minutes of input from muscle nociceptors are sufficient.

When noxious stimuli are applied in animal experiments, a frequent finding is that nociceptive neurons do not only respond to the stimulus but also increase their sensitivity during repeated stimulation. This means that the discharge of a nociceptive cell may grow larger even though the stimulus strength is constant. In patients this mechanism can lead to an increase in subjective pain when the peripheral lesion is unchanged or even improving objectively. Such changes in the processing of nociceptive information usually occur following strong or long-lasting (repeated) noxious stimulation – the underlying neuronal mechanisms are often called modulation or neuroplasticity.

The term "modulation" is mostly used for characterizing a change in the discharge of a neuron under the influence and in the presence of a modulating factor (e.g., a sensitizing substance). This definition implies that the neuron regains its original properties if the modulating factor is no longer present. In contrast, "neuroplasticity" describes longer-lasting alterations of neuronal properties (e.g., during development or learning processes). In animal experiments, the latter term is often used to characterize changes that outlast a triggering stimulus.

Basically, three steps of central sensitization can be distinguished: (1) functional changes that express themselves as a higher responsiveness of central neurons to noxious stimuli, (2) metabolic changes that occur not only in neurons but also in glial cells, and (3) structural changes that perpetuate the hyperexcitable state. These steps do not occur subsequently but start almost simultaneously. However, the time course of the steps appears to be different. In the following sections, although the steps are addressed one after the other, it is recognized that this separation is artificial.

Central sensitization in chronic muscle pain patients is a clinical problem because treatment is much more difficult after central nervous neuroplastic changes have occurred. The functional reorganization of the spinal cord and of higher nociceptive centers is akin to an unwanted learning process. Of course it would be best to block the afferent input from muscle nociceptors as early and completely as possible but the muscle pain of most pain patients is already chronic when they first see a doctor. With chronic muscle pain patients, no immediate therapeutic success can be expected because the neuroplastic changes in the CNS need time to reverse.

For a better understanding of this section, the key processes of central sensitization are described at the level of a single neuron. The resulting changes in the connectivity of dorsal horn neurons will be addressed later.

4.5.2 Lesion-Induced Functional Changes

When the same noxious stimulus is applied repeatedly (every 1–2 s) in animal experiments, dorsal horn neurons tend to increase their response magnitude. This behavior is called wind-up (Wall and Woolf 1986). The central neuron is progressively sensitized by the repeated nociceptive input. At first, the changed responsiveness is usually transient. This short-lasting increase in neuronal responsiveness appears to be due to the release of pain-modulating substances such as SP. The presynaptic terminal of the nociceptive fiber contains SP in coexistence with glutamate (cf. Fig. 4.3), and there is evidence showing that SP is released predominantly by high-frequency discharges in the afferent fiber. As a result of the simultaneous release of SP, the action of glutamate on the postsynaptic neuron is enhanced. This process is often called "modulation" of pain processing by SP.

After their induction by a nociceptive input the neuroplastic changes may become independent of the input. This has been shown in a study of the hyperexcitability of rat dorsal horn neurons following the induction of an inflammation of the paw (Hylden et al. 1989).

In dorsal horn neurons neuroplastic changes require input via unmyelinated or thin myelinated afferent fibers, i.e., afferent activity in thick myelinated fibers is not effective. For unknown reasons, input via muscle afferents is more effective than cutaneous input for inducing prolonged changes in neuronal behavior (Wall and Woolf 1984).

4.5.3 Events Leading to Hyperexcitability of Central Neurons

Most of the data in the following sections were obtained in experiments on rats in which an experimental inflammation of the GS muscle was induced. In these rats, the nociceptive group III and IV fibers in the GS muscle exhibit an increased activity for the duration of the myositis (1–12 days). Therefore, these myositis rats can be used as a model of a tonic–chronic muscle lesion that is characterized by a continuous nociceptive input to the spinal cord. Acute cases of myositis (particularly dermatomyositis) are painful, but in chronic myositis dysesthesia and muscle weakness prevail (Helmers and Lundberg 2008). Considering the short life expectancy of a rat, approximately 2 years under laboratory conditions, a duration of 6–12 days is assumed to be chronic for this species.

The hyperexcitability of central neurons is the most obvious expression of central sensitization. At the single cell level the hyperexcitability leads to resting discharge and an increased responsiveness to peripheral stimuli.

Figures 4.9 and 4.10 show the changes that occur in the synapse depicted in Fig. 4.3, when a prolonged noxious stimulus is present in the periphery of the body. Recent data (see below) indicate that a high discharge frequency is not required for this effect; low-frequency input or even subthreshold potentials in postsynaptic neurons are sufficient.

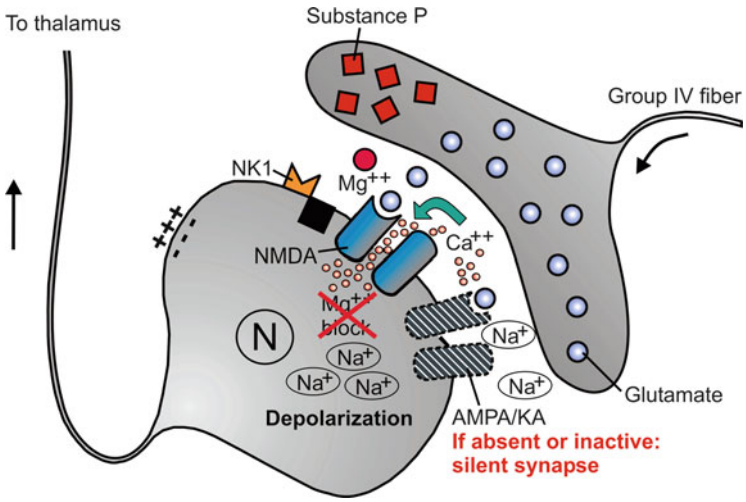

Fig. 4.9 Sensitization of a spinal dorsal horn neuron I. Weak, transient pain (e.g., after an injury) is mediated mainly by opening of the AMPA/KA channel by glutamate. Under normal circumstances, the NMDA channel is blocked by a Mg^{++} ion, and therefore cannot be opened. The neuron shown is assumed to have only ineffective AMPA/KA channels whose Na^{+} permeability is very low, i.e., the synapse is silent or sleeping. If the nociceptive group IV fiber releases glutamate for a prolonged period of time, a sufficiently high number of Na^{+} ions enter the postsynaptic cell through the AMPA channel and produce a persistent depolarization (render the inside more positive). The depolarization brings the membrane potential closer to firing threshold; therefore, now small additional EPSPs can excite the cell. The positive charges of the Na^{+} ions inside the cell expel the positively charged Mg^{++} ion out of the NMDA channel, and remove its block. If now glutamate molecules bind to the NMDA receptor, the channel opens and Ca^{++} ions enter the cell (*green arrow*). The calcium ions act as second messengers that activate other intracellular second messengers. The persistent depolarization is the first step in the sensitization

As mentioned above, weak and transient pain after a short-lasting noxious stimulation (e.g., a trauma) is mediated mainly by the opening of AMPA channels by glutamate. Under normal circumstances, the NMDA channel is blocked by a Mg^{++} ion and cannot contribute to the excitation of the postsynaptic neuron. In Fig. 4.9 the neuron is assumed to have only ineffective Na^{+} channels, i.e., the synapse is silent or sleeping. All activity arriving presynaptically is "stuck" at the synapse and not transmitted to higher centers.

If the nociceptive group IV fiber is active for a prolonged period of time, a sufficiently high number of Na^{+} ions enter the postsynaptic cell through the relatively impermeable AMPA channel and produce a persistent depolarization. The depolarization brings the membrane potential closer to firing threshold; therefore, small additional EPSPs can now excite the cell. The persistent depolarization is the first step of central sensitization.

The positive charges of the Na^{+} ions inside the cell push the positively charged Mg^{++} ion out of the NMDA channel and thus open the channel. If glutamate now binds to the NMDA receptor, the channel opens and calcium ions (Ca^{++}) enter the

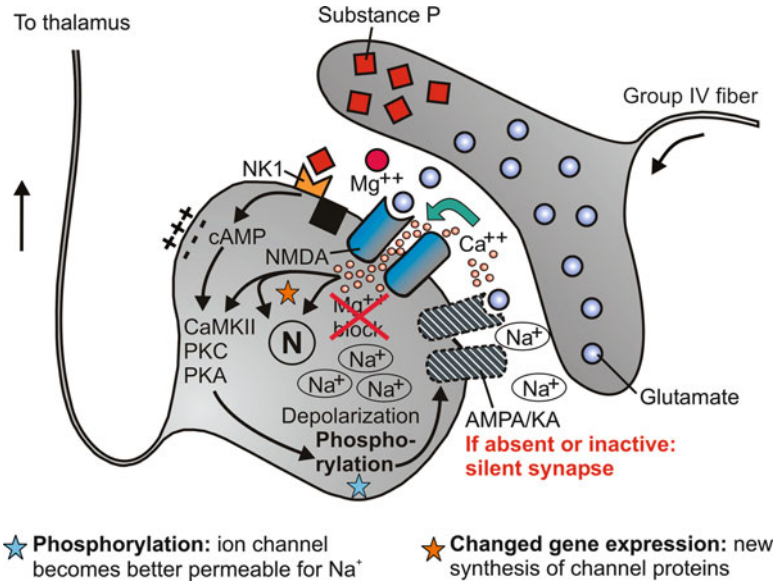

Fig. 4.10 Sensitization of a spinal dorsal horn neuron II. Substance P contributes to the sensitization, in that it binds to the NK1 receptor and activates (among other actions) the cAMP. This results in an activation of protein kinases such as CaMK II (calmodulin-dependent kinase II), PKA and PKC (protein kinase A and C). The protein kinases phosphorylate channel proteins, and thus increase the permeability of the channels for Na^+ and Ca^{++}. The phosphorylation also enhances the sensitivity of the receptors to glutamate. The phosphorylation of ion channel proteins is the second step of the central sensitization. In the long run, a change in gene expression will occur. This can lead to the de novo synthesis of NMDA and AMPA/KA ion channels that are integrated in the membrane, and increase the excitability of the neuron

cell from the outside (Fig. 4.9). The calcium ions act as second messengers that activate other intracellular second messengers. In Fig. 4.10, an increase of cAMP is shown which results in an activation of protein kinase A and/or C (PKA, PKC). Protein kinases are enzymes that can phosphorylate channel proteins. Phosphorylation means that phosphate residues are coupled to the protein molecules of the channels. This makes the ion channels better permeable to Na^+ and Ca^{++} and it also increases the sensitivity of the receptors to glutamate. The phosphorylation takes just a few minutes to develop and it represents an almost immediate and short-lasting increase in synaptic effectivity (Liu and Sandkühler 1998; Millan 1999; Usunoff et al. 2006). The phosphorylation of ion channel proteins is the second step of the central sensitization.

Over time, if the pathologic nociceptive input persists, a long-lasting change will occur, namely a change in gene expression. This can lead to the de novo synthesis of channel proteins (NMDA and non-NMDA channels). Collectively, the sensitizing processes result in a postsynaptic neuron that has a higher density of transmitter receptors in its membrane and possesses ion channels with a higher permeability. Therefore, it reacts more strongly to all discharges arriving at the synapses on its

surface. The neuron has become hyperexcitable. The changes in gene expression and the resulting structural alterations are the third step in central sensitization. The increased ion channel density and permeability lead to the transition from an ineffective connection to a persistent synaptic connection with consistent and effective signal transmission.

As shown above, a nociceptive dorsal horn neuron has two basic ways of functioning. Normally (1), it is activated by a short-lasting painful stimulus, most often an acute trauma. The resulting activity has a relatively high discharge frequency but a short duration, it will lead to transient pain but not to long-lasting changes in neuronal responsiveness. Under pathological circumstances (2), when there is a persistent lesion in the periphery, the long-lasting nociceptive input increases the excitability of the central neuron by opening NMDA channels and changes in gene expression. These changes need time to reverse. Figure 4.11 depicts some of the electrical events in a postsynaptic neuron. During activation under normal circumstances, the neurotransmitter glutamate opens the AMPA channels and Na^+ ions enter the cell (**b**). This results in a short-lasting EPSP that brings the negative membrane potential closer to the firing threshold (**c**, *dashed thick line*). After a few ms, the EPSP is over and the membrane potential is back to the initial level of about −65 mV. In the presence of a continuous input from a chronic peripheral lesion, the EPSPs occur more frequently and the cell is persistently depolarized. Now the membrane potential is close to the firing threshold all the time and small additional depolarizations are sufficient to make the cell fire (stimulus *S* in **c**). The cell is hyperexcitable. Panel **d** shows a novel therapeutic effect of the hyperexcitability, namely drugs that open K^+ channels (specific neuronal potassium channel openers (Peretz et al. 2005)). Opening of potassium channels leads to an outward K^+ flux, because the potassium concentration inside a neuron is higher than in the synaptic space. This ion flux removes positive charges from the inside, induces a negative potential change similar to an inhibitory postsynaptic potential (IPSP), and ideally brings the depolarized membrane potential back to the normal negative value (**e**). The excitability-decreasing action of potassium channel-opening drugs has also been used in the treatment of epilepsy. An alternative approach would be to open chloride channels. This leads to an influx of Cl^- ions, because the chloride concentration is higher outside the cell, and likewise shifts the membrane potential towards more negative values.

The above model of central sensitization is similar to data obtained from hippocampal neurons in studies of learning processes. The process of increasing neuronal excitability by a relatively short-lasting input is called long-term potentiation (LTP). The name is derived from the experimental finding that, after a short-lasting high-frequency input to the hippocampal network, a single electrical stimulus leads to much larger synaptic potentials than it did before the high-frequency stimulation. At present, it is difficult to say how strong the parallels between learning processes in the hippocampus and changes in dorsal horn excitability during chronic pain really are. Moreover, the LTP is just one out of many models of central sensitization.

However, the statement appears justified that the transition from acute to chronic pain in patients resembles an (unwanted) learning process at the spinal

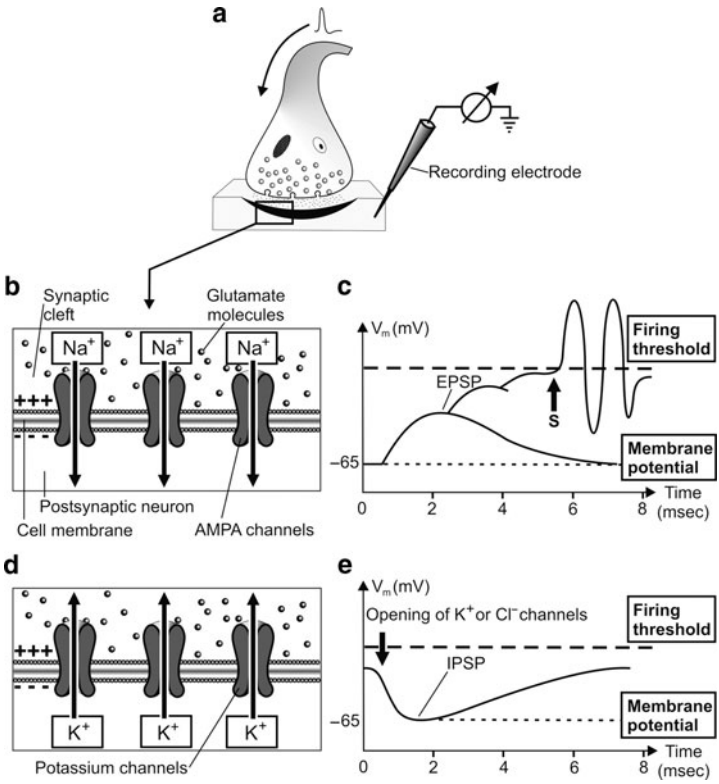

Fig. 4.11 Persistent depolarization in a spinal dorsal horn neuron. **a** Overview of a synapse with a presynaptic terminal, synaptic cleft, and a recording electrode in the postsynaptic neuron. Part of the synaptic cleft and the cell membrane of the postsynaptic neuron is shown at higher magnification in **b** and **d**. When action potentials arrive at the presynaptic terminal, glutamate opens the AMPA channels and Na^+ ions enter the cell (**b**). This results in a transient depolarization (excitatory postsynaptic potential, EPSP) that brings the negative membrane potential (V_m) closer to the firing threshold (*dashed thick line* in **c**). Normally, the EPSP is over within several ms, and the membrane potential has returned to the initial level of about −65 mV. **c** A continuous input from a chronic peripheral lesion leads to a summation of the EPSPs, and the cell is persistently depolarized. The membrane potential is close to the firing threshold all the time, and small additional depolarizations are sufficient to make the cell fire (stimulus S in c). The cell is hyperexcitable. **d** A novel therapeutic approach is to treat the hyperexcitability by opening K^+ channels with specific neuronal potassium channel openers. The opening of potassium channels leads to an outward K^+ flux, which removes positive charges from the inside, and thus renders the intracellular V_m more negative. Usually, such a potential change is elicited by inhibitory transmitters that elicit an inhibitory postsynaptic potential (IPSP). Ideally, the outflow of K^+ brings the depolarized membrane potential back to the normal negative value (**e**)

and higher levels. In the treatment of muscle pain, the nociceptive input from muscle should be abolished as early as possible, not only to relieve the patient's pain but also to prevent the development of chronic neuroplastic changes in the central nervous system.

In patients central sensitization may be an important factor for postoperative pain, part of which appears to be due to a central change following the noxious input that is inevitably associated with surgical interventions. Local anesthesia of the operation site (in addition to general anesthesia) has been suggested long ago as a possible means of preventing the intraoperative central sensitization (Wall 1988). Therefore an effective treatment of acute muscle pain does not only abolish the pain and restores normal function but also prevents the central sensitization. It is conceivable that — if the treatment fails — the prolonged and repeated input from muscle nociceptors triggers events in the CNS that eventually lead to a chronic pain condition.

Usually, two clinical sequelae of central sensitization are distinguished, namely primary and secondary hyperalgesia. The term primary hyperalgesia describes increased pain and allodynia in the region of a peripheral lesion, and can be explained by increased excitability of damaged nociceptors and dorsal horn neurons supplying the region of the lesion. Secondary hyperalgesia is present if, in addition, low-intensity stimulation of body regions surrounding the lesion elicits pain. In these regions the tissue and receptors are completely intact. The secondary hyperalgesia can be explained by assuming that hyperexcitable nociceptive dorsal horn neurons (1) have acquired effective input from regions they do not normally supply, and (2) respond to innocuous input.

4.5.4 Sequelae of Central Sensitization

4.5.4.1 Increased Resting Activity of Dorsal Horn Neurons

The increased resting activity found in peripheral muscle nociceptors after induction of an experimental myositis (cf. Fig. 3.21) occurred also in dorsal horn neurons. Again, the neurons had very little resting activity in rats with intact GS muscle, whereas in chronic myositis animals there was an increase both in the proportion of active neurons (Fig. 4.12a) and discharge rate (Fig. 4.12b). At the dorsal horn level there was an amplification of the discharge activity because the mean discharge rate of peripheral group IV receptors was approximately 1 Hz (cf. Fig. 3.21), whereas dorsal horn neurons in chronic myositis animals had a mean discharge rate of about 3 Hz (approximately 180 impulses/min; right bar in Fig. 4.12b). Possible explanations for this amplification are 1. central sensitization and 2. convergence in the dorsal horn, i.e., one single neuron received synapses from many nociceptors of the GS muscle.

An interesting feature of the resting activity of dorsal horn neurons was that many neurons exhibited very short intervals between their action potentials (2–3 ms; see right insert in Fig. 4.12). These short intervals are particularly effective for synaptic transmission, because the EPSPs elicited by them in neurons of higher centers are likely to superimpose and reach firing threshold. An EPSP usually lasts

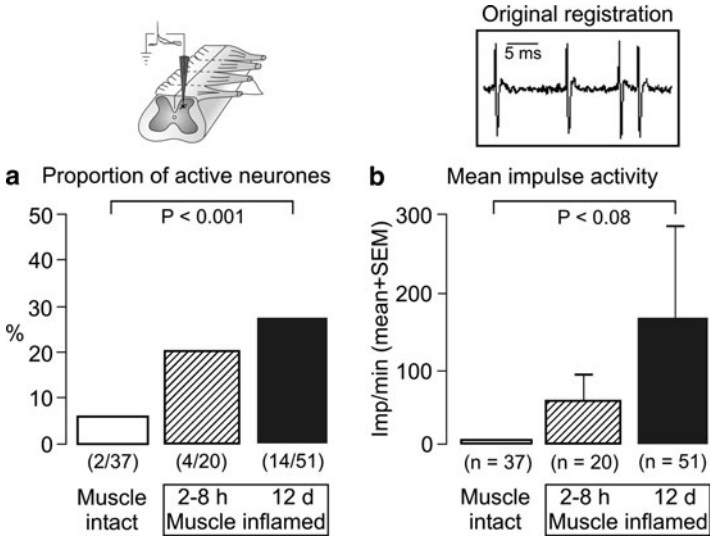

Fig. 4.12 Resting activity of dorsal horn neurons during an experimental muscle inflammation. The data were obtained in microelectrode recordings from dorsal horn neurons in rats (*left inset*). Both the proportion of active neurons (**a**) and the mean impulse activity (**b**) increased in myositis rats. The resting activity of dorsal horn neurons in chronic myositis animals was approximately 3 Hz (**b**). Many neurons in myositis animals exhibited very short intervals between their action potentials (2–3 ms; *right inset*). These short intervals are particularly effective for synaptic transmission

5–10 ms; therefore, the EPSP evoked by the second action potential starts when the first EPSP starts to rise.

4.5.4.2 Appearance of New Receptive Fields

An example of a neuroplastic change in a neuron following noxious stimulation of skeletal muscle is shown in Fig. 4.13 (Hoheisel et al. 1993). At the beginning of the recording the neuron had a single HTM receptive fields (RF) in the proximal biceps femoris muscle (black area), i.e., the neuron required noxious pressure (Nox. p. deep) of this area for activation (Fig. 4.13a). An injection of a painful dose of bradykinin (BK) into the tibialis anterior (TA) muscle led to the appearance of two new high-threshold RFs, one in the TA at the injection site and a second one in the deep tissues of the dorsum of the paw (Fig. 4.13b, hatched areas). Fifteen minutes after BK injection the new RFs were still present and now the initially high-threshold RF in the biceps femoris muscle had a low mechanical threshold (stippled). The appearance of the new RF in the TA is probably due to the opening of ineffective synaptic connections between the TA and the recorded neuron. The new RF in the deep dorsum of the paw cannot be attributed to a peripheral effect – rather

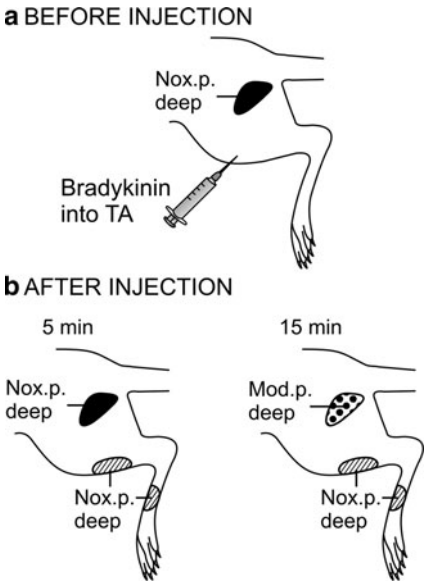

Fig. 4.13 Appearance of new receptive fields after a noxious stimulus. Data from dorsal horn recordings. At the beginning of the recording (**a**), the neuron had only a high-threshold mechanosensitive receptive field (RF) in the biceps femoris muscle (*black area*), i.e., the neuron responded only to deep noxious pressure stimulation (*Nox. p. deep*) of this area. An injection of a painful dose of bradykinin into the tibialis ant (*TA*) muscle was followed by the appearance of two new high-threshold RFs, one in the TA at the injection site and a second one in the deep tissues of the dorsum of the paw (*hatched areas* in **b**). Fifteen min after bradykinin injection, the new RFs were still present, and now the initially high-threshold RF in the biceps femoris muscle had a low mechanical threshold (*stippled*). The appearance of the new RF in the TA is probably due to the opening of formerly ineffective synaptic connections between the TA and the recorded neuron

the opening of silent connections due to sensitization of the dorsal horn neuron is the most likely explanation. The new RFs persisted for more than 15 min, i.e., much longer than the input elicited by the BK injection which lasts for a few minutes at most (Mense and Meyer 1988).

The lowering in threshold of the RF in the biceps femoris muscle can likewise be explained by central sensitization. The neuron that originally responded exclusively to input from nociceptive fibers was now driven by non-nociceptive afferents. This finding demonstrates that, following sensitization, nociceptive central cells may respond to input from sensitive mechanoreceptors. The possible neuroanatomical basis for this effect is given in Fig. 4.14). The neuron recorded from (Fig. 4.14a) had synapses from nociceptive and non-nociceptive peripheral receptors on its surface. The nociceptive synapses of afferents from the biceps femoris muscle (muscle A) were effective and excited the neuron. The nociceptive synapses from the TA muscle (muscle B) and the deep tissues of the dorsum of the paw were initially ineffective. Following sensitization of the neuron by the BK-induced nociceptive input, the neuron was hyperexcitable and responded to the formerly ineffective

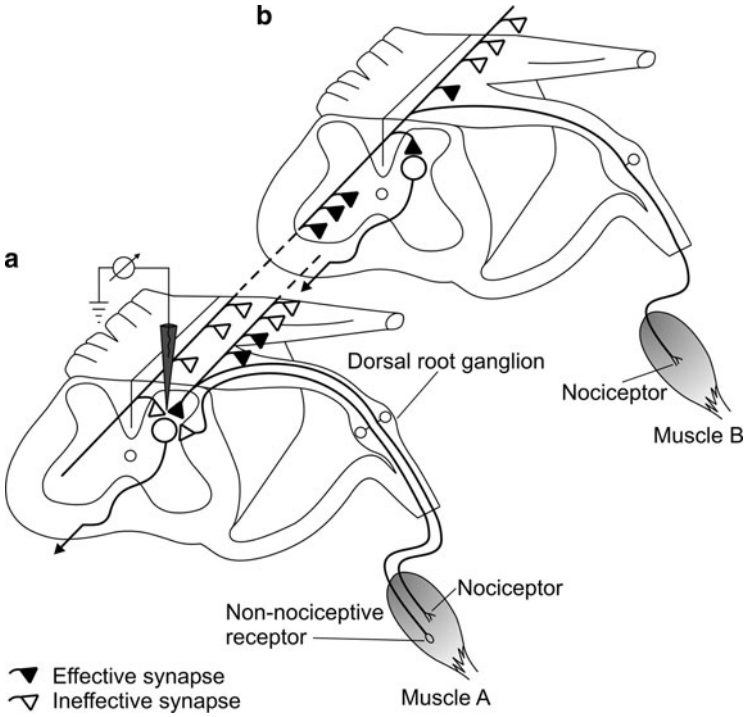

Fig. 4.14 Possible explanation for the acute opening of ineffective synapses. The figure is supposed to explain the bradykinin effect shown in Fig. 4.13. The basic arrangement of the synapses is that nociceptive afferent fibers have effective contacts (*filled triangles*) with neurons in 2–3 segments of the spinal cord and many more ineffective synapses with neurons in adjacent segments (*open triangles*). The neuron recorded in Fig. 4.13 had effective synapses with nociceptive afferents from the biceps femoris (muscle A) which excited the neuron. The nociceptive synapses from the TA muscle (muscle B) and the deep tissues of the paw (not shown) were initially ineffective. Further ineffective synapses originated from non-nociceptive synapses in the biceps muscle (muscle A). Following sensitization of the neuron by the bradykinin-induced nociceptive input from muscle B, the neuron was hyperexcitable and responded to the formerly ineffective input from the nociceptors in muscle B and the deep tissues of the paw. The ineffective synapses with the nonnociceptive mechanoreceptors in muscle A were likewise opened. This latter change caused the drop in the mechanical threshold of the RF in the biceps femoris muscle

input. This means that the ineffective synapses of the nociceptive afferents from the TA and paw were opened by an input via the nociceptive synapses from the biceps femoris muscle. This mechanism is called "heterosynaptic potentiation" or facilitation by some. Using the same terminology, the mechanism shown in Figs. 4.9 and 4.10 is a "homosynaptic potentiation," because the potentiation is due to an activation of the same synapse that was excited by the sensitizing input. The lowering of the mechanical threshold of the RF in the biceps muscle 15 min after BK injection is probably due to the opening of the formerly ineffective synapses with non-nociceptive afferents in that muscle (muscle A).

How does a patient feel these changes? An example would be a trigger point in the TA muscle that sends nociceptive information to the spinal cord. The input sensitizes neurons that process nociceptive information from the biceps muscle. The neurons lower their threshold in the innocuous range, which the patient probably feels as tenderness in that muscle. Thus, the described changes could be the basis for referred tenderness from the TA to the biceps femoris muscle.

4.5.4.3 Lesion-Induced Changes in the Wiring of the Dorsal Horn

Of course, under pathological circumstances the changes in neuronal responsiveness described in the preceding section do not occur in just a few neurons but in an entire population of cells that have synaptic connections with the site of a painful lesion. Eventually, several segments of the spinal cord will be affected. These changes can be best studied in animal models of pathological lesions that are associated with a tonic or chronic nociceptive input to the spinal cord. One of these models is a muscle inflammation.

A few hours after induction of a myositis in the GS muscle of rats, the number of neurons responding to a standard electrical stimulus applied to the muscle nerve was significantly increased (Hoheisel et al. 1994a; Fig. 4.15). The effect was not restricted to the normal target segments of the GS muscle nerve (L4 and L5) but extended also to the segments L3 and L6. By target area we understand those regions in the spinal cord where dorsal horn neurons can be excited by input from the nerve. In the myositis animals, the input from the inflamed muscle excited neurons in segments that do not normally respond to GS muscle input. It is worth mentioning that a very low discharge frequency in unmyelinated muscle afferents was sufficient for inducing this myositis-induced reorganization of the spinal cord. (cf. Fig. 3.21).

As shown in Fig. 4.15, neurons in segment L6 (that supply the pelvis and proximal tail in the rat) and neurons in segment L3 (that process input from the innervation territory of the femoral nerve) responded to GS input in myositis rats. Thus, the target area of the GS nerves in the spinal cord had increased within a few hours. One possible explanation for the expansion of the myositis-induced excitation to adjacent segments is that ineffective synaptic connections between muscle afferents and neurons in these segments became more effective (Li and Zhuo 1998). Apparently, the GS muscle has effective connections with dorsal horn neurons in its main target segments L4 and L4 in the rat, and in addition ineffective connections with neurons in adjacent segments.

The lesion-induced expansion of the target area of peripheral input may be the basis for referral of muscle pain and the subjective sensation of the spread of pain. When, for instance, neurons in L6 are excited by input from the GS muscle they transmit the signal “painful stimulus in the pelvis” to higher centers. As soon as the neurons in L6 are excited (by pathological input from the GS, by normal input from the pelvis, or by local trauma in the spinal cord) a patient will feel pain in the pelvic area because higher order neurons cannot identify the origin of the nociceptive

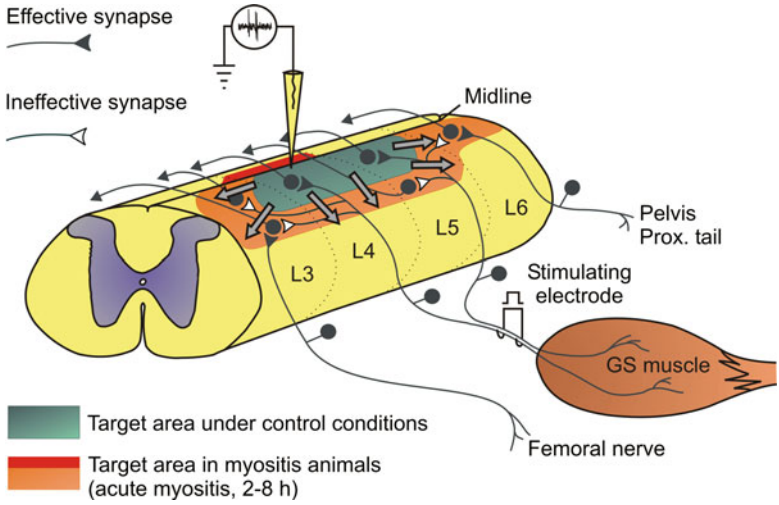

Fig. 4.15 Functional reorganization of the wiring in the spinal cord during a pathological muscle injury. A few hours after induction of a myositis in the GS muscle of rats, a systematic search for dorsal horn neurons responding to input from that muscle was made with microelectrode recordings (the spinal target area of the GS muscle afferents was determined). Before induction of the myositis, neurons responding to an electrical standard stimulus of the GS muscle nerves (stimulating electrode) were found only in the segments L5, L4 and parts of L3 (*green area*). Within a few hours of a muscle inflammation, the target area had expanded and included now the entire segment L3 and L6 (*red area*). Apparently, the long-lasting input from nociceptors in the inflamed GS muscle had sensitized the neurons in the segments L3 and L6, and had opened formerly ineffective synaptic connections with the muscle in those segments

input. Therefore, this lesion-induced expansion of the excitation in the spinal cord may well be the mechanism behind the referral of muscle pain, in this case from the GS muscle to the pelvic area. The mechanisms of pain referral will be dealt with in more detail in Chap. 5.

In the myositis experiments the muscle itself was not stimulated, because the nociceptors in the inflamed muscle were most probably sensitized (see Chap. 3). When the muscle itself is stimulated, an increased response of the dorsal horn neurons can be due to peripheral or central sensitization. The electrical stimulation of the muscle nerve circumvents the sensitized muscle nociceptors. An increased responsiveness of central neurons has the same sequelae as a sensitization of peripheral nociceptors, namely allodynia and hyperalgesia of muscle pain in patients.

Figure 4.15 includes the appearance of new RFs, as shown in Fig. 4.13: in intact animals, the neuron in the segment L6 (Fig. 4.15) has effective synapses (only one is shown) with the pelvic area and ineffective synapses with the GS muscle. After induction of an acute myositis in the GS, the ineffective synapses of the L6 neuron with the GS muscle are opened. In an experiment in which the neuron's discharges are recorded it would initially respond only to stimulation of the pelvic area, because it has effective synaptic connections with that area. After induction of

the myositis it would exhibit a new RF in the GS muscle in addition to the old one in the pelvis.

The general concept emerging from the above data is that each body region has a target area in the spinal cord or brainstem where the effective synaptic connections of that area are situated. Around this target area is a sort of "halo" that contains ineffective (silent) synapses from other body regions. Under pathologic conditions the ineffective synapses can be opened and thus new connections are formed in the CNS. There is evidence from animal experiments showing that the number of silent synapses in the CNS is higher than those of effective (open) ones (Mokin et al. 2007).

When the central nervous sensitization has become chronic it is largely independent of further input from the damaged muscle. In their model of acid-induced muscle hyperalgesia Sluka et al. (2001) have shown that an interruption of the muscle input by local anesthesia or dorsal rhizotomy 24 h after induction of the sensitization did not abolish the hyperalgesia. This finding clearly shows the importance of an early and effective therapy in patients with muscle pain. If the therapy is delayed or ineffective, the transition to a chronic pain state is likely to occur.

Data obtained in several animal models of chronic lesions of subcutaneous tissues, e.g., chronic polyarthritic rats (Calvino et al. 1986) or rats with a subacute inflammation of the hindpaw (Hylden et al. 1989) all point in the same direction, namely that an inflammation of deep tissues induces an enhanced excitability in dorsal horn neurons which is reflected in increased background discharge, enlarged and/or additional RFs, enhanced responsiveness to mechanical stimuli, and increased convergence from peripheral sources (e.g., skin and deep tissues). All these changes are indications of central sensitization, i.e., the neurons have become more excitable because of the sustained nociceptive input from deep tissues.

The lesion-induced enhanced excitability of central nociceptive neurons appears to be associated with an increased expression of the messenger ribonucleic acid (mRNA) of the immediate early gene (IEG) c-fos in the nuclei of the neurons. This process indicates a change in gene expression of the postsynaptic neurons; c-fos in turn controls the expression of the preprodynorphin mRNA (Draisci and Iadarola 1989). The increased expression of IEGs is one of the cellular reactions to noxious stimuli. Whether the reaction is a specific effect of noxious input or whether it also occurs in response to innocuous stimulation is still a matter of discussion. However, a noxious input appears to be the most effective way of increasing the expression of c-fos (Coggeshall 2005). The IEG c-fos controls the synthesis of a protein (c-FOS protein) that acts as a transcription factor. The protein influences the synthesis of cellular proteins and is thus capable of changing the functional properties of the cell (Dragunow et al. 1989).

The increased resting activity in nociceptive dorsal horn cells may cause the spontaneous pain that is present in many arthritis and myositis patients. If increased resting activity occurs in non-nociceptive cells it may evoke dysesthesias. The tenderness of an inflamed tissue is due not only to a sensitization of peripheral nociceptors but also to a sensitization of dorsal horn neurons. Tenderness and/or

hyperalgesia can be explained not only by a general enhancement of excitability but also by an enlargement of the RFs. A larger mean size of the RFs is likely to lead to a greater overlap between RFs and thus to an increase in the number of neurons that are excited by a given noxious stimulus.

4.5.5 Neuromodulatory Substances Involved in Myositis-Induced Rewiring of Spinal Connections

The opening of ineffective synapses is generally assumed to be due to the release of neuromodulatory substances from presynaptic terminals. Normally, the terminals release the neurotransmitter glutamate as the main transmitter for nociceptive information, but under pathological circumstances the terminals or the postsynaptic cells can release additional agents. Neuromodulatory substances include all neuropeptides and other agents that interfere with the effects of neurotransmitters and change the excitability and responsiveness of central neurons. In the following sections, two of these modulators are presented in more detail, namely SP and nitric oxide (NO).

4.5.5.1 Substance P

As pointed out above, SP may be involved in the induction of central sensitization by causing long-lasting depolarization predominantly in nociceptive central nervous cells. Its main action is to contribute to the activation of the intracellular second messengers such as cAMP (cf. Fig. 4.10; for a review, see Millan 1999).

The combined effect of SP acting on NK1 receptors and glutamate acting on NMDA-channels has been proposed as a possible mechanism for the sensitization of STT cells, which may underlie the development of hyperalgesia in patients (Dougherty and Willis 1991).

The activation of NMDA and NK1 receptors also appears to contribute to the myositis-induced sensitization of dorsal horn neurons. Evidence supporting this assumption was obtained in rat experiments, in which intrathecal administration of antagonists to NK1 and NMDA receptors prevented the expansion of the spinal excitation to the segment L3 in animals with a myositis of the GS muscle (Hoheisel et al. 1997). A block of the AMPA receptors had no significant influence on the expansion. This result is in accordance with the general view that AMPA channels are more important for spinal transmission under normal circumstances whereas NMDA channels are responsible for central sensitization under pathological conditions. With regard to the importance of AMPA channels for central sensitization, a difference between muscle- and joint-induced hyperalgesia may exist, because joint hyperalgesia has been reported to be reduced by administration of an AMPA receptor antagonist (Sluka et al. 1994).

4.5.5.2 Nitric Oxide

Chronic allodynia and hyperalgesia represent enhanced responses to stimulation which are largely due to an activation of the NMDA channel. Allodynia and hyperalgesia can occur with or without spontaneous pain. The mechanisms underlying hyperalgesia on the one hand and spontaneous pain on the other appear to be distinct.

In electrophysiological experiments on animals the most likely correlate of spontaneous pain is the resting activity of central nociceptive neurons, i.e., impulse activity in the absence of intentional stimulation. Normally, nociceptive neurons have no or only little resting activity, but in the presence of a longer-lasting peripheral lesion they become active. The increase in resting activity does not appear to be due to activation of NMDA channels but rather to a change in the release of NO (Hoheisel et al. 2000). NO is a small gaseous molecule and — in contrast to other neurotransmitters and neuropeptides — diffuses through all cell membranes. Therefore, its action is not restricted to the neuron where it has been synthesized. NO diffuses out of the cell and influences all neurons in a certain volume of central nervous tissue including neighboring neurons and terminals from afferent fibers (Fig. 4.16). Several lines of evidence have shown that both NO and cyclic guanosine monophosphate (cGMP, a second messenger) are involved in nociceptive processing (Meller and Gebhart 1993; Duarte and Ferreira 2000; Tegeder et al. 2002).

In the CNS, NO is synthesized in neurons that contain the enzyme nitric oxide synthase (NOS). NOS can be activated by Ca^{++} ions that enter the postsynaptic cell through the NMDA channel. NO activates the soluble form of the guanylyl cyclase and thus increases the synthesis of cyclic guanosine monophosphate (cGMP, Knowles et al. 1989; Fig. 4.16). Blocking the spinal NOS with intrathecal (i.t.) L-NAME in animal experiments led to a significant increase in background activity only in nociceptive neurons (Hoheisel et al. 2000). This finding indicated that NO is released tonically in the dorsal horn and inhibits the background discharge of the neurons. In contrast to the increased background activity induced by L-NAME the mechanical responsiveness of the neurones was decreased by i.t. L-NAME. This is yet another example of the frequent finding that the resting activity and mechanical excitability, respectively, of nociceptive dorsal horn neurons can change independently.

Normally, enough NO appears to be released in the spinal cord or brainstem to prevent resting activity in nociceptive neurons. However, in the presence of nociceptive input from a peripheral lesion, the release of NO is reduced, and this leads to resting activity in dorsal horn neurons and to spontaneous pain in patients. Simultaneously the reduced NO release should prevent hyperalgesia, because an experimental reduction of the NO level led to a decreased mechanical responsiveness. However, the allodynia- and hyperalgesia-promoting influence of an activation of NMDA channels and NK1 receptors appears to be stronger than the action of NO in this respect. Therefore, spontaneous pain is often accompanied by stimulation dependent allodynia and/or hyperalgesia.

In the spinal cord of animals with an acute myositis (10 h duration) the number of cells with NOS immunoreactivity (cells that could be visualized with antibodies

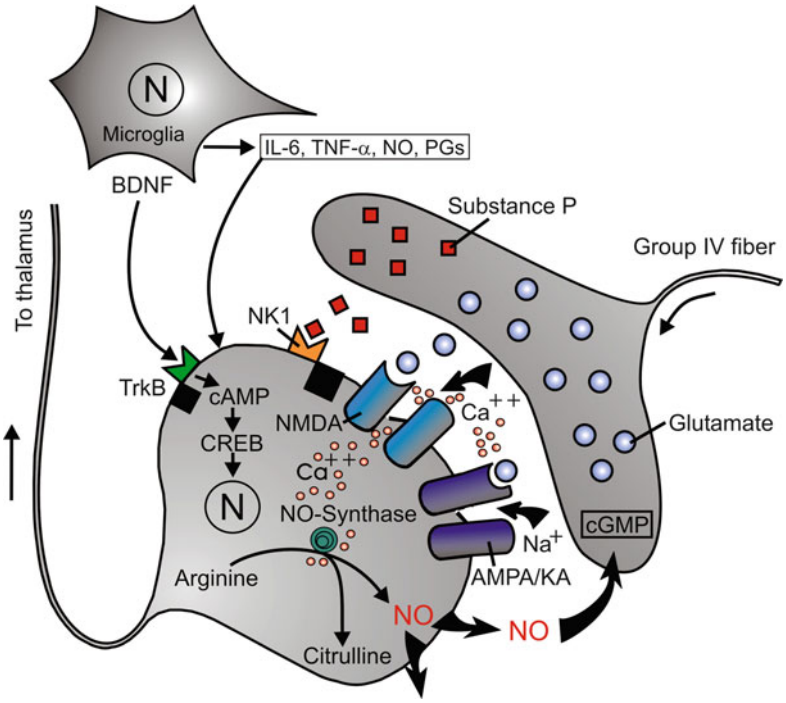

Fig. 4.16 Nitric oxide (*NO*) as a sensitizing agent. Normally, nociceptive neurons have no or only little resting activity, but they become active when there is a longer-lasting injury in the body periphery. The increase in resting activity appears to be due to an enhanced release of NO. NO is synthesized from arginine in neurons that contain the enzyme nitric oxide synthase (NOS). NOS can be activated by Ca^{++} ions that enter the postsynaptic cell through the NMDA channel. NO diffuses out of the cell and influences all neurons and glial cells in a volume of central nervous tissue around the cell. Its main action is to increase the synthesis of cyclic guanosine monophosphate (cGMP (cyclic guanosine monophospate), a second messenger; cf. Fig. 4.17). The increase in cGMP in neurons and glial cells sensitizes the cells. The sensitization is expressed mainly in higher resting activity, which is assumed to be responsible for spontaneous pain in patients

to the enzyme that synthesizes NO) was significantly increased. However, after a chronic myositis (12 days duration) the cell number was decreased. Apparently the afferent input from a chronically inflamed muscle reduces the NOS activity in dorsal horn cells. The NO-synthesizing neurons behave like a sensor for peripheral lesions and signal a chronic painful lesion by a decrease in NOS activity. As a lack of NO in the spinal cord has been shown to increase the resting activity in nociceptive dorsal horn neurons (see above and Hoheisel et al. 2000) the reduction in the number of NO-synthesizing neurons may be responsible for the spontaneous muscle pain or dysesthesia in patients.

The role of NO in nociception and pain is controversial in the literature with some groups regarding it as a pronociceptive (pain-promoting) and some as an antinociceptive (pain-inhibiting) agent. Recent data from animal experiments may

resolve at least some of the discrepancies in the literature. The data show that NO and cGMP (cGMP is a second messenger that needs NO for synthesis, Fig. 4.17a) have different actions at the spinal and supraspinal level. When substances that decrease the NO and cGMP levels (e.g., L-NAME) are administered at the spinal level (i.t.), the resulting lack of NO was found to be pronociceptive in that it increased the activity of nociceptive neurons. This means that at the spinal level both NO and cGMP are needed to prevent spontaneous activity in nociceptive neurons. When applied supraspinally (by injection into the third cerebral ventricle), the blocker

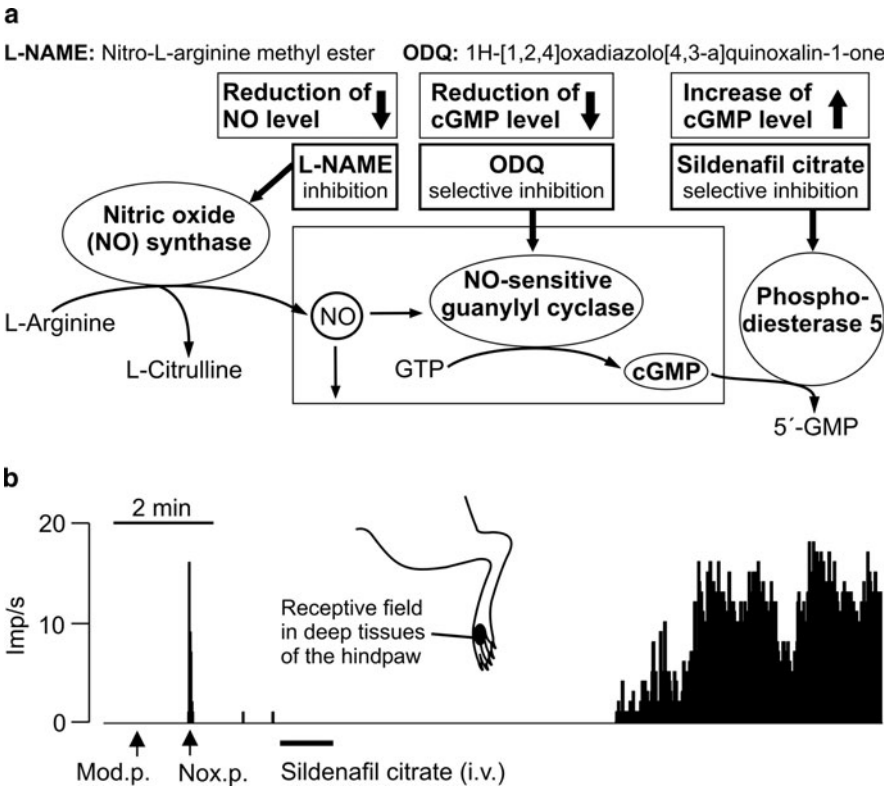

Fig. 4.17 Synthesis of cGMP and neuronal effects of increased spinal cGMP. **a** Synthesis pathway of cGMP. NO is required to activate the NO-sensitive guanylyl cyclase that produces cGMP from guanosine triphosphate (GTP). cGMP is degraded by the enzyme phosphodiesterase 5 to 5′-guanosine monophosphate (5′-GMP). L-NAME blocks the NOS and thus decreases the NO level; ODQ inhibits the NO-sensitive guanylyl cyclase and decreases the cGMP level. Sildenafil citrate is a selective blocker of phosphodiesterase 5, and therefore increases the cGMP level. **b** Recording from a single nociceptive dorsal horn neuron in the rat that required noxious mechanical stimulation (*Nox. p.*) of the deep tissues of the dorsum of the paw for excitation. Intravenous injection of sildenafil citrate excited the nociceptive dorsal horn neuron after a delay of approximately 10 min. A possible explanation for this excitatory action of sildenafil is that it crossed the blood–brain barrier and increased the cGMP level in supraspinal centers. Here cGMP activated descending pain-facilitating tracts and excited nociceptive dorsal horn neurons

L-NAME had no action on nociceptive dorsal horn neurons (Hoheisel et al. 2005a). However, intracerebroventricular injection of 8-Bromo-cGMP (a membrane permeable form of cGMP) had an excitatory action on dorsal horn neurons showing that an increase in cGMP at the supraspinal level was pronociceptive.

Collectively, the data indicate that at the spinal level a *lack* of NO and cGMP is pronociceptive, whereas at the supraspinal level, an *increase* of NO and cGMP has such an action. When blockers of the enzyme phosphodiesterase 5 that degrades cGMP (such as sildenafil; Goldstein et al. 1998) are administered i.v. or i.m., the supraspinal action prevails and the increased cGMP level in the supraspinal centers excites the nociceptive dorsal horn neurons (Fig. 4.17b). Because of the capacity of sildenafil to cross the blood–brain barrier (Milman and Arnold 2002), the excitatory effects of systemic sildenafil on spinal neurones were probably due to an action on supraspinal centres. Therefore, the excitatory action of systemic sildenafil on nociceptive dorsal horn neurons is probably due to the activation of descending pain-facilitating tracts that originate at supraspinal levels (see below).

A peripheral site of action for the sildenafil-induced excitation is unlikely, because the peripheral action of sildenafil appears to be antinociceptive rather than pronociceptive (Jain et al. 2001).

Other explanations for the seeming discrepancy in the published literature are that NO has different actions on neurons in different locations of the spinal gray matter (Pehl and Schmidt 1997), that it sensitizes nociceptive neurons to external stimuli (Lin et al. 1999), or that low doses of NO reduce, and high doses increase, allodynia and hyperalgesia in animal experiments (Sousa and Prado 2001).

Data from clinical trials show that following oral treatment of erectile dysfunction with sildenafil — which increases cGMP levels throughout the body — some patients and healthy subjects develop headache (Kruuse et al. 2002) and spontaneous muscle pain mainly in the lower back (Olsson et al. 2000; Lim et al. 2002). The fact that sildenafil has no influence on cerebral hemodynamics but causes headache (Kruuse et al. 2002) indicates that nonvascular mechanisms are involved in the sildenafil-induced pain, e.g., sildenafil may influence nociceptive processing via the NO-cGMP pathway by increasing spinal or supraspinal levels of cGMP and exciting nociceptive spinal neurons. Headache and low back pain appear to be an unwanted but frequent side-effect of the sildenafil treatment.

4.6 Neuroplasticity as a Basic Principle in Central Sensitization

Neuroplastic excitability changes of central neurons following a high-frequency input have been studied mainly in the hippocampus where LTP is a common observation. LTP represents a neuroplastic change that is characterized by a long-lasting increase in neuronal excitability following a short-lasting high-frequency input. LTP is considered an important component of learning processes. The data presented in the previous sections show that at the spinal level neuroplastic changes occur which resemble LTP in many ways.

When noxious stimuli are applied repeatedly in animal experiments a frequent finding is that nociceptive neurons do not only respond to the stimulus but also increase their sensitivity during repeated stimulation. This process, called wind-up or temporal summation, is assumed to be an integral mechanism of neuronal function and depends on the activation of central NMDA receptors (Eide 2000). In patients this mechanism can lead to an increase in subjective pain when the peripheral lesion is unchanged or even improving objectively.

In dorsal horn neurons neuroplastic changes require input via unmyelinated or thin myelinated afferent fibers, i.e., afferent activity in thick myelinated fibers is not sufficient. For unknown reasons input via *muscle* C-fibers is more effective than cutaneous input in inducing prolonged changes in neuronal behavior (Wall and Woolf 1984). The excitability changes of the neuron shown in Fig. 4.13 are a rather acute example of plastic behavior. One possible interpretation of the data is that the dorsal horn neurons possess synaptic connections which are ineffective under normal circumstances ("unmasking" of central synapses, cf. Wall 1977). Comparable effects have been observed in neurons of the subnucleus caudalis and oralis of the trigeminal spinal tract nucleus, i.e., in those nuclei where afferent fibers from the head region terminate (Hu et al. 1992). SP [probably together with calcitonin gene-related peptide (CGRP; Hoheisel et al. 1994b)] is surely one of the factors that are capable of unmasking neuronal connections in the dorsal horn.

4.7 Central Sensitization Induced by Subthreshold Synaptic Potentials in Dorsal Horn Neurons

In the literature there are many studies on the sensitization of CNS neurones and most of these studies use high-frequency electrical stimulation (around 100 Hz) to induce long-term potentiation (LTP), that is, a long-lasting increase in neuronal excitability after a single bout of stimulation. Low-frequency stimulation (LFS), on the other hand, has been reported to induce mainly long-term depression (LTD) or depotentiation, that is, a long-lasting decrease in excitability (Froc and Racine 2005; Ikeda et al. 2006). Recently, the sensitizing action of LFS has attracted a lot of interest. In rat slices of the hippocampus in vitro, LFS at 1 Hz was found to induce a novel form of LTP characterized by slow onset and independence from activation of NMDA receptors (Lante et al. 2006). In superficial dorsal horn neurons in vitro, LFS of afferent C fibers likewise has been reported to induce LTP (Ikeda et al. 2006). In these cells Ca^{++} is mobilized from intracellular stores during low-level presynaptic activation which then could lead to a sensitization.

LFS reflects the pathophysiologic situation much better than high-frequency stimulation, because – particularly in chronic muscle pain conditions – the afferent input does not reach high frequencies (in inflamed muscle approximately 1 Hz, cf. Fig. 3.21). However, this low-frequency input has an enormous influence on the excitability of dorsal horn neurons.

Recent findings of our group show that even *subthreshold* synaptic potentials in dorsal horn neurons are sufficient to cause sensitization of dorsal horn neurons. A convenient method for eliciting subthreshold potentials in the dorsal horn is the intramuscular injection of nerve growth factor (NGF). NGF is primarily known as a neurotrophic substance that promotes the development of the nervous system, particularly nociceptive and sympathetic neurons. The neurotrophin is synthesized in skeletal muscle and has a strong sensitizing action on nociceptors in pathologically altered tissue (Pezet and McMahon 2006).

The action of NGF on nociception from muscle has been studied with injections into the masseter muscle in humans. The growth factor had peculiar properties in that it did not evoke any sensation during and immediately after the injection but induced muscle allodynia and hyperalgesia that lasted for more than 1 week (Svensson et al. 2003). At the time of the study it was unknown if the sensitization was due to peripheral or central processes. Although i.m. injection of NGF did not evoke immediate pain in humans, recent rat experiments showed that NGF injected into the GS muscle excited a large proportion of muscle nociceptors (Fig. 4.18; Hoheisel et al. 2005b). Despite the excitation of a large proportion of muscle nociceptors rats did not exhibit any pain-related behavior during NGF injection into the GS muscle. One possible explanation for the lack of pain was that the NGF-induced input from muscle excited just a few dorsal horn neurons at a low frequency, or evoked mainly subthreshold synaptic potentials in these neurons. Subthreshold potentials are not transmitted to higher nociceptive centers and therefore do not elicit pain.

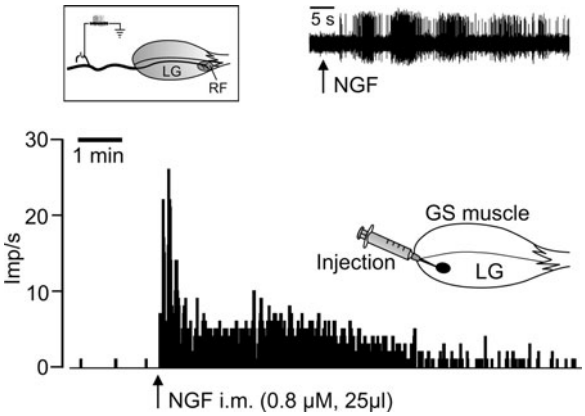

Fig. 4.18 Excitation of a muscle nociceptor by nerve growth factor (NGF). The receptor had a high mechanical stimulation threshold and was assumed to be a nociceptor. *Left inset*: set-up used for recording the discharges of the single group IV muscle afferent from the muscle nerve. *Right inset*: original registration of part of the fiber's response to NGF. The main figure shows the histogram of the activity shown in the *right inset*. The *upward arrow* marks the time of injection (concentration of the NGF solution was 0.8 μM). The *grey area* is the site from where the receptor could be excited by noxious pressure. *LG*, lateral head of the GS muscle

We tested this hypothesis by recording the reactions of dorsal horn neurons to NGF injections into the GS muscle. In these experiments, intracellular recordings were required, because only with this technique can subthreshold synaptic potentials be seen. As expected, NGF elicited mainly subthreshold synaptic potentials in dorsal horn neurons. Just a few neurons fired action potentials at a low frequency (Fig. 4.19; Graven-Nielsen et al. 2006; Hoheisel et al. 2007).

The NGF effects on rat dorsal horn neurons may explain why human subjects and experimental animals did not have subjective sensations when the growth factor was injected: the spinal activity was simply too low to excite higher nociceptive centers. The NGF-induced excitation was "stuck" in the dorsal horn. However, considering the long-lasting allodynia and hyperalgesia following intramuscular NGF injection in humans, the subthreshold potentials must have sensitized the

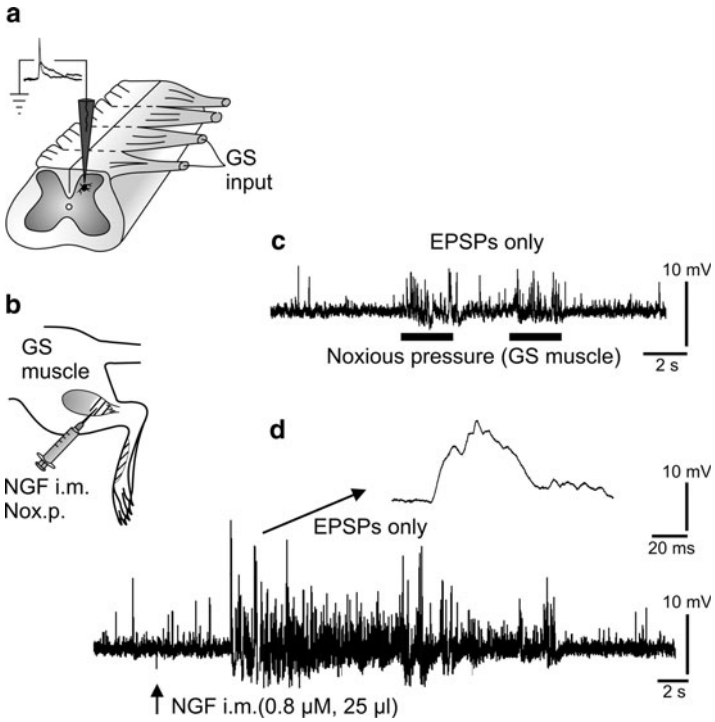

Fig. 4.19 Response of a single dorsal horn neuron to an NGF injection into the GS muscle. Intracellular recordings from dorsal horn neurons were made to visualize subthreshold synaptic potentials (excitatory postsynaptic potentials, EPSPs). **a** Set-up used for the recording. **b** Injection of NGF (same concentration as in Fig. 4.18) into the high-threshold receptive field of the neuron. In the neuron shown, NGF elicited only subthreshold synaptic potentials both to noxious pressure of the GS muscle (**c**) and to injection of NGF into that muscle (**d**). The *inset* in **d** shows one potential of the recording at a faster time base, to make sure that the potential was not an action potential but an EPSP (action potentials have a duration of 1–2 ms; the potential shown lasted approx. 60 ms and consisted of several superimposed EPSPs)

dorsal horn neurons. In fact, intracellular recordings from dorsal horn neurons already showed the first signs of sensitization a few minutes after NGF injection into the GS muscle. Neurons that had reacted to electrical stimulation of the GS muscle nerve with subthreshold potentials before NGF fired action potentials after NGF. In these experiments electrical stimulation of the GS nerve was used, therefore the possibly sensitized muscle nociceptors were not involved in increased responsiveness of the dorsal horn neurons. In recent studies on NGF-induced sensitization in rat and mouse, likewise an early allodynia/hyperalgesia has been reported (Malik-Hall et al. 2005; Hathway and Fitzgerald 2006).

In clinical muscle pain research, hypertonic saline (5%) is a well-established pain stimulus. It causes immediate pain of moderate intensity when injected intramuscularly (Capra and Ro 2004; Schmidt-Hansen et al. 2006). For rat group IV receptors from muscle, NaCl 5% is a strong stimulus, but it differs from NGF in that it excites not only nociceptors but also low-threshold mechanosensitive (presumably non-nociceptive) free nerve endings (Hoheisel et al. 2004). Thus, the pattern of afferent activity reaching the spinal cord after i.m. injection of NGF and hypertonic saline is different. In contrast to the intramuscular NGF injection — which elicited mainly subthreshold potentials in dorsal horn neurons — 5% saline evoked a high-frequency discharge of action potentials in a large proportion of dorsal horn neurons. This high-frequency discharge is probably transmitted to higher nociceptive centers and causes pain.

The findings presented so far may explain why the injection of NGF is not painful, whereas the injection of hypertonic saline is. The sensitizing action of NGF on dorsal horn neurons must be due to subthreshold synaptic potentials in dorsal horn neurons, because the main effects of NGF i.m. in dorsal horn neurons are subthreshold synaptic potentials (Hoheisel et al. 2007). The strong sensitizing action of NGF-induced subthreshold potentials at the spinal level indicates that for dorsal horn sensitization conscious sensations are not required.

As pointed out earlier, the action of NGF on muscle free nerve endings is unique in that it excites exclusively nociceptive units (Hoheisel et al. 2005b). Nociceptive afferent fibers from muscle and other tissues possess TTX-resistant (TTX-r) Na^+ channels (Akopian et al. 1999; Steffens et al. 2003). Fibers equipped with these channels appear to carry information to the spinal cord, which is particularly effective in sensitizing sensory neurons.

In behavioral experiments, in which mechanical stimulation of the GS muscle was used to study allodynic and hyperalgesic effects of i.m. injection of NGF, the neurotrophin had a clear sensitizing action (Fig. 4.20). In these experiments, the NGF-induced sensitization involved the activation of NMDA ion channels, because the simultaneous injection of NGF and ketamine — a noncompetitive antagonist of the NMDA receptor — into the GS prevented the NGF-induced allodynia and hyperalgesia to mechanical stimulation. In the experiment shown in Fig. 4.20 the muscle was tested with mechanical stimuli, therefore, sensitization of peripheral nociceptors by NGF had to be taken into account. However, recent recordings from single GS group IV-fibers showed that the sensitization of unmyelinated muscle afferents after NGF i.m. took 3–5 days to develop (V. John,

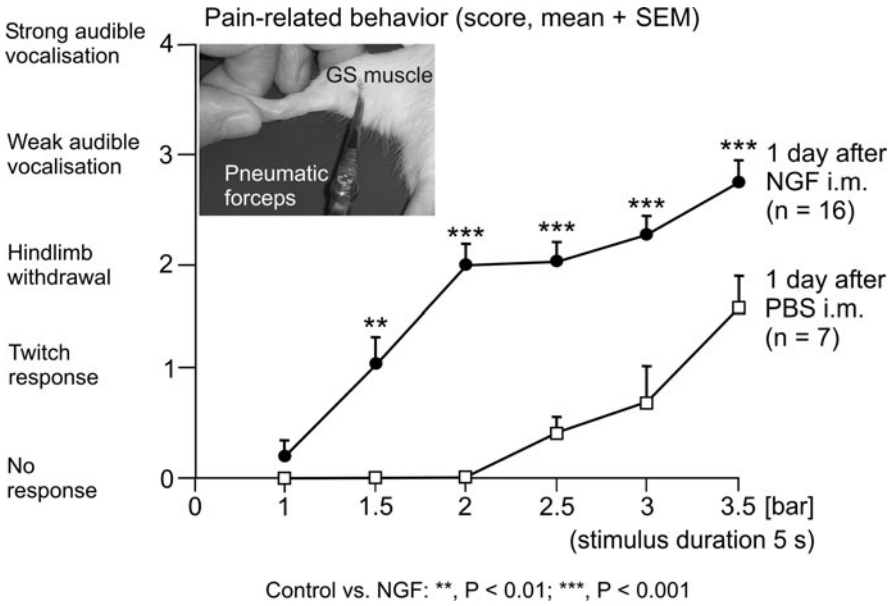

Fig. 4.20 Pain-related behavior of rats to pressure stimulation of the GS muscle before and 1 day after injection of NGF into the GS. The pressure stimuli were applied with a pneumatic forceps that could be closed at defined forces. The intensity of the pressure is given in the pressure unit "*bar*." The pain-related behavior of the animals was determined with a score from no response (0) to strong vocalization (4). In control rats that received an injection of vehicle [phosphate buffered saline (*PBS*), *open squares*], the pressure–pain threshold was 2 bars; in animals 1 day after NGF injection into the GS muscle (*filled circles*), it was less than 1 bar. After NGF, allodynia was present up to a stimulus intensity of 2 bar: a previously non-painful pressure induced a medium-level pain-related behavior. Above 2 bar, hyperalgesia occurred: here, previously weakly painful stimuli elicited relatively strong pain

U. Hoheisel, S. Mense, unpublished). Therefore, the NGF-induced allodynia and hyperalgesia observed in the behavioral experiments must have been due mainly to effects on central neurons (central sensitization).

The sensitizing action of low-frequency or even subthreshold input to the CNS — such as induced by NGF — may be of particular importance for the development of chronic muscle pain because painful conditions of muscle tissue are typically associated with low-frequency (as opposed to high-frequency) activation of nociceptors. The sensitizing action of subthreshold or low-frequency spinal activity offers an intriguing explanation for some chronic muscle pain syndromes such as work-related musculoskeletal disorders (Novak 2004; Sbriccoli et al. 2004). It is conceivable that persons who perform monotonic contractions with the same muscle or muscle compartment (e.g., musicians, assembly belt workers) acquire microtraumas in the overused muscle. The microtraumas may elicit subthreshold potentials or low-frequency discharges at the spinal level. Apparently, these potentials do not evoke subjective sensations in the beginning but sensitize central

neurons. If the work is continued, the central sensitization may develop into a chronic muscle pain syndrome. The danger of acquiring a work-related muscle disorder is particularly great if the work is performed under time pressure and psychic stress (Hughes et al. 2007). This may be due to the fact that under these circumstances the muscles or parts of a muscle are contracted involuntarily in an uncoordinated way and do not relax between contractions.

Such a mechanism fits well with the so-called Cinderella hypothesis. It states that during monotonous work at low force level, just a few — and always the same — type I motor units are activated, which have the lowest activation threshold and therefore are the first to be recruited and the last to be derecruited. These muscle fibers do most of the work and are likely to be overloaded (Kadefors et al. 1999; Hostens and Ramon 2005). If the nociceptors in the overloaded motor units elicit subthreshold potentials in nociceptive dorsal horn neurons, chronic painful work-related muscle disorders could be an example of central sensitization by subthreshold synaptic potentials.

4.8 The Role of Glial Cells in Central Sensitization

In the preceding chapters and sections all mechanisms leading to muscle pain have been attributed to processes in neurons. It has long been known, however, that in the CNS the number of glial cells is approximately 10 times greater than that of neurons. The three main types of glial cells in the CNS are (Fig. 4.21):

1. *Astrocytes* that contribute to the development of the blood brain barrier and form glial scars after CNS lesions
2. *Oligodendrocytes* that build myelin sheaths around myelinated central nervous axons, and
3. *Microglia* that differ from the former two in that they are immunocompetent cells, move towards the site of a lesion, and can perform phagocytosis of necrotic cells. They are the macrophages of the CNS

Only recently has the involvement of glial cells in pain mechanisms been appreciated. The oligodendrocytes do not appear to be of importance for nociception and central sensitization, but microglia and astrocytes have been shown to be activated by peripheral pathological changes including inflammation (Dong and Benveniste 2001; Watkins and Maier 2002). The term "activation of glial cells" mainly describes changes in the metabolism of the cells that lead to the de novo synthesis and release of sensitizing substances. The glial activation is reflected in morphological changes, namely a withdrawal of dendritic processes and reduction of arborization. Activated glia release cytokines and other substances such as proinflammatory interleukins, tumor necrosis factor-α (TNF-α), NO, prostaglandins, ATP, and brain-derived neurotrophic factor (BDNF) in the CNS (cf. Fig. 4.16). These substances sensitize sensory neurons, i.e., they increase central nervous excitability. BDNF binds to the G-protein-coupled tyrosine kinase B (TrkB)

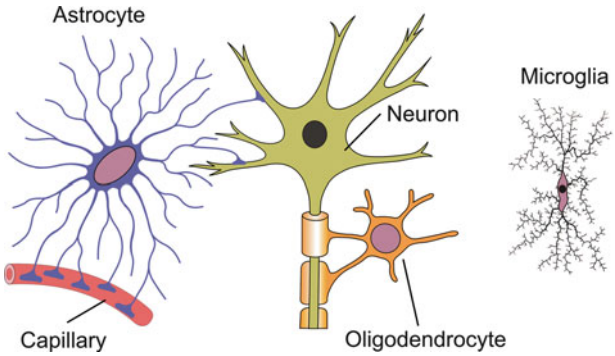

Fig. 4.21 The three main types of glial cells in the CNS. *Astrocytes* are situated between blood vessels and neurons. They contribute to the development of the blood brain barrier and form glial scars after CNS lesions. *Oligodendrocytes* build myelin sheaths around myelinated central nervous axons. *Microglia* are immunocompetent cells, move towards the site of a lesion, and remove cell debris by phagocytosis. They are the macrophages of the CNS, and essential for the sensitization of neurons

receptor in the membrane of the postsynaptic cell and thus starts an intracellular cascade leading to changes in the activity of cAMP and protein kinases. Altogether these changes are called neuroinflammation; they are considered to be an essential part of central sensitization (Hunt and Mantyh 2001; Marchand et al. 2005).

Twelve days after induction of a chronic inflammation of the rat GS muscle, astrocytes in the dorsal horn exhibited a plumper shape in the morphological evaluation; apparently, they had retracted some of their processes. In addition they showed an increase in the content of an intermediary filament that is characteristic of astrocytes, the glial fibrillary acidic protein (GFAP). They also synthesized more fibroblast growth factor 2 (FGF2). All these changes are signs of activation (Tenschert et al. 2004). Activated astrocytes are known to be capable of releasing proinflammatory cytokines such as interleukin 6 and TNF-α, and therefore may contribute to the myositis-induced sensitization of nociceptive dorsal horn neurons (Dong and Benveniste 2001; Kostrzewa and Segura-Aguilar 2003).

Microglial cells are likewise activated by a chronic experimental myositis: they exhibit a rounder shape with fewer arborizations. This microglial activation appears to be a key factor in the behavioral changes of myositis rats. In the exploration (open field) test, these animals exhibit a marked reduction in their exploratory locomotor activity when they are placed in a new and larger cage. Figure 4.22 shows such an experiment: before induction of the myositis, the rats crossed approximately 60 squares of the cage bottom during the first 5 min of their exploration movements. One day after induction of the myositis, animals of the control group — which did not receive any treatment — showed a significant reduction in their exploratory activity. The number of squares crossed dropped to less than 20 and stayed at that level for the rest of the observation period (12 days), i.e. the rats exhibited a myositis-induced reduction of motor acitvity.

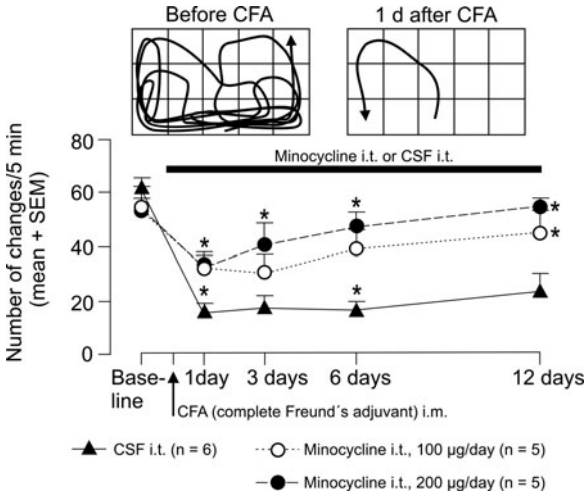

Fig. 4.22 Effect of blocking spinal microglial cells on chronic pain behavior. The data were obtained in a test of the exploratory activity of the animal. The rats were placed in a large cage the bottom of which was divided into squares. The untreated rats explored the cage and crossed more than 50 squares in the *left inset*. One day after induction of a chronic myositis of the GS muscle with complete Freund's adjuvant (CFA), the exploratory locomotor activity was significantly reduced (*right inset, filled triangles* in the diagram). After blocking the activation of the microglial cells with minocycline i.t., the myositis-induced reduction of the exploratory behavior was significantly attenuated after 3–12 days. Minocycline was administered with an implanted osmotic pump that delivered the drug continuously for 12 days. *CSF*, artificial cerebrospinal fluid (vehicle)

The treatment group — which likewise had a myositis — received minocycline i.t., a tetracyclin derivative that blocks the activation of microglial cells without having much effect on the other glial cells or neurons. Minocycline was administered via an intrathecal catheter that was connected to a subcutaneously implanted osmotic mini pump. The treatment started just before induction of the myositis and continued for the following 12 days. Six to 12 days after starting the minocyclin treatment, the exploratory activity of the myositis rats was largely restored, whereas the untreated myositis group still exhibited a significant reduction of exploratory activity (Fig. 4.22; M. Chacur, D. Lambertz, U. Hoheisel, and S. Mense, unpublished).

4.9 The Transition from Acute to Chronic Muscle Pain

The opening of formerly silent synapses and other neuroplastic changes in the CNS is an important step in the transition from acute to chronic pain, because they can persist in some patients (Woolf and Salter 2000). Another step in the direction of chronic pain are lesion-induced metabolic changes in sensory spinal neurons. As an

example of such metabolic changes, NO-synthesizing cells have been described above.

In the long run, repeated activation of the NMDA channel will probably lead to the formation of a persistent synaptic connection through the strengthening of ineffective synapses which originally only elicited subthreshold EPSPs. This mechanism is assumed to play a role in learning processes at higher levels of the CNS.

The last step in the transition from acute to chronic muscle pain is persistent morphological changes in the circuitry of the spinal dorsal horn or brain stem. These changes consist of sprouting of the spinal terminals of afferent fibers, and of de novo formation and broadening of synaptic contacts (Sperry and Goshgarian 1993). Through these structural alterations, the initially functional changes become permanent and the function of the spinal cord is persistently altered.

A completely different mechanism leading to hyperexcitability of neurons and chronic pain is excitotoxicity (Yezierski et al. 1998). Excitotoxicity means that a strong nociceptive input releases large amounts of SP and glutamate simultaneously. This leads to simultaneous opening of all calcium-permeable ion channels (mainly NMDA channels). The postsynaptic cells are swamped with Ca^{++} that activates all enzymes that are present in the cytoplasm. Among these enzymes are some that are dangerous for the cell because they activate the genetic mechanism for the programmed cell death (apoptosis) or lead directly to the destruction of the cell (necrosis; Fig. 4.23). An important aspect of this mechanism is that inhibitory interneurons are particularly sensitive to excitotoxicity. Normally, these interneurons depress tonically the activity of nociceptive central neurons. Therefore, after the excitotoxic death of the interneurons the spinal cord is devoid of tonic inhibition and the nociceptive neurons in that area are chronically disinhibited and hyperactive. This mechanism may be of importance for patients who have fibromyalgia-like pain after a whiplash injury. In one study, more than 20% of these patients were reported to develop a fibromyalgia syndrome (FMS) (Buskila et al. 1997).

Another pathologic mechanism of a persistent change in the inhibitory network of the spinal cord is a dysfunction of the GABA-induced inhibition of postsynaptic neurons (cf. Fig. 4.3). Normally, the inhibitory interneurons use GABA (or glycine) as a transmitter to open Cl^- channels in the membrane of the neuron. This leads to an influx of negative electric charges and therefore to a hyperpolarization that moves the membrane potential away from the firing threshold. The net effect is a decreased excitability of the postsynaptic neuron (Fig. 4.24a). The Cl^- ions are removed from the cell by a K^+/Cl^- transporter that exchanges K^+ against Cl^-. Under pathologic conditions (e.g., neuropathic nerve injury, inflammation) the transporter may not function properly and Cl^- ions accumulate in the postsynaptic neuron. When the Cl^- channel is now opened by GABA, Cl^- ions leave the cell and cause a depolarization instead of a hyperpolarization (Fig. 4.24b). Thus, the postsynaptic neuron can be excited by GABA. This means that one of the most powerful inhibitory mechanisms is no longer functional. On the contrary, the

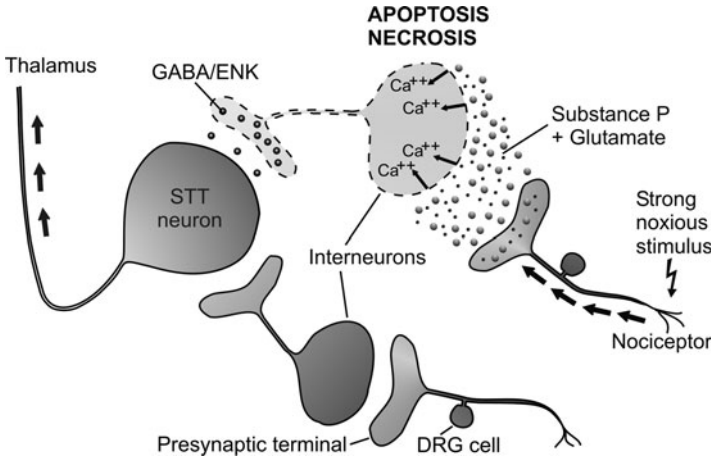

Fig. 4.23 Excitotoxicity as a possible mechanism of chronic pain after a strong trauma. The high-frequency nociceptive input associated with the trauma releases large amounts of SP and glutamate simultaneously from presynaptic terminals. This leads to simultaneous opening of all calcium-permeable ion channels, including the NMDA channels. The postsynaptic cells is swamped with Ca^{++}, which activates many enzymes in the cytoplasm. Among these enzymes are some that lead to the destruction of the cell by apoptosis or necrosis. Interneurons that use GABA or enkephalin (ENK) for inhibiting nociceptive neurons are particularly sensitive to excitotoxicity. *DRG*, dorsal root ganglion cell; *STT*, spinothalamic tract

classic inhibitory transmitter GABA now excites the postynaptic neuron (Nabekura et al. 2002; for a review, see Price et al. 2005).

Central nervous plasticity and the opening of silent synapses may also be an important factor for postoperative pain in patients, part of which seems to be due to a central change following the noxious input that is inevitably associated with surgical interventions. Local anesthesia of the operation site (in addition to general anesthesia) has been suggested as a possible means of preventing the intraoperative central sensitization (Wall 1988).

In this context, the treatment of acute muscle pain gets a new meaning: in addition to abolishing the pain and restoring normal function, treatment should aim at preventing the central sensitization. It is conceivable that — if the treatment fails — the prolonged and repeated input from muscle nociceptors triggers events in the CNS that eventually lead to a chronic pain condition (Sutula et al. 1988).

4.10 Nociceptive Processing at the Trigeminal Level

In this section, only the basic structure and function of the trigeminal system is outlined. Nociception at the trigeminal level is dealt with in detail in Chap. 9 in the companion volume by Mense and Gerwin (2010).

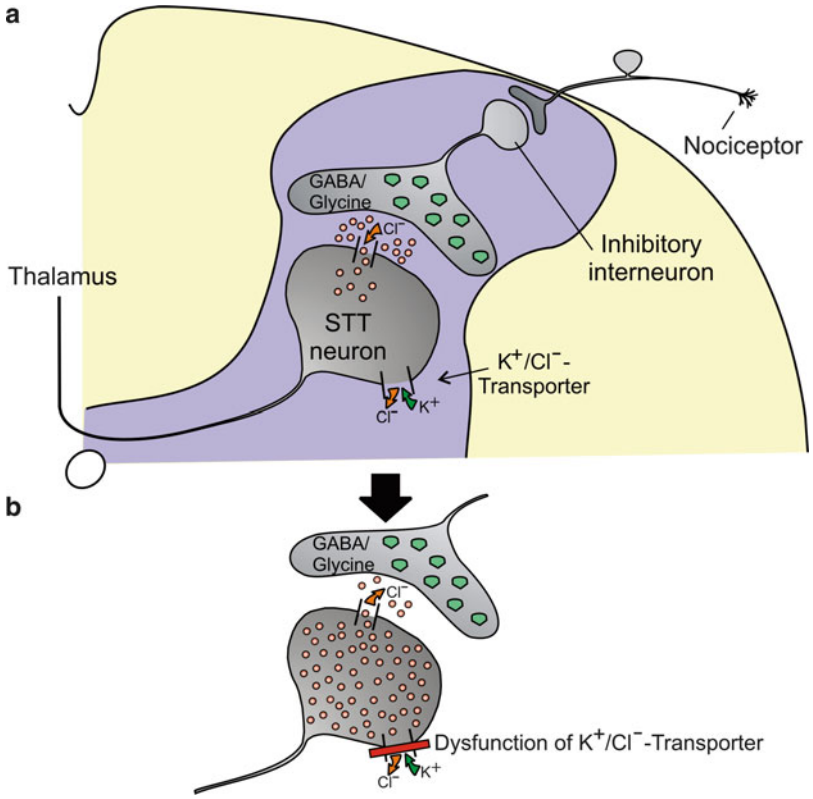

Fig. 4.24 Dysfunction of the GABA-induced inhibition of postsynaptic neurons as a possible mechanism of chronic pain. Normally, inhibitory interneurons use GABA (or glycine) as a transmitter to open Cl^- channels in the membrane of the neuron. This leads to an influx of negative electric charges into the spinothalamic (STT) neuron and therefore, to a hyperpolarization. The hyperpolarization decreases the excitability of the postynaptic neuron. The Cl^- ions are removed from the cell by a K^+/Cl^- transporter that exchanges K^+ against Cl^- (**a**). Under pathologic conditions, the transporter may not function properly, and Cl^- ions accumulate in the STT neuron. When the Cl^- channel is now opened by GABA, Cl^- ions leave the cell and cause a depolarization instead of a hyperpolarization (**b**). Thus, the postsynaptic neuron can be excited by GABA, i.e., the classic inhibitory transmitter GABA acts as an excitatory transmitter

The trigeminal nerve — the fifth cranial nerve — supplies oro-facial tissues such as the teeth, facial skin, temporomandibular joint, and musculature. In addition to non-nociceptive primary afferent fibers, for instance from cutaneous mechanoreceptors or muscle spindles and tendon organs, this nerve also contains small-diameter fibers that terminate in nociceptors. (Lam et al. 2005; Sessle 2000). As in other body regions, the activation of nociceptors leads to motor reflexes and pain sensations (Trulsson 2006). The general response behavior of nociceptive endings is very similar to that of nociceptors in other tissues in that they are activated by strong mechanical stimuli, inflammatory substances such as prostaglandins, and

BKs, and exhibit peripheral sensitization when the oro-facial tissues are pathologically altered.

Interestingly, substances released from postsynaptic sympathetic fibers such as noradrenaline increase the excitability of oro-facial nociceptors but only in traumatized or otherwise lesioned tissue. Under these conditions, α-adrenergic receptors on nociceptive afferents are upregulated and the endings become sensitive to noradrenaline whereas normally they are not affected by noradrenaline. When the nociceptive endings are sensitized they may contribute to painful conditions such as complex regional pain syndrome (Sessle 2006).

There is evidence showing that — in addition to the other pain-mediating receptor molecules mentioned above for nociceptors in extremity muscles — nociceptors in the tooth pulp and jaw muscles are sensitive to glutamate. The nociceptive endings in masticatory muscles contain NMDA receptors and injection of glutamate into those muscles elicits pain in humans by activating the NMDA receptors.

Another important finding is that oro-facial muscle nociceptors show clear gender differences in their responsiveness to glutamate in that women feel more pain during injections of glutamate (Sessle 2006). This sex difference at the level of the peripheral nociceptive endings indicates that not all gender differences to painful stimuli are due to central pain processing or psychological factors. It suggests that peripheral mechanisms may contribute to the overrepresentation of women in some chronic muscle pain syndromes such as temporomandibular disorders.

The trigeminal system differs from the rest of the somatic somatosensory system in that the cell bodies of the primary afferent fibers are situated partly in the mesencephalic trigeminal nucleus and partly in the trigeminal ganglion (Gasserian or semilunar ganglion) on the lateral surface of the pons. The mesencephalic nucleus contains only the cell bodies of proprioceptive afferent fibers, e.g., from muscle spindles and tendon organs. There are no synapses in the mesencephalic nucleus – it resembles a spinal ganglion that lies within the brainstem. The other two trigeminal nuclei are true nuclei that process sensory information and form synapses with primary afferent fibers. The information in non-nociceptive mechanoreceptive afferents is processed in the pontine (or principal) trigeminal nucleus, whereas the nociceptive and thermoreceptive fibers project to the spinal trigeminal nucleus (Fig. 4.25). These latter fibers ascend or descend in the brainstem to form the trigeminal spinal tract. From this tract, collaterals arise that terminate in the spinal subdivisions of the trigeminal sensory nuclear complex in the brainstem (Sessle 2000).

The most important center for the processing of nociceptive information from the masticatory muscles is the caudal subnucleus of the spinal trigeminal nucleus (or pars caudalis of the spinal trigeminal nucleus). It has a laminar structure similar to that of the spinal dorsal horn and continues into the cervical spinal dorsal horn. The general response properties of neurons in the caudal subnucleus of the spinal trigeminal nucleus resemble those described above for the spinal dorsal horn. They possess the same receptor molecules for glutamate (e.g., NMDA) and SP (NK1) in

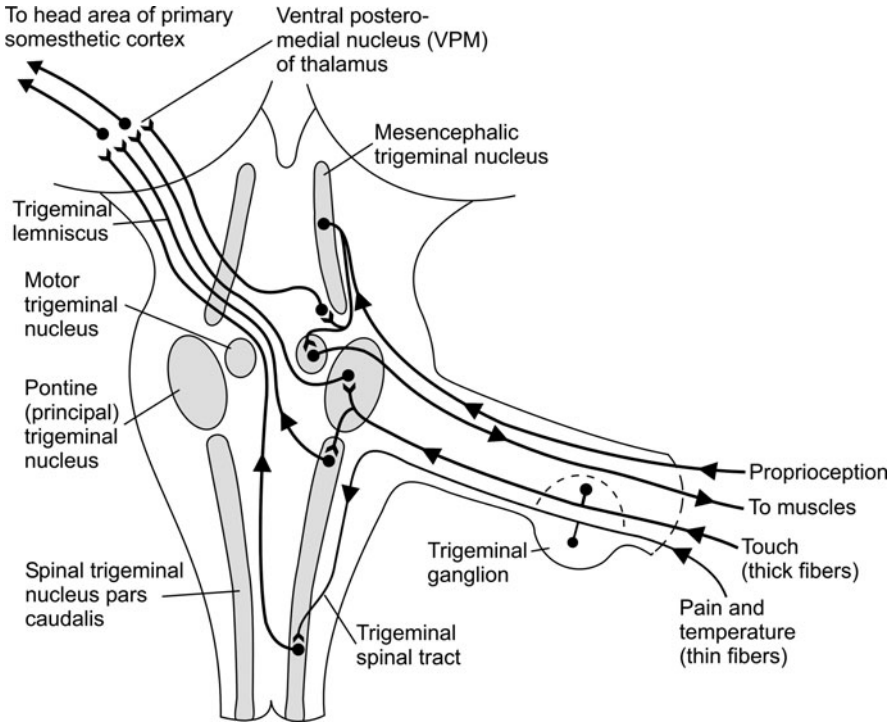

Fig. 4.25 Overview of the trigeminal system. The cell bodies of the primary afferent fibers are situated partly in the mesencephalic trigeminal nucleus and partly in the trigeminal ganglion (Gasserian or semilunar ganglion). The mesencephalic nucleus contains only the cell bodies of proprioceptive afferent fibers, e.g., from muscle spindles. It resembles a spinal ganglion that lies within the brainstem. The other two trigeminal nuclei are true nuclei that have synapses with primary afferent fibers. The information in non-nociceptive mechanoreceptive afferents is processed in the pontine (or principal) trigeminal nucleus, whereas the nociceptive fibers project to the spinal trigeminal nucleus, pars caudalis. Mainly the latter fibers ascend or descend in the brainstem to form the trigeminal spinal tract. From that tract, collaterals originate that terminate in the spinal trigeminal nucleus. The most important center for the processing of nociceptive information from the masticatory muscles is the caudal subnucleus (or pars caudalis) of the spinal trigeminal nucleus. The axons of the cells of the pontine and spinal trigeminal nuclei form the trigeminal lemniscus before they terminate in the ventral posteromedial (VPM) nucleus of the thalamus, the posterior group and the medial thalamus. From the thalamus, the nociceptive fibers project to the cortical nociceptive areas, including the primary somatosensory cortex

their membrane. The neurons likewise exhibit an extensive convergent input from low- and high-threshold primary afferent fibers. This input convergence may explain the poor localization of pain that is typical of pain from deep oro-facial tissues (Sessle 2006).

The axons of the cells of the pontine and spinal trigeminal nuclei form the trigeminal lemniscus before they terminate in the ventral posteromedial (VPM) nucleus, the posterior group, and the medial thalamus. Some of these projections

are indirect and include polysynaptic pathways that may involve the RF. From the thalamus, the nociceptive fibers project to the cortical nociceptive areas including the SI (Fig. 4.25; see below).

Increased responsiveness in the sense of central sensitization is likewise present in the trigeminal system and is based on the same mechanisms as at the spinal level (e.g., activation of NMDA channels and opening of ineffective synapses). The main cause for such an increased responsiveness is injury to peripheral nerves or oro-facial tissues. In animal experiments central sensitization can be induced by an inflammation (Chiang et al. 1998).

The lesion-induced central sensitization may be accompanied by changes in motor reflexes in jaw-opening and jaw-closing muscles that are dependent upon data processing in subnucleus caudalis (Sessle 2006). One example of a motor reflex elicited by noxious stimulation of the oro-facial tissues is the jaw-opening reflex. However, stimulation of periodontal or peri-implant mechanoreceptors can also evoke motor reflexes (Trulsson 2006; Jacobs and van Steenberghe 2006). To what extent motor reflexes (e.g., cocontraction of antagonistic masticatory muscles) may underlie the pain of temporo-mandibular pain, tension-type headache, or other forms of chronic oro-facial muscle pain syndromes is a matter of debate. The neural apparatus for such a mechanism exists: there are abundant connections between oro-facial receptors (both nociceptive and non-nociceptive ones) and motor nuclei in the brainstem. Moreover, the activity of masticatory muscles is under the control of cortical and limbic centers and is modulated by peripheral disorders and central pain-modulating systems (Sessle 2006).

4.11 Pain-Modulating Pathways

In addition to the systems addressed below, there are more pain-modulating (mainly antinociceptive) systems in the spinal cord and supraspinal centers. For a review of these systems, see Sandkühler (1996).

4.11.1 Segmental Inhibition of Dorsal Horn Neurons

Activity in myelinated afferent fibers has long been known to inhibit the responses of nociceptive dorsal horn neurons to noxious stimuli (Wall and Cronly-Dillon 1960; Gregor and Zimmermann 1972). This effect has mainly been studied in nociception from the skin. The afferents producing the inhibition include thick myelinated Aβ-fibers and thin myelinated Aδ-fibers: the former supply low-threshold mechanosensitive (non-nociceptive, e.g., tactile) receptors, whereas the latter terminate in both nociceptive and non-nociceptive receptors (Fig. 4.26; Sandkühler 1996; Liu et al. 1998). This type of inhibition is often called segmental (or afferent) as opposed to the descending inhibition (see below).

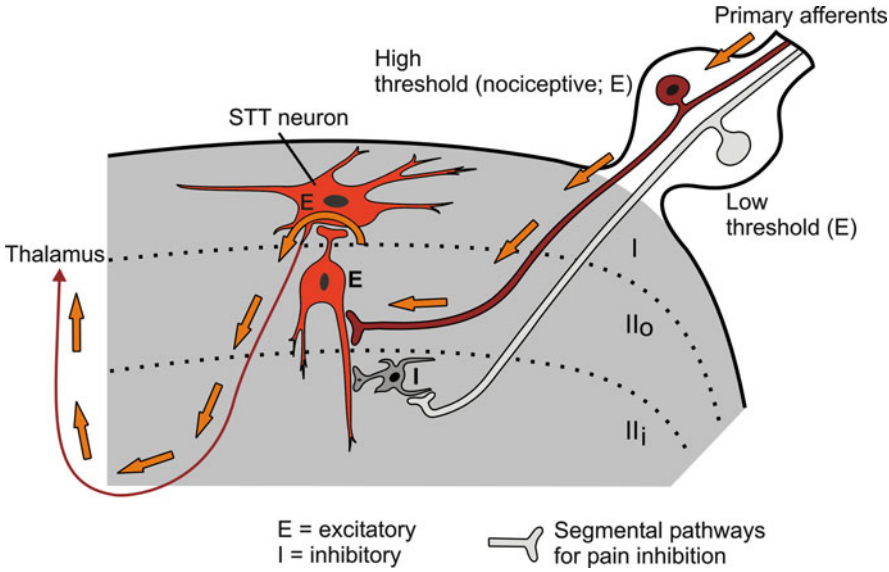

Fig. 4.26 Segmental (afferent) inhibition of dorsal horn neurons. The figure shows the most superficial part of the spinal dorsal horn with three layers (lamina *I*, *IIo* (outer lamina II), *IIi* (inner lamina II). The principle of this type of inhibition is that activity in low-threshold myelinated afferent fibers inhibits the responses of nociceptive dorsal horn neurons to noxious stimuli. The inhibition is due to an activation of an inhibitory interneuron (*gray*; *I*) by the low-threshold afferents. The afferents producing inhibition include thick myelinated Aβ-fibers and thin myelinated Aδ-fibers: the former supply low-threshold mechanosensitive (non-nociceptive, e.g., tactile) receptors, whereas the latter terminate in both nociceptive and non-nociceptive receptors. *STT*, spinothalamic neuron; the *orange arrows* indicate the normal pathway for nociceptive information

Any individual who receives a painful blow to the body automatically rubs the skin around the painful region and thus elicits segmental inhibition. Animals exhibit a similar behavior by licking an injured part of the body. The resulting input via myelinated mechanosensitive fibers combined with a liminal activation of Aδ- nociceptors effectively inhibits pain transmission at the spinal level (Fields 1987). Massage treatment is an effective method of activating thick myelinated afferents. Therefore, the pain-relieving action of this treatment may be (partly) due to segmental inhibition.

Transcutaneous electrical nerve stimulation (TENS) is another technique for exciting thick myelinated afferent fibers and inducing segmental inhibition. This method of controlled electrical activation of thick afferents in a peripheral nerve through the intact skin can be used in the treatment of chronic pain. In these cases, it is assumed to inhibit hyperexcitable nociceptive dorsal horn neurons. TENS can also be of benefit for some patients with neuropathies. Here, the increased excitability of dorsal horn neurons is thought to be due to a disinhibition of nociceptive central neurons caused by a decrease in the activity of the thick myelinated fibers. The TENS method can restore part of this tonic afferent activity in non-nociceptive fibers.

4.11.1.1 Gate Control Theory

The theory was put forward by Melzack and Wall (1965). It extended the concept of pain inhibition through activity in thick fibers (which close a "pain gate") by adding excitatory unmyelinated fibers to the system (which open the gate). The neuronal spinal circuit underlying the system is shown in Fig. 4.27. The gate proper is represented by the inhibitory cell in the substantia gelatinosa (SG) or Rexed's lamina II, the transmission (T) cell, and the synapses on these cells. The unmyelinated fibers were assumed to increase the excitability of nociceptive neurons (transmission cells) in the spinal cord by inhibiting the interneuron in the SG of the dorsal horn, thus causing disinhibition (excitation) of the transmission neuron. The transmission cell is connected to other neurons that form the "action system" which elicits a variety of responses, including pain if the gate is open.

The novel concept behind the theory was that the output of the transmission cell – the intensity of pain – depends on the balance between the activity in myelinated (pain-inhibiting) and unmyelinated (pain-promoting) fibers. This aspect was new and important because the causal relation between the presence of a noxious stimulus and subjective pain sensations was abolished. The gate control theory was also able to explain cases of pain, for instance in the Guillain-Barré syndrome or other neuropathies, where often no painful lesion is present,

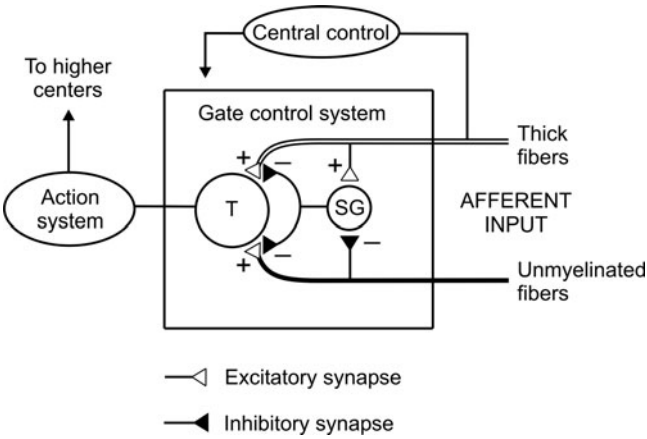

Fig. 4.27 Spinal circuit underlying the gate control theory. The gate proper is represented by the inhibitory cell in the substantia gelatinosa (*SG*) or Rexed's lamina II, the nociceptive transmission cell (*T*) and the synapses on these cells. The *upper half of the figure* is similar to the segmental inhibition: myelinated fibers excite the SG neuron and thus inhibit the transmission of the nociceptive activity. The unmyelinated fibers are assumed to increase the excitability of nociceptive neurons (transmission cells) in the spinal cord by inhibiting the SG cell, thus causing disinhibition (excitation) of the transmission neuron. The transmission cell is connected to other neurons which form the "action system" that elicits a variety of responses including pain if the gate is open

but the primary problem is rather a reduction of the input via myelinated afferent fibers.

Originally the modulating influence of the afferent fibers was assumed to act presynaptically (Fig. 4.27), but a postsynaptic action directly on the transmission cell is also possible (Wall 1978). An important aspect of the theory — which is often overlooked — is that the spinal gate control system is under the control of supraspinal pain-modulating centers which can interfere with the system and inhibit or increase pain.

In particular, one of the new postulates of the gate control theory, namely that unmyelinated afferent fibers open a spinal gate, has been controversely discussed a few years after its publication (Gregor and Zimmermann 1972). A theoretical problem of the proposed spinal circuit is the existence of unmyelinated fibers that have an excitatory synapse on the output neuron (the T cell) and inhibitory contacts with the inhibitory SG interneuron (see Fig. 4.27). If the published circuit is taken literally the presence of inhibitory and excitatory synapses in the same fiber violates the principle that a neuron is either excitatory or inhibitory at all of its terminals. This criticism could be overcome by adding an inhibiting interneuron between the unmyelinated fiber and the transmission cell, but then the theory loses the simplicity and clarity which makes it so attractive.

4.12 Pain-Modulating Descending Pathways

There is accumulating evidence that the transmission of nociceptive information in the spinal cord is under biphasic modulation from supraspinal structures, i.e., there are pain-inhibiting and pain-facilitating descending pathways (for recent reviews, see Porreca et al. 2002; Gebhart 2004; Fields 2004). These descending influences originate in brainstem centers and are modulated by cortical and subcortical centers. The neurons in the rostral medulla — one of the areas where descending pain-modulating tracts originate — are known to have axonal arborizations that extend caudally to virtually all spinal segments. Therefore, these cells can influence nociceptive neurons in the entire spinal cord and brainstem and thus can change the pain sensations in large regions of the body (Fields et al. 1995).

4.12.1 The Descending Pain-Inhibiting (Antinociceptive) System

Both the pain-inhibiting and pain-facilitating system are closely interconnected, but in this section each system is addressed separately.

The information from muscle nociceptors is predominantly transmitted to spinal dorsal horn neurons at the origin of the STT (Gingold et al. 1991) and ascends in that tract. The ascending tract fibers give off collaterals that make synaptic contacts

with neurons in the rostral medulla (including cells in the nucleus raphe magnus, NRM) and in the PAG matter of the mesencephalon. Figure 4.28 shows the basic structure of the system as described by Basbaum and Fields (1984).

The descending antinociceptive system has three levels. The cells of origin are situated in the mesencephalon, in the PAG. The next level is the rostral ventral medulla where the NRM and lateral nuclei of the reticular formation are located. Later, cells in the dorsolateral pontine tegmentum (the ventral part of the pons) were added (Fields and Basbaum 1999). In these nuclei a multitude of pathways originate that descend the whole length of the spinal cord in the dorsolateral funiculis and make synaptic contacts with each spinothalamic neuron and other cells that transmit nociceptive information to higher centers. These tract cells are situated in the spinal cord which represents the third level of the descending system. Thus, the spinal neurons are the main target of the descending pain-inhibiting system. This is an important point because it means that the nociceptive information is blocked or attenuated before it reaches higher centers.

There is evidence that parts of the descending antinociceptive system are tonically active (see below). Therefore, there is a basic inhibition of the spinal transmission of the information from peripheral nociceptors. We would probably all be in pain if the tonic inhibition was too weak or not present at all. This normal level of activity of the descending antinociception is not fixed but can be modulated (increased or decreased) by influences from cortical neurons, the amygdala, and the hypothalamus (cf. Fig. 4.28). Some of the neurotransmitters used by the system are shown in Fig. 4.29. The basic activity of the descending system appears to be controlled by a short chain of two neurons in the PAG, one of which uses the neurotransmitter enkephalin and the other one GABA (enkephalin is an endogenous opioid with morphine-like actions, it is synthesized from endorphin by splitting). Both neurons are inhibitory, and when the activity of the enkephalinergic neuron is increased, it inhibits the GABAergic neuron and thus disinhibits the neuron that projects caudad to the NRM. The inhibition of the spinothalamic neurons in the spinal cord is mainly caused by the transmitter serotonin (5-hydroxytryptamine, 5-HT) that is released by the descending fibers of the NRM. Note that there is an additional pathway from the RVM to the spinal cord which uses norepinephrine (NE) as a transmitter. Most of the cells using NE are situated in the locus coeruleus that likewise can be considered part of the descending antinociceptive system (Basbaum and Fields 1984).

Every time a nociceptive signal ascends the STT, the neurons in the PAG and NRM are excited by the collaterals of the STT. This inhibits the spinothalamic neurons at the spinal level via the descending pathways. Normally the inhibition is not strong enough to block the spinal transmission of nociceptive signals completely, otherwise there would be no pain following noxious stimulation. However, there are situations in which nociception is suppressed completely. An example is soldiers in combat, who often do not feel pain when they are wounded in action. Under this extreme stress, the descending antinociceptive system is maximally activated by impulses originating in the amygdala and hypothalamus.

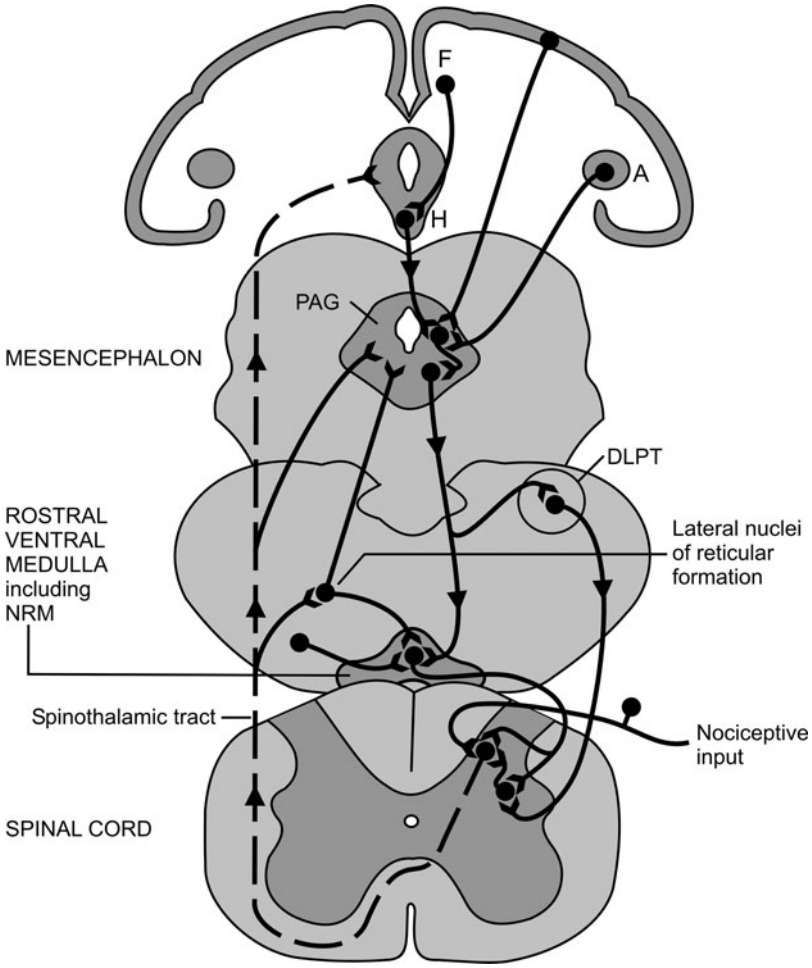

Fig. 4.28 The descending pain-inhibiting (antinociceptive) system. The cells of origin are situated in the *PAG* of the mesencephalon, the next level is the rostral ventral medulla (RVM), where the nucleus raphe magnus (*NRM*) and lateral nuclei of the reticular formation are located. The figure shows an oblique section through the medulla oblongata and the pons, therefore it shows also the nuclei in the dorsolateral pontine tegmentum (*DLPT*). In the pons and medulla, pathways originate that descend the whole length of the spinal cord and make synaptic contacts with each nociceptive projecting neuron in the spinal cord. The spinal cord is the main target of the descending pain inhibition. The afferent information from peripheral nociceptors is predominantly transmitted to neurons at the origin of the spinothalamic tract, and ascends in that tract. The tract fibers give off collaterals that make synaptic contacts with neurons in the rostral medulla and pons as well as in the periaqueductal gray matter (*PAG*) of the mesencephalon. The activity of the descending antinociceptive system can be modulated (increased or decreased) by influences from cortical neurons, the frontal brain (*F*), the amygdala (*A*), and the hypothalamus (*H*)

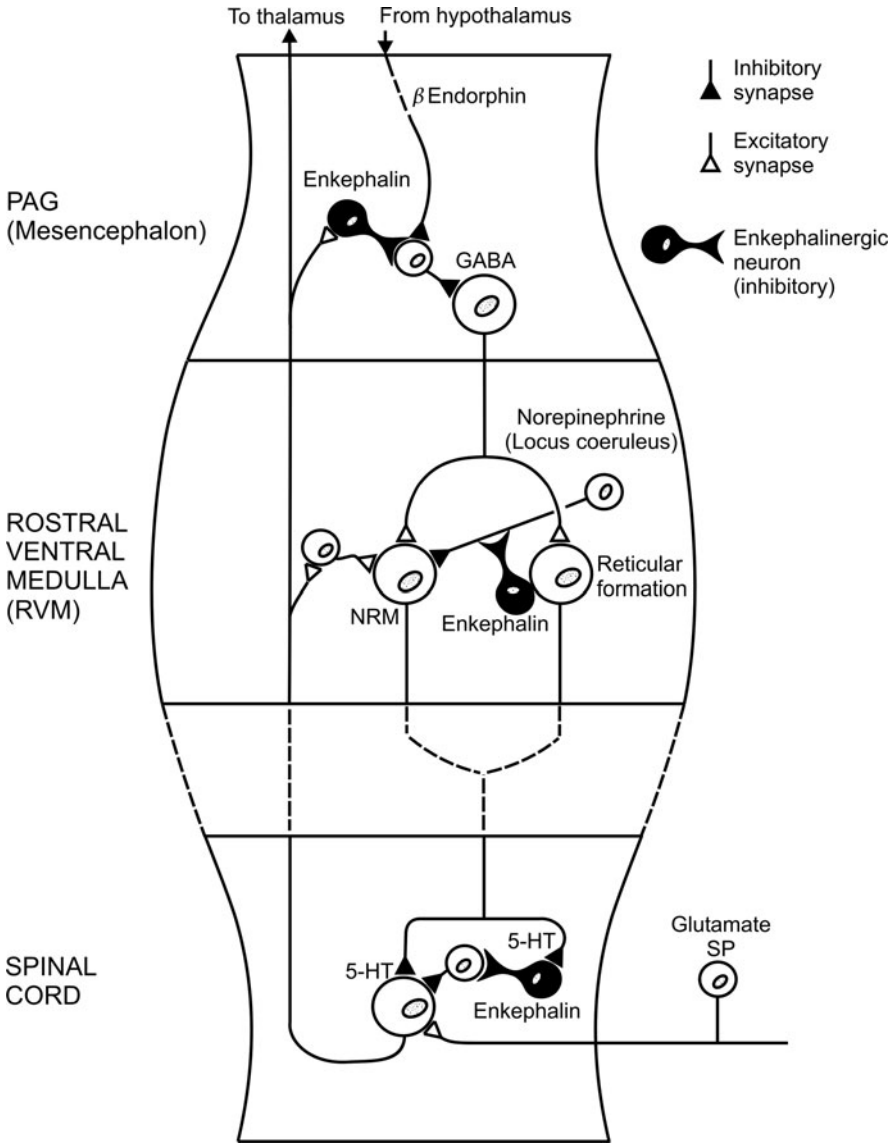

Fig. 4.29 Neurotransmitters used by the descending antinociceptive system. The basic activity of the system is controlled by a short chain of two neurons in the PAG, one of which uses the neurotransmitter enkephalin and the other one GABA. Both neurons are inhibitory, and when the activity of the enkephalinergic neuron is increased, it inhibits the GABAergic neuron and thus disinhibits the neuron that projects caudad to the NRM and lateral reticular formation. The inhibition of the spinothalamic neurons in the spinal cord is mainly caused by the transmitter serotonin (5-hydroxytryptamine, 5-HT) that is released by fibers from the NRM. There is an additional connection from the locus coeruleus to the NRM (and probably also directly to the spinal cord), which uses norepinephrine as a transmitter

In addition to providing pain control the descending antinociceptive system has a survival function. It can prevent nociception-induced motor reflexes such as the flexion reflex which may interfere with the flight reaction required in a life-endangering situation. Examples are animals in herds which are attacked and wounded by predators. For the wounded animal the only way it can save its life is to stay in contact with the herd and flee.

4.12.1.1 Tonic Inhibition of Neurons Mediating Deep Somatic Pain

In animal experimentation cooling of the dorsolateral spinal cord between the medulla and the spinal dorsal horn can be used to test if the descending antinociception is tonically active. A cold block interrupts neuronal activity, but does not excite fibers or neurons. If there is an effect of the cold block on neurons caudal to the block, it must be due to tonic activity in pathways traversing the cooling site.

Using this technique, the activity of dorsal horn neurons driven by input from deep somatic tissues (muscle, joint, fascia) was markedly influenced. The cooling induced an increase in resting activity, in response magnitude to noxious stimulation, in muscle convergence from different receptor types, and in the number of RFs per neuron (Hong et al. 1979; Yu and Mense 1990a). These data show that dorsal horn neurons that presumably mediate deep pain are subjected to a strong and tonic descending inhibition. A similar tonic descending inhibition has been reported for neurons with input from joints (Cervero et al. 1991).

The tonic nature of the descending inhibition can be best explained by assuming that a neurotransmitter is continuously released in the PAG or RVM. As stated above, the main transmitters of the descending antinociceptive system are endogenous opioids, NE, and serotonin. Transmitter antagonists injected into the third cerebral ventricle in rats can reach the supraspinal antinociceptive centers because a liquor–brain barrier does not exist. In the study by Yu et al. 1991,the only substance that abolished the tonic inhibitory influence on dorsal horn neurons with input from deep nociceptors was the opioid antagonist naloxone. Neither the α-adrenergic receptor blocker phentolamine nor the serotoninergic blocker methysergide were effective in this regard .

A controlled activation of the descending antinociceptive system would be the ideal therapy for chronic painful muscle disorders. Systematic studies addressing this question are not available, but there is some indirect evidence that the effects of massage and acupuncture may at least partly be mediated by the descending inhibition.

The afferent pathway activating the antinociceptive system probably includes at least two types of afferent unit:

1. Non-nociceptive receptors in deep tissues with slowly conducting afferent fibers (e.g., low-threshold mechanosensitive and ergoreceptive muscle afferents) which are likely to be strongly excited by massage and muscular contractions. Long-lasting physical exercise such as marathon running is known to have an

analgesic action and induce an elevated mood (joggers become "high" after a while). The analgesia can lead to lesions of the skeletomotor system because overuse of muscles and joints is not perceived as painful (Sanchez et al. 2006).

2. An important input for acupuncture effects and also for the effects of strong massage stimuli (e.g., periosteal massage) presumably reaches the spinal cord via nociceptive thin myelinated afferents from deep somatic tissues including muscle (discussed in Sandkühler 1996). The classical Chinese needle acupuncture requires deep penetration of subcutaneous tissues for proper treatment of functional disturbances, e.g., 4 cm deep in the stomach point 31 (An outline of Chinese Acupuncture 1975).

An interesting aspect of the descending antinociceptive system is its tonic nature. A dysfunction or simple reduction in its tonic activity will lead to a disinhibition of nociceptive dorsal horn neurons and increase the excitability of these cells. In this situation no afferent nociceptive input is necessary to induce a painful state. A reduced descending inhibition may occur because of statistical reasons: the distribution of the activity of the descending system in a large population of individuals is unknown, but it is likely to have a peak as well as minimal and maximal values. If an individual has a tonic inhibition at the lower end of the distribution, this person may be particularly susceptible to the development of chronic painful disorders. On the other hand, individuals at the upper end of the distribution — who have a high antinociceptive activity — may experience strong pain without becoming chronic pain patients. These considerations are admittedly speculative, but they offer a simple explanation as to why, out of a number of patients with the same injury, only some develop chronic pain.

It is conceivable that a pathological disorder of the descending antinociceptive system could result in a chronic disinhibition of the dorsal horn neurons that mediate muscle pain. In patients, this could lead to generalized spontaneous pain and hyperalgesia predominantly in muscle and other deep somatic tissues. Such symptoms are characteristic of the FMS. The pathomechanism of FMS will be discussed in more detail in Chaps. 4 and 5 in the companion voulme by Mense and Gerwin (2010).

4.12.1.2 Descending Facilitation of Nociceptive Dorsal Horn Neurons

Dorsal horn neurons have long been known to be subjected not only to descending inhibitory but also to facilitating or excitatory influences (Light et al. 1986; McMahon and Wall 1988; Fields and Basbaum 1999). Facilitation means that the reaction of a spinal neuron to a noxious stimulus is enhanced. One site of origin of the descending facilitation is the rostroventral medulla (RVM; Fields and Basbaum 1999; Vanegas and Schaible 2004). In chronic pain patients, descending modulatory influences from supraspinal structures can switch from inhibitory to facilitatory, and thus can contribute to the pain. Usually, both the inhibitory and facilitatory influences are activated simultaneously, but in some chronic pain

conditions the inhibitory component prevails, and in others the facilitatory (Vanegas and Schaible 2004).

Some of the facilitating pathways originate in nuclei of the RVM, i.e., in the same area where antinociceptive cells are located (Fields 1992; Fields and Basbaum 1999; Vanegas and Schaible 2004). A transmitter substance used by this system to facilitate spinal neurons is serotonin (5-HT) acting on 5-HT_1 receptors (Zhuo and Gebhart 1991). This finding demonstrates that serotonin can inhibit (in the descending antinociceptive system) or facilitate spinal neurons. The difference in the action of 5-HT depends on the receptor molecules that are present in the membrane of the postsyanaptic cell.

The RVM is the most important source of descending neurons that use 5-HT as a transmitter. Some of these cells inhibit spinal neurons when activated, some excite the spinal cells, and some have no recognizable action. A characteristic feature of the facilitating neurons is that they fire a short burst of action potentials just before a behavioral reaction to a painful stimulus takes place. An example of such a response is the tail flick in experiments on rats (Fig. 4.30b). In this test, the tail of the animal is heated by radiant heat or immersion in hot water until the animal withdraws the tail from the heat source with a sudden flicking movement.

The cells that produce a short-lasting discharge just before the flick occurs have been called "on-cells": they probably start the nociceptive tail flick reflex by facilitating the responses of spinal dorsal horn neurons to the noxious stimulus (Fields and Basbaum 1999). The on-cells in the RVM are influenced through connections with the PAG, and one mechanism of activating the on-cells in the RVM through this connection is an increased level of prostaglandin E2 (PGE2) in the PAG. Microinjections of PGE2 into the PAG have been shown to produce hyperalgesia by activating the on-cells in the RVM (Heinricher et al. 2004).

Another effect of the activation of the descending facilitating pathway is the wind-up response of dorsal horn neurons which is present in arthritic rats. It is interesting to note that in these animals wind-up occurs in response to A-fiber stimulation (Herrero and Cervero 1996). This A-fiber-induced wind-up is an indication of dorsal horn hyperexcitability because normally the wind-up response requires C-fiber input. In patients, a wind-up response of nociceptive cells to A-fiber input is likely to lead to allodynia.

In contrast, "off-cells" of the RVM stop discharging just before the tail flick occurs. These neurons probably inhibit nociceptive dorsal horn neurons. The off-cells are tonically active and therefore could provide the permanent depression of the excitability of spinothalamic neurons (see above). As can be seen in Figs. 4.28–4.30, enkephalin can activate the descending inhibition (the off-cells) at all levels of the descending pain-modulating systems. After administration of morphine the on-cells are silent and the off-cells exhibit ongoing activity (Cheng et al. 1986; Vanegas and Schaible 2004). Therefore, the tail flick does not occur when the heat stimulus exceeds pain threshold. The morphine treatment of patients probably has the same effect: the descending pain inhibition is activated, and simultaneously the pain facilitating system is inhibited. This combined effect results in analgesia.

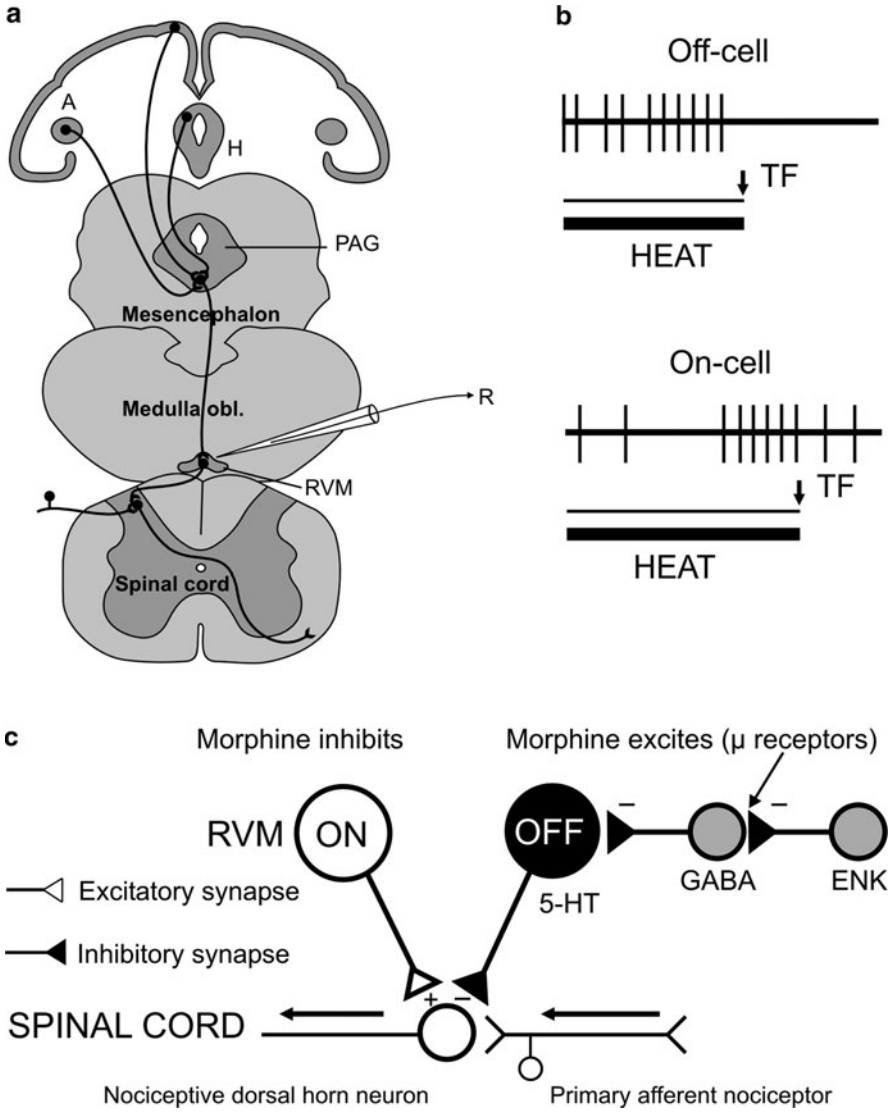

Fig. 4.30 Relationship between descending inhibition and descending pain facilitation. The RVM is the most important source of neurons that use 5-HT as a transmitter in the spinal cord (**a**, **c**). Some of these cells *inhibit* spinal neurons (off-cells), some *excite* the spinal cells (on-cells), and some have no recognizable action. The pain-facilitating neurons fire a short burst of action potentials just before a behavioral reaction to a painful stimulus takes place. An example of such a response is the tail flick in experiments on rats. The on-cells produce a short-lasting discharge just before the flick occurs (**b**, *lower panel*); they probably start the nociceptive reflex by facilitating the responses of spinal dorsal horn neurons to the noxious stimulus. In contrast, off-cells of the RVM stop discharging just before the tail flick occurs (**b**, *upper panel*). These neurons inhibit the transmission of nociceptive information in the spinal cord (**c**). **c** Enkephalin (ENK) activates the off-cells at all levels of the descending pain-modulating systems by binding to the μ-opioid receptors on the GABAergic neurons. Actually the off-cells are disinhibited, because the enkephalinergic cells inhibit the GABAergic cells in the RVM, which leads to a disinhibition of the off-cells. Morphine mimics the action of ENK

Collectively, the data show that the sensation of pain depends not only on the presence of a noxious stimulus but also on a large number of modulating factors. If the pain-inhibiting pathways are highly active, no pain will be felt although a noxious stimulus is present. On the other hand, if the pain-facilitating mechanisms are more active than normal (or if the tonically active pain-inhibiting tracts are dysfunctional) pain can be experienced in the absence of a noxious stimulus.

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Chapter 5
Referral of Musculoskeletal Pain

Thomas Graven-Nielsen and Siegfried Mense

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Abstract Pain referral can pose a serious problem for the diagnosis and treatment of muscle pain because it leads to a mislocalization of the pain by the patient. Referral of pain originating in muscles can be elicited experimentally in a relatively high proportion of healthy subjects. Pain and tenderness can be referred to muscle from other muscles, joints, viscera, and as pain originating in the central nervous system. Clinically, muscle pain referred from other muscles has the typical characteristics of deep-tissue pain and can be elicited, e.g., by local pressure also from muscles that appear to be normal. Referral of pain from joint to muscle is frequent; it often occurs in muscles crossing the joint. Finally, pain can be experienced in muscle as an expression of central pain, i.e., pain due to lesions of the central nervous system. A prominent example of such a muscle pain is phantom limb pain.

In the second part of the chapter, potential mechanisms of pain referral are discussed as well as the differences between Head zones and referred pain in the strict sense. Basically, pain referral appears to result from nociceptive information taking a wrong path in the spinal cord and reaching (somatotopically) inappropriate dorsal horn neurons. The convergence-projection theory by Ruch is still the central concept for the explanation of referred pain. It states that a given dorsal horn neuron receives synaptic connections from two separate innervation areas (convergent input), and that the neuron induces subjective pain in only one (and always the same) area, even when it is excited from the other area. The theory explains the referred pain in the skin from painful viscera. Typical examples of muscle pain referred from viscera include the chest-wall pain of cardiac infarction and the flank pain of renal calculi. A more recent version of the theory states that normally only one of the convergent connections is sufficiently effective to fire the neuron; the other elicits just subthreshold potentials in the neuron. However, the ineffective connections can become effective if there is a long-lasting lesion in the region of the ineffective connection (somatotopically inappropriate connections are opened). Thus, the nociceptive information takes a wrong course in the spinal cord and the pain is mislocalized.

5.1 Introduction

A characteristic feature of referred pain from muscle or viscera is that the patient feels pain not (only) at the site of the lesion but (also) at a distance from the lesion. Referral of pain is typical of muscle pain and does not occur in cutaneous pain. Referral of pain is of clinical importance, because it leads to a mislocalization of the pain source by the patients. If the practitioner is not familiar with this phenomenon, he/she will tend to treat the area of pain referral, particularly if the patient feels the most intense pain in this area (Staff 1988). Such a treatment is not successful, because in the referred pain region the tissue is normal and no nociceptors are active. Because of the referral the pain is often misdiagnosed. An example is that trigger points (TrP) in the upper trapezius characteristically refer the pain up the

back of the neck into the head. This type of muscle pain is often misdiagnosed as tension-type headache.

A remarkable feature of the referral of muscle pain is that it is often not confined to the borders of one dermatome or myotome, i.e., the referral can occur to muscles of myotomes that belong to spinal segments other than that supplying the tissue lesion (Travell and Rinzler 1952). Bogduk (1980) has likewise shown that electrical stimulation of the dorsal ramus of a lumbar spinal nerve in patients leads not only to referred pain in the region supplied by the ventral ramus of the same nerve, but also to pain in segments supplied by other spinal nerves: electrical stimulation of the dorsal ramus of the fourth lumbar nerve caused referred pain not only in the innervation territory of the femoral nerve (which originates partly from the ventral ramus L4) but also in the inguinal region (which is mainly supplied by the spinal nerve L1). A clinically important aspect of muscle pain is that it cannot only be referred to other tissues but also can be the result of referral from other sources of pain. It is well documented that visceral pain (e.g., from cardiac infarction or renal calculosis) can be referred not only to the skin but also to skeletal muscle (Sinclair et al. 1948; Travell and Rinzler 1952; Giamberardino et al. 1990). The visceral pathology responsible for the referred pain is commonly verified by imaging techniques or blood tests. However, other sources of referred pain to muscle (e.g., painful joints or other muscles, see below) are not so readily demonstrable, therefore they are often overlooked. The mechanisms underlying pain referral are still unsolved, but some potential explanations are available and are discussed in Sect. 5.7 of this chapter.

5.2 Occurrence of Local and Referred Pain

Referred pain has been described for more than a century, but still no strict definition exists. Originally, the terms “referred tenderness and pain” were coined by Head (1893) and used to describe pain perceived remote from the site of origin or pain locus. This definition, however, does not allow a distinction to be made between spread of pain and actual referred pain. In this chapter, referred pain defines pain occurring outside and remote from the local pain area. The spread of pain around a nociceptive muscle locus is difficult to differentiate from referred pain due to the diffuse characteristics of deep tissue pain. Whether or not the mechanisms causing spread of muscle pain are different from those underlying referral is unknown. Possibly, referral of muscle pain to closely neighboring regions is perceived as spread. This might underestimate the involvement of referred pain in many clinical conditions. In myofascial pain patients, TrPs typically refer pain to distant deep somatic structures (Simons et al. 1999). Interestingly, the referral from muscle typically occurs to other deep somatic structures (muscles, tendons, joints; Hockaday and Whitty 1967; Graven-Nielsen et al. 2002), but not to the skin. This is

a difference from visceral pain, which is often associated with regions of hypersensitivity in the skin (Head zones; Ness and Gebhart 1990).

5.3 Experimental Musculoskeletal Pain Referral in Humans

Referred pain from muscle has been widely explored with injections of hypertonic saline (Kellgren 1938; Graven-Nielsen 2006) and a typical example is shown in Fig. 5.1, but referred pain from other musculoskeletal structures has also been investigated (Fig. 5.2). Experimental muscle pain has resulted in pain models with localized pain and other models with distinct referred pain (Fig. 5.3). The tibialis anterior and infraspinatus muscles typically refer pain to distinct areas not included in the local pain area, whereas saline-induced biceps brachii muscle pain, for example, is not referred. Substantial clinical knowledge exists concerning the patterns of referred muscle pain from various skeletal muscles after activation of TrPs (Simons

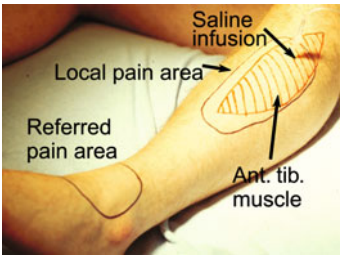

Fig. 5.1 A typical experimental condition where referred pain was induced by noxious stimulation of the tibialis anterior muscle; 0.5 ml hypertonic saline (1 M) was injected in a healthy subject. The subject scored the pain intensity on a visual analog scale, indicated the pain areas and drew the pain areas on an anatomical map

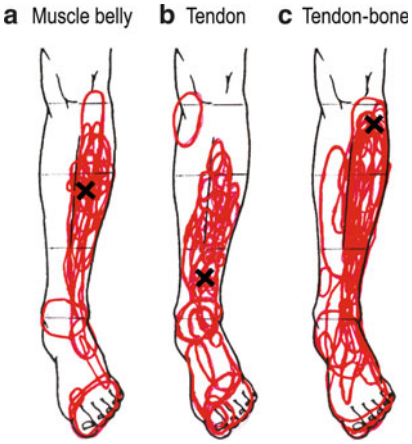

Fig. 5.2 Superimposed bodychart pain drawings following hypertonic saline injections into the muscle belly (**a**), tendon (**b**), and proximal tendon–bone junction (**c**) of the tibialis anterior muscle in 18 subjects. The three different stimulation sites were all accompanied by pain referral. Based on data from Gibson et al. (2006)

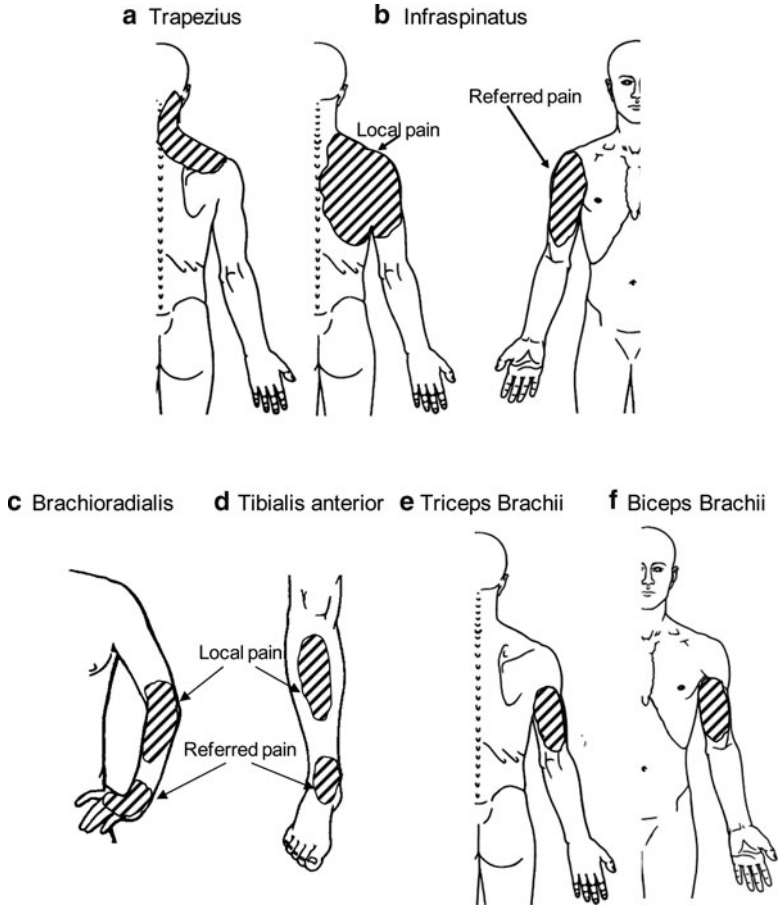

Fig. 5.3 Areas of experimentally induced local and referred pain. Hypertonic saline (0.5 to 1 ml, 1 M) was injected into m. trapezius (**a**), infraspinatus (**b**), brachioradialis (**c**), tibialis anterior (**d**), triceps brachii (**e**), and biceps brachii (**f**). The subjects ($n = 9 – 15$) outlined the area of pain on body maps. Saline-induced pain in tibialis anterior and infraspinatus showed distinct referred pain areas (not included in the local pain area), whereas the other muscles show more localized pain around the injection site. Drawings based on data from previous studies (Birch et al. 2001; Ervilha et al. 2004; Johansen et al. 1999)

et al. 1999) and these descriptions generally fit with the experimental referred pain pattern. In early reports, Kellgren (1938) concluded that referred pain followed a segmental pattern. Supporting this view, both the tibialis anterior muscle and the typical referred pain areas (ankle) are included in myotomes/sclerotomes related to the L5 and L4 vertebral levels. A similar segmental relation can be found for referred pain from m. infraspinatus and m. brachioradialis.

Other findings suggest, however, that the distribution of referred pain does not always follow a strict segmental pattern; i.e., referred pain is not confined to the

myotome, sclerotome or dermatome that processes afferent input from the painful muscle. In fact, referred pain to areas three segments rostral to the electrically stimulated dorsal root has been reported (Bogduk 1980). Often referred muscle pain occurs in segmental areas neighboring the segment supplying the painful muscle.

A feature of referred pain is the unidirectionality of occurrence; e.g., injections of hypertonic saline into m. tibialis anterior typically evoke referred pain to the ankle, but strong pressure stimulation of the ankle does not cause pain in the tibialis anterior muscle (Graven-Nielsen 2006). Similar findings have been reported for other muscles but there are a few examples (Feinstein et al. 1954) suggesting that referred pain can also be bidirectional: experimental jaw-muscle pain can cause referred pain to the teeth (Svensson et al. 1998), and odontogenic pain may mimic jaw-muscle and facial pain (Wolff 1963; Falace et al. 1996), illustrating the potential for a bidirectional mechanism for referred pain in the trigeminal system.

5.3.1 Pain Referral is a Time-Dependent Process

Saline-induced referred pain is delayed approximately 20 s compared to the appearance of local pain (Graven-Nielsen et al. 1997c). In referred pain induced by continuous intramuscular electrical stimulation, the local pain is instantaneous and constant, and in this model also, referred pain is delayed compared to the local pain (Laursen et al. 1997). This indicates that in the mechanism of pain referral a time-dependent process is involved. There is also an increase of referred pain with time. More subjects developed referred pain after 15 min of experimentally induced muscle pain compared with the initial phase of pain (Graven-Nielsen et al. 1998). The frequency of referred pain after prolonged mechanical stimulation of the tibialis anterior muscle is likewise significantly higher than after brief stimulation (Gibson et al. 2006).

On the other hand, in an experimental condition with constant muscle pain intensity, the referred pain intensity declines over time, and when the local pain decreases the referred pain vanishes before the local pain (Graven-Nielsen et al. 1997c). One possible explanation for this finding is that an inhibitory process acts specifically on the central mechanism for referred pain and not on the source of pain.

5.3.2 Local and/or Referred Pain

The distribution of local and/or referred pain after noxious muscle stimulation can be classified into three groups: (1) subjects with local and referred pain, (2) subjects with referred pain only, and (3) subjects with local pain only (Fig. 5.4a). For subjects developing both local and referred pain there is a clear correlation between the local and referred pain intensity (Fig. 5.5, red symbols). Similar correlations

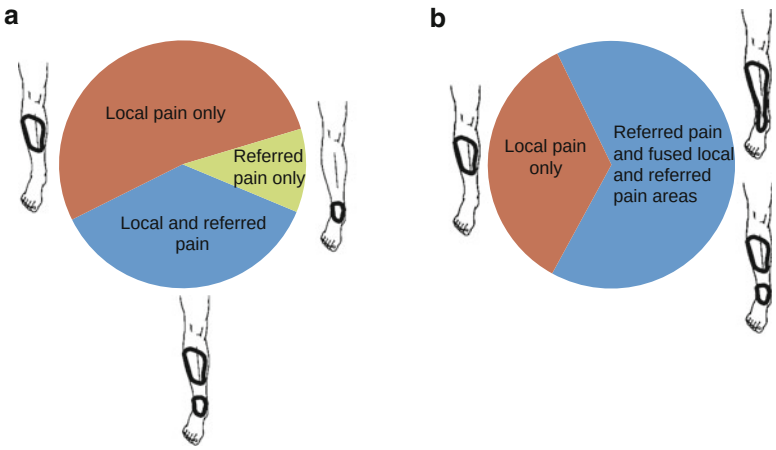

Fig. 5.4 **(a)** Fractions of subjects (based on 115 injections of hypertonic saline into m. tibialis anterior) developing only local pain (pain around the injection site sometimes spreading to a larger area e.g., the ankle), only referred pain (located outside the injection site) or both (pain around the injection site and another distinct area outside the injection site e.g., the ankle). **(b)** In high intensity pain conditions, the pain areas are enlarged and the local and referred pain areas are typically fused. The fraction of subjects perceiving pain in the area typical for referred pain from the tibialis anterior (distal to a line connecting the malleolus), eventually spreading from the tibialis anterior muscle, is substantially higher than that of the subjects developing a distinct area of referred pain separated from the pain in the tibialis anterior muscle, as illustrated in **(a)** with *green* and *blue*. Based on data from Graven-Nielsen (2006)

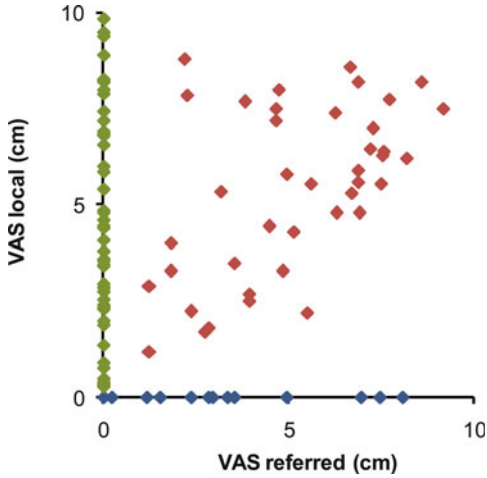

Fig. 5.5 Scores of local and referred pain intensity after injection of hypertonic saline (0.5 ml, 1 M) into m. tibialis anterior. The average pain intensity, was assessed after pain had vanished, on a visual analog scale (*VAS*) where 0 cm indicated "no pain" and 10 cm "most intense pain." Three to eight repeated injections of hypertonic saline separated by 1 week in 23 subjects (115 injections). Three groups of subjects are identified; those developing only local pain (*green symbols*), only referred pain (*blue symbols*), and both local and referred pain (*red symbols*). Based on data from Graven-Nielsen (2006)

between the overall pain intensity and the areas of pain (Graven-Nielsen et al. 1997a, 1997b; 2003); Laursen et al. 1997 or occurrence of referred pain (Jensen and Norup 1992) has been reported previously. The size of the pain areas is correlated to the pain intensity and, therefore, the local pain area may expand into the referred pain area. In such a condition, the referred pain area will be included in the local pain area, resulting in underestimates of the number of subjects with referred pain. In the example shown in Fig. 5.5, approximately 46% of all injections evoked true referred pain (i.e., not enclosed in the local pain area; Fig. 5.4a, green and blue portions). However, 65% of subjects developed pain referred to the ankle area, or pain that expanded from the injection site to the typical area for referred pain (distal to a line connecting the malleoli; Fig. 5.4b, blue portion). Similar underestimations have been reported in another study where 36% developed true referred pain, and approximately 80% developed pain in the area typical for the referred pain (Graven-Nielsen et al. 2003). This is in line with other observations on the frequency of referred pain that is in the range of 40–80% of subjects for the tibialis anterior muscle pain (Graven-Nielsen et al. 1997a, 1997b, 1997c, 2002).

It is not clear why some muscles evoke referred pain, and why other muscles elicit only local pain. Similar observations have been made in myofascial pain patients in whom TrP stimulation of some muscles refers pain just to the close vicinity of the TrP, and stimulation of other muscles induces referred pain in a body region at a great distance from the TrPs (Simons et al. 1999). Of particular interest are subjects who develop only referred pain and no local pain (Fig. 5.5, blue symbols). This is a parallel to referred pain from viscera where local pain is often absent (Ness and Gebhart 1990). One possible explanation for this finding is that endogenous inhibitory systems have different levels of activity and different effects on local and referred pain. As mentioned in Chap. 4, the descending pain-inhibiting system is tonically active. The spontaneous activity in this system is likely to be different in different individuals. Another explanation is that the stimulated part of a muscle has no effective connections to dorsal horn neurons, but only ineffective (silent) synapses on somatotopically inappropriate neurons (see below).

A convincing explanation for the differences mentioned above is not available. Possibly, in the subjects different subgroups of intramuscular nociceptors are excited by the saline; however, in the light of recent findings from animal experiments (Hoheisel et al. 2005) this is unlikely, because in these experiments, hypertonic saline excited all free nerve endings. Another possibility is that the variability in the occurrence of local and referred pain depends on anatomical variations within the muscle. Injections of hypertonic saline into the motor endplate zone were found to evoke higher pain intensities and larger referred pain areas compared to a control site (Qerama et al. 2004). This suggests that specific muscle structures are more effective in evoking referred pain than others. However, such a difference in referred pain areas between endplate zone and control site was not found after capsaicin-induced muscle pain (Qerama et al. 2004). On the other hand, capsaicin and hypertonic saline injected in the endplate

region and capsaicin injected in the control point induced more pain than hypertonic saline in the control point (Qerama et al. 2004). Together this indicates that a critical pain intensity is the main determinant for induction of referred muscle pain, or that the fiber population excited by capsaicin – the specific ligand of the TRPV1 receptor (cf. Chap. 2) – is particularly effective in inducing referred pain. As discussed above, differences in the efficacy of central nervous connections are likewise possible. It is conceivable that some muscle nociceptors have only few effective and a majority of ineffective (sleeping) connections with dorsal horn neurons. Normally, these ineffective connections do not elicit subjective sensations. However, if the stimulus is strong or long-lasting, these connections can be "opened" and cause referred pain.

5.3.3 Need of Afferent Input from the Area of Referred Pain

Referred pain can be induced in an anesthetic limb but with a 40% reduction in referred pain intensity (Laursen et al. 1999). In line with this, referred pain has been induced in structures with sensory loss due to spinal injury or nerve lesion (Doran and Ratcliffe 1954; Whitty and Willison 1958), in phantom limb (Harman 1948), and in anesthetic limbs (Feinstein et al. 1954; Kellgren 1938). The referred pain in these cases had unchanged or slightly decreased intensity. The importance of peripheral input from the referred pain area is not clear, however. Hockaday and Whitty (1967) concluded that referred pain is inconstantly diminished by local anesthetic infiltration of the referred pain area. This suggests that sensory input from the periphery is partly needed for induction of referred pain. A differential nerve block of the afferent fibers from the ankle area showed that the referred pain intensity decreased when blocking the myelinated fibers and no further reduction was found when blocking nonmyelinated fibers (Laursen et al. 1999). Furthermore, the proprioceptive afferent fibers became inefficient when the referred pain intensity decreased to a lower intensity during the differential nerve block, suggesting that these fibers might act as the peripheral component of referred pain (Laursen et al. 1999). In general, articular receptors show no resting activity (Schaible and Grubb 1993), but there are examples from joint afferent recordings with irregular resting activity (Schaible and Schmidt 1983; Just and Heppelmann 2001) especially for units sensitive to non-noxious movements (Schaible and Schmidt 1984; 1988). Thus, referred pain from the ankle area (Laursen et al. 1999; Graven-Nielsen et al. 2002, 2003, 1997c, 1998) might partly be due to facilitation of spontaneous sensory input from the ankle joint. Additional afferent activity from the referred pain area might also be facilitated. This is in line with deep-tissue hyperalgesia to pressure in areas innervated by a branch of the afferent fibres also innervating the referred pain area (Graven-Nielsen et al. 2002). The degree of peripheral sensory input involved in referred pain may vary among various sites for referred pain (e.g., muscle versus joint) explaining the inconsistency in effects of anesthetizing the referred pain area.

5.4 Experimental Pain Referral in Musculoskeletal Pain Patients

The distribution of experimentally induced referred muscle pain seems to be changed in chronic musculoskeletal pain conditions (Arendt-Nielsen and Graven-Nielsen 2003); e.g., fibromyalgia patients experience stronger pain and larger referred areas after saline-induced muscle pain compared to matched controls (Sörensen et al. 1998). Interestingly, these manifestations were present in lower limb muscles where the patients typically do not experience ongoing pain. In patients, substantial *proximal* spread of the experimentally-induced referred pain areas was found, in contrast to healthy control subjects who mainly show *distal* referral. Furthermore, extended referred pain areas from the tibialis anterior muscle have been shown in patients suffering from chronic whiplash pain; the extended areas of referred pain were also found in the neck/shoulder region (Johansen et al. 1999). Similarly, in patients with temporomandibular pain disorders enlarged pain areas were found after experimental masseter muscle pain (Svensson et al. 2001). In patients suffering from chronic ostereoarthritic knee pain, extended areas of saline-induced referred pain have been found (Bajaj et al. 2001). This shows that noxious joint input to the central nervous system facilitates the mechanisms of referred pain from muscle, possibly due to plastic changes in the involved neural components. Extended referred pain areas from the tibialis anterior muscle, indicating central sensitization, have also been shown in low back pain patients (O'Neill et al. 2007). Enlarged referred pain areas in pain patients suggest that the efficacy of central processing is increased (central sensitization). Moreover, the expansion of referred pain areas in fibromyalgia patients was partly inhibited by an NMDA receptor antagonist (ketamine). This indicates that the opening of NMDA receptors in the CNS — which is a key component of central sensitization — is one of the mechanisms underlying pain referral (Graven-Nielsen et al. 2000).

5.5 Clinical Pain Referred from Muscle

Usually, muscle refers pain to other deep somatic structures, i.e., muscles, joints, ligaments, and tendons. This is a clear difference from visceral pain which is mainly referred to the skin.

The following considerations and findings will demonstrate that muscles and related deep tissues serve as a common denominator for the expression of nociceptive input from many other tissues.

5.5.1 Referral from Myofascial Trigger Points

Referral of pain is a typical feature of muscle pain, and TrP in muscles are a well-known source of referred pain. The location to which pain is referred from a TrP

in a given muscle is relatively constant; therefore, referred pain patterns could be constructed. However, not all TrP refer pain, and in some cases the referred pain does not follow the published patterns. The more constant patterns of the most commonly involved muscles were published in 1952 by Travell and Rinzler and subsequently presented in more detail for all major muscles (Travell and Simons 1992; Simons et al. 1999; see also Chap. 2 in the companion volume by Mense and Gerwin (2010)). Also from apparently normal muscle, pain can be referred in response to the application of focal pressure. This pain is usually experienced as deep-tissue pain, which includes muscles.

5.5.2 Referral from Other Sensitive Locations in Muscle

Hong et al. (1996) examined muscle sites for referred pain that showed no evidence of being a TrP and were not close to a latent TrP or taut band. Referred pain was elicited by pressure stimulation from 23% of these sites. Muscles with active TrPs appeared to be more sensitive. The corresponding site in muscles with active TrPs produced referred pain from 47% of the sites.

Hong (1996) classified these sites in normal muscle that refer pain as sensitive loci. These sensitive loci seem to be widely distributed throughout the muscle and in the musculotendinous junction. It is a clinical observation that the musculotendinous junctions of muscles harboring active TrPs are tender and produce referred pain when compressed. Likewise, injection of saline in tendon, tendon–bone junction, and muscle in non-TrP all evoked referred pain (Gibson et al. 2006). Therefore, the finding that referred pain can be elicited from a muscle site does not identify that site as a TrP.

5.6 Pain Referred to Muscle

Pain and tenderness can be referred to muscle from joints, other muscles, viscera, and as pain originating in the central nervous system. Therefore, the clinical finding that a muscle is painful does not imply that the source of pain is in that muscle. The muscle in which the pain is felt can often only serve as a starting point for finding the source of the pain, which is really what requires treatment. In many cases of muscle pain the patient's pain complaint is likely to originate elsewhere.

5.6.1 Referral from Joints

In 1938, Kellgren described pain referred from joint capsules when injected with hypertonic saline. McCall et al. (1979) published patterns of deep pain referred from the zygapophyseal joints between L1 and L2 and also between L4 and L5 to the lateral hips and upper thigh. Often, the referred, deep-tissue pain patterns from

cervical zygapophyseal joints overlap with the referred pain from TrPs in muscles crossing those joints (Bogduk and Simons 1993). Symptomatic joints can sometimes also refer pain to muscles at a relative long distance. Another clinical example is the pain referral to the knee from a symptomatic hip. The muscles crossing or acting on involved joints are likely to develop TrPs (Lewit 1991), thus producing a secondary, muscle-induced pain because of the joint problem.

5.6.2 Referral from Viscera

Physicians are aware of the referred chest-wall pain of cardiac infarction (for instance in the pectoralis muscle (Travell and Rinzler 1952)) and the flank pain of renal calculi (Vecciet et al. 1990). Besides spontaneous muscle pain, a visceral lesion can also induce hyperalgesia in skeletal muscle. An example of such a referred hyperalgesia in muscle is the hyperalgesia of the obliquus externus m. in patients with calculi in the upper renal tract (Vecciet et al. 1990). This effect could be mimicked in rats in which a renal calculosis was experimentally induced. The animals exhibited hyperalgesia measured as a lowering in electrical pain threshold in the obliquus ext. m. Interestingly, in both patients and rats there was a correlation between the number of colics and the degree of hyperalgesia; apparently the hyperalgesia became more severe with every colic (Giamberardino et al. 1990). The reason for the referred muscle hyperalgesia in calculosis rats is probably hyperexcitability of dorsal horn neurons induced by the nociceptive input from the viscera (Giamberardino et al. 1996).

5.6.3 Referral from the Central Nervous System

A special type of referred pain is the pain arising within the central nervous system (central pain) that is experienced in deep tissues including muscles. In these cases, the source of pain is a lesion within the CNS and the pain is felt somewhere else. Examples are phantom limb pain (Flor 2008) and central pain experienced as a result of spinal cord injury or lesions of the thalamus. If the central lesion is minimal and causes no other symptoms, muscle pain of this type can be mistaken as pain referred from other peripheral tissues.

5.7 Possible Mechanisms of Pain Referral

5.7.1 General Considerations

In the literature several neuroanatomical and neurophysiological models of referred pain have been suggested. Most models explain why higher brain centers cannot

identify correctly the actual afferent input source. The referred pain models must account for several key characteristics. Referred muscle pain is: (1) a deep sensation felt in a distant structure, (2) delayed in onset compared to the local pain, (3) typically unidirectional in appearance, (4) dependent on the muscle pain intensity, (5) partly dependent on somatosensory afferent input from the referred pain area although it can be induced in anesthetic areas, and (6) facilitated in chronic musculoskeletal pain patients.

As stated in previous chapters, input convergence from various sources is a common wiring principle in the spinal cord. In fact, many dorsal horn neurons with input from muscle nociceptors also receive input from visceral nociceptors. Therefore, the referral concepts developed for visceral pain (convergence-projection theory by Ruch (1949) and convergence-facilitation theory by McKenzie (1909) may also apply to muscle pain. However, there are some differences between these theories and more recent views: (1) muscle pain is rarely referred to the skin, whereas skin referral is common for visceral pain, and (2) the concept of neuronal plasticity — changes in central nervous excitability and wiring by a painful input — was not yet known when the theories were put forward.

A central assumption of all these concepts is that higher central nervous centers are unable to localize the peripheral lesion correctly because the information provided by neurons in lower centers (e.g., in the spinal cord) is equivocal or misleading. The reason for the mislocalization of the pain source is the convergent wiring in the central nervous system so that higher centers cannot identify the actual input source. All recent animal studies on dorsal horn neurons have supported this aspect of the convergence-projection theory by showing that cells driven by nociceptive afferent fibers from muscle (Hoheisel and Mense 1989, 1990; Yu and Mense 1990), joint (Schaible et al. 1987), and viscera (Cervero 1983; Foreman et al. 1984) exhibit an extensive convergence from these sources, often in addition to input from the skin.

A problem for our present understanding of pain referral is that many of the neurons with muscle input have additional receptive fields (RFs) in the skin, but referral of muscle pain (experimental and pathological) to the skin does not seem to occur (Lewis 1942). Apparently, there are convergent neurons that mediate cutaneous pain more or less exclusively, because normally the synapses with the other input sources are not efficient enough to drive the cell to firing threshold. Under pathological circumstances, however, when the input from visceral nociceptors is strong, then these cells can be driven by the visceral input. This process may explain referral to the skin. The problem with this mechanism is that it works only if the input from muscle nociceptors differs basically from that of visceral nociceptors. Otherwise referral of muscle pain to the skin should be common. Admittedly, the nature of these differences is not known.

A basic principle of our current understanding of referred muscle pain is that dorsal horn neurons can change the efficacy of their synaptic connections, depending on the nature of the input (nociceptive vs non-nociceptive, muscle vs skin, etc). Thus the input convergence onto a given neuron is not a constant feature; it may develop under the influence of a peripheral lesion. One has to

imagine that the surface of each neuron is covered by thousands of synapses from various input sources. Some of these synapses are effective (open) and can drive the neuron, others are ineffective and cause just subthreshold potentials in the neuron. The important point is that the subthreshold input can become effective under pathological circumstances. This means that a given neuron can acquire new RFs in the presence of nociceptive input (Hoheisel et al. 1993). Muscle input has long been known to be particularly effective in increasing the excitability of central neurons (Wall and Woolf 1984). Such a stimulus-induced formation of new RFs or changes in existing RFs in animal experiments takes several minutes. This finding speaks against the assumption that the occurrence of new RF is brought about by the use of fixed connections: referral takes time and occurs predominantly if the pain is of high intensity or long duration (see above). A possible interpretation of these data is that the referral of muscle pain reflects the formation of new effective central nervous connections and thus may be another aspect of neuroplasticity (for a review of referral mechanisms, see Mense 1994).

5.7.2 Branching of Primary Afferent Fibers

Branching of primary afferent fibers exists, but its involvement in referral mechanisms is questionable. In animal experiments in which the impulse activity of single primary afferent fibers from muscle was recorded, a few units were encountered that could be activated from two separate areas of the muscle (Mense and Meyer 1985). In the deep tissues of the cat tail, primary afferent units were found that had one RF in deep somatic tissues (muscle, joint, periosteum) and another one in the skin distal to the deep RF (Mense et al. 1981). For the referral of muscle pain, only fibers with long branches supplying different types of tissue (e.g., two different muscles, or muscle and joint) are of importance, i.e., the common branching of sensory fibers close to their peripheral terminal is not relevant in this regard. A hypothetical example of a branched primary afferent fiber supplying two different muscles is shown in Fig. 5.6. The example is hypothetical because such a branching pattern has never been described. Theoretically, the arrangement shown could explain the referral of pain from muscle B to muscle A, if the assumption is made that the dorsal horn neuron mediates pain from muscle A irrespective of from where the neuron is excited. If single fibers with branches supplying two muscles really exist, the referral should be working in both directions (bidirectional referral, see above), i.e., painful stimulation of the region of referral should elicit pain at the initial site of pain.

The sensations elicited by activity in a primary afferent fiber with RFs in two different tissues probably depend on its central connections: if the fiber is connected to neurons mediating nociception from the skin, pain may also be felt in the region of the cutaneous RF when the deep RF is stimulated (Sinclair et al. 1948). However, this mechanism does not explain why muscle pain is not referred to the skin but

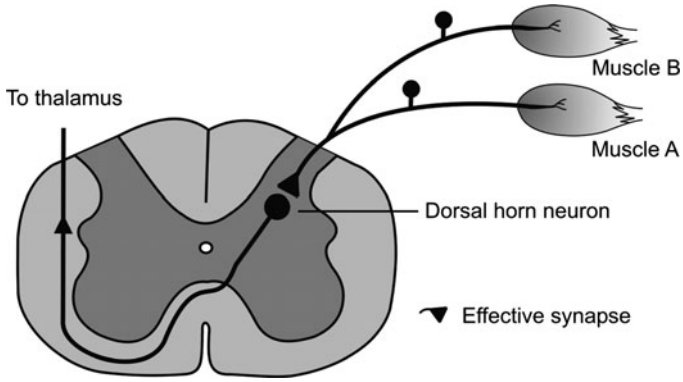

Fig. 5.6 Branched axon theory of pain referral. The figure shows a primary afferent neuron that gives rise to a peripheral axon with two long branches that terminate in nociceptors in muscle A and muscle B. This arrangement could theoretically explain referral of muscle pain from muscle B to A if the assumption is made that the nociceptive dorsal horn neuron mediates pain in muscle A irrespective of from where the neuron is activated. Thus, a noxious stimulus to muscle B could lead to pain perceived in muscle A

to other deep tissues, although practically all neurons with nociceptive input from deep tissues also have convergent connections from the skin. An alternative assumption is that the branched fibers with two RFs are connected to central neurons mediating deep pain, and that referred deep pain is elicited by noxious stimulation of the cutaneous RF. However, everyday experience shows that by pinching of the skin no deep sensations can be evoked. Moreover, the branched axon theory does not explain the delay between lesion and pain referral. Therefore, this assumption has to be discarded.

As early as 1948, Sinclair and colleagues put forward the hypothesis that action potentials originating in the deep RF of a branched fiber antidromically invade its cutaneous branch and release "irritating" substances from this branch via the axon reflex. The irritating substances were assumed to sensitize nociceptors in the vicinity of the antidromically invaded branch. In the light of more recent findings, neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) could play the role of the irritating substances. Both peptides are present in free nerve endings of skin and muscle and are released during neuronal activity. Nowadays, these neuropeptides would be subsumed under the term "inflammatory mediators or substances."

When the deep branch of the branched axon is activated by a noxious stimulus, the resulting sensitization of nociceptors around the branch in the skin may lead to the cutaneous hyperalgesia that often accompanies muscle pain (Sinclair et al. 1948). However, sometimes muscle pain has been described to be associated with cutaneous hypoalgesia, which is not explained by the axon reflex. The axon reflex is likewise not an explanation for pain referred to a completely denervated body region (see above).

The hypothesis of Sinclair and coworkers requires primary afferent units with long branched axons supplying two different deep somatic tissues. There are reports (Devor et al. 1984; Pierau et al. 1984) showing that fibers with long branches are rare (a few percent of all afferent fibers). Referral of muscle pain is such a common phenomenon that it is difficult to imagine that it is based on a few branched primary afferent fibers.

One important central effect of activity in nociceptive afferent fibers with multiple deep RFs is probably to contribute to the diffuse nature of muscle pain, since multiple RFs of primary afferent fibers reduce the spatial resolution of the nociceptive system.

Theoretically, branched axons could be involved in the referral of muscle pain if some branches of the axon are assumed to be unresponsive to external stimuli, but can be made responsive via the axon reflex. This means that the concept of "silent" or "sleeping" nociceptors is adapted to a single branch of a nociceptive primary afferent fiber. Such silent nociceptors have been described in tissues other than muscle (joint, skin, viscera; Grigg et al. 1986; Handwerker et al. 1991; Cervero and Jänig 1992; see Chap. 3). These receptors could not be activated by mechanical stimuli under normal conditions, but in inflamed tissue the endings responded readily to local stimuli, such as pressure stimulation, joint movement, or urinary bladder distension. It is conceivable that originally a nociceptive fiber has only one excitable branch, and when the tissue harboring this branch is inflamed or lesioned the strong afferent activity "awakes the sleeping branch" via the axon reflex. Such a mechanism could explain spontaneous referred pain if the formerly unresponsive ending has acquired resting activity, but it cannot explain cases who present with referred pain only.

5.7.3 Input Convergence on Spinal Neurons as the Basis for the Convergence-Projection and Convergence-Facilitation Theory of Pain Referral

5.7.3.1 The Convergence-Projection Theory by Ruch

As mentioned above, the convergence-projection theory by Ruch (1949) is still the central concept for the explanation of referred pain. The theory states that referral takes place if afferent fibers from two different sources (e.g., viscera and skin) have synaptic contacts with the same dorsal horn neuron. If the neuron is part of pathways mediating cutaneous pain, it will signal this information to higher centers also when it is activated by afferents from viscera. In this situation higher centers cannot identify the actual location of the lesion. Note that, in this case, the mislocalization of visceral pain to the skin is due to the fact that afferent fibers from the viscera are connected a priori to cells mediating cutaneous pain from a body region which is remote from the visceral lesion.

In Fig. 5.7 the theory has been adapted to a situation where pain is referred from a proximal muscle A to a distal muscle B. The dorsal horn neuron has convergent connections from both muscles and, therefore, can be excited by input from both muscles. If the neuron sends its messages into a pathway that mediates pain from the distal muscle B, its activation will elicit pain in the distal muscle irrespective of from where it is excited. Thus, activation of the neuron from nociceptors in the proximal muscle A will elicit pain in the distal muscle B.

Several aspects of referred pain that have been addressed above are not explained by the convergence-projection theory: (1) referral of pain requires a certain minimum intensity of pain at the site of the original lesion, but the spinal circuitry of Ruch's theory suggests that referral should occur as soon as pain is elicited from the original lesion, (2) pain referral takes time (of the order of seconds/minutes), and (3) referral often occurs to regions outside the segment of the original lesion, whereas the theory postulates that input convergence occurs onto a neuron pool in the same segment. The first two points suggest that there is a neuroplastic component in the referral of pain, and the third point indicates that a simple convergence of two afferents within the same spinal segment is not sufficient to explain referral.

As to the main postulate of the theory, there is no doubt that extensive convergence exists at the spinal level. This has been shown in electrophysiological experiments on rat and cat dorsal horn neurons that process convergent input from viscera and skin (Cervero 1983; Giamberardino and Vecchiet 1995) or from various somatic structures (skin, muscle, joint (Schaible et al. 1987; Hoheisel and Mense 1990; Yu and Mense 1990). The convergence expressed itself in the presence of

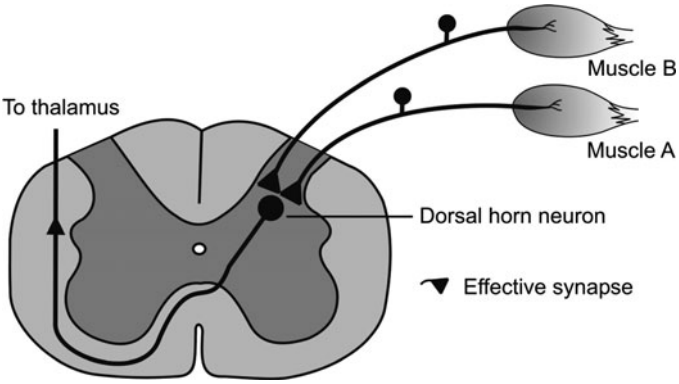

Fig. 5.7 Modified convergence-projection theory of pain referral by Ruch (1949). The theory has been adapted to a situation where pain is referred from a proximal muscle A to a distal muscle B. The dorsal horn neuron has convergent connections from both muscles and, therefore, can be excited by input from both muscles. If the neuron sends its messages into a pathway that mediates pain from the distal muscle B, its activation will elicit pain in the distal muscle irrespective of from where it is excited. Thus, activation of the neuron from nociceptors in the proximal muscle A will elicit pain in the distal muscle B

two or more regions from which a given dorsal horn neuron could be activated. In neurons having one high-threshold mechanosensitive (HTM) RF in deep tissues, the other RF often was similarly HTM and located in the skin. This finding supports the hypothesis that neurons with convergent inputs are involved in cutaneous hyperalgesia accompanying muscle pain if two assumptions are made: (1) the neuron is connected to central pathways mediating cutaneous pain, and (2) there is a continuous impulse traffic from the deep RF which sensitizes the dorsal horn neuron (in the sense of the convergence-facilitation theory of McKenzie (1909; see below). However, frequently the second RF in the skin was low-threshold mechanosensitive (LTM) which does not fit with the above interpretation unless it is assumed that this type of neuron elicits cutaneous hyperesthesia (increased sensitivity to nonpainful stimuli) instead of hyperalgesia (increased sensitivity to painful stimuli).

5.7.3.2 The Convergence-Facilitation Theory by McKenzie

The main statement of the convergence-facilitation theory of pain referral (McKenzie 1909) is that continuous impulse traffic from one peripheral source can enhance the responses of a CNS neuron to the input from a second source. As pointed out in Chap. 4, many anatomically existing (preformed) synaptic connections on dorsal horn neurons are functionally ineffective, i.e., impulse activity arriving in the presynaptic terminal has only a negligible effect on the postsynaptic neuron. One possible explanation for the lack of efficacy is that presynaptic activity causes only subthreshold synaptic potentials in the membrane of the postsynaptic neuron. Subthreshold potentials do not excite the postsynaptic neuron, but may sensitize it. When the nociceptive input is long-lasting or of high frequency the sensitization renders the neuron hyperexcitable, and the formerly ineffective connections become effective.

Neuroanatomical data indicate that the spinal terminations of primary afferent fibers from a muscle can extend over many segments in the spinal cord; for the GS muscle nerve in the cat, branches of primary afferent fibers were found as cranially as the brainstem (Mense and Craig 1988). However, in neurophysiological experiments in which the electrical activity of dorsal horn neurons is recorded, maximal electrical stimulation of the GS muscle nerve excites neurons only within a few segments of the spinal entry zone of that nerve. This finding suggests that most of the spinal branches of a given nerve are ineffective in driving dorsal horn neurons. These functionally ineffective spinal terminations or synapses are probably much more numerous than the effective synapses and extend over a larger distance than the latter. In Fig. 4.16 such an arrangement is depicted.

The ineffective synaptic connections are highly important in central neuroplastic changes during pathophysiological forms of pain, because when they have become effective, completely new connections may form in the CNS. The ineffective connections or synapses are probably the basis of pain referral and for the transition from acute to chronic pain.

The transformation from ineffective to effective connections takes just a few minutes. Experiments employing intracellular recordings from dorsal horn neurons in the rat showed that subthreshold potentials in a dorsal horn neuron can become suprathreshold within 30 min after a nociceptive input from the GS muscle (Hoheisel et al. 2007) or new receptive fields can develop within a few minuets (Hoheisel et al. 1993). Such a change leads to an increase in dorsal horn convergence by a mechanism that is shown in Fig. 5.8. Originally, the afferent fiber from muscle A had effective connections with dorsal horn neuron A only, whereas the afferent from muscle B had effective connections with neuron B and ineffective connections with neuron A. Normally, neuron A will be excited only by afferents from muscle A, and neuron B only by afferents from muscle B. The ineffective connection between muscle B and neuron A will elicit subthreshold synaptic potentials in neuron A. After the synaptic efficacy of the connection between muscle B and neuron A has been enhanced (e.g., by a longer-lasting input from a lesion in muscle B), neuron A can also be excited from muscle B. However, when neuron A is activated by the formerly ineffective afferent from muscle B, neuron A will still send the message "pain in muscle A" to higher centers. Thus, Fig. 5.8 is a dynamic model of pain referral from muscle B to muscle A. The main difference from Ruch's concept is that the pathway of pain referral is ineffective in the

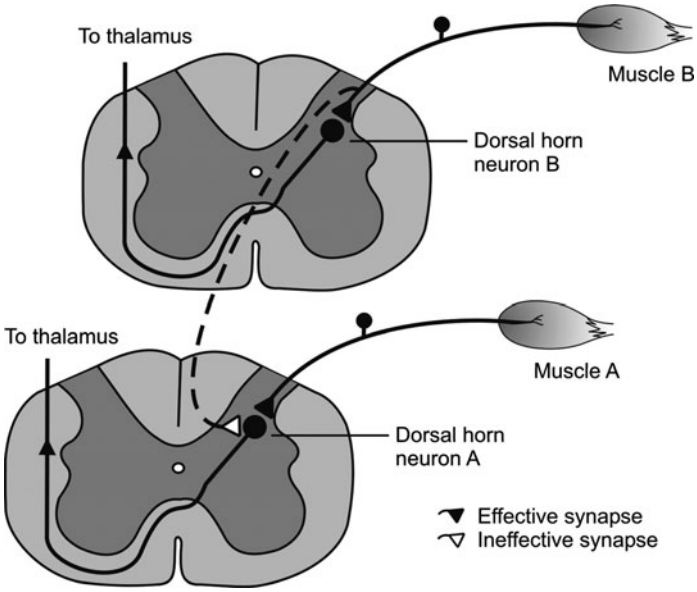

Fig. 5.8 Acute formation of a convergent input by opening a formerly ineffective connection. Muscle A has an effective (suprathreshold) connection with neuron A; muscle B has an effective connection with neuron B and an ineffective (subthreshold) connection with neuron A (*dashed line*). If the ineffective connection becomes effective, neuron A can be excited from both muscles A and B. Thus, painful stimulation of muscle B can elicit referred pain in muscle A (in addition to local pain in muscle B that is mediated by neuron B)

beginning and becomes effective under the influence of a long-lasting and strong painful stimulus. The wiring shown in Fig. 5.8 reflects the convergence-facilitation hypothesis of McKenzie (1909).

In animal experiments in which the activity of single dorsal horn neurons is recorded, the opening of new connections (the transition from ineffective to effective synapses) to a given neuron can be recognized by (1) the formation of new RFs and (2) a lowering in stimulation threshold of preexisting RFs. This situation has been depicted in Fig. 4.13. The opening of a new connection shown in Fig. 5.8. can also be described by saying that neuron A acquired a new RF in muscle B. A likely interpretation of all these findings is that a noxious stimulus somewhere in the periphery leads to widespread changes in the efficacy of synapses and thus in the responsiveness of dorsal horn neurons.

Another factor influencing input convergence and its efficacy is the descending pain modulating system (see Chap. 4; Bouhassira and Danziger 2006). In rat experiments, blocking the system, e.g., by cooling of the spinal cord rostral to the recording site, led to an increase in the number of RFs in dorsal horn neurons and to a change in stimulation threshold of existing RFs (Yu and Mense 1990). These findings demonstrate that many of the synaptic connections in the dorsal horn are not constant in their efficacy but can be changed by various factors. Therefore, one major factor for pain referral may be a dysbalance between descending inhibitory and facilitatory pathways that leads to the opening of formerly ineffective connections in the spinal cord.

The appearance of new RFs adds a dynamic component to the convergence projection theory with a time course similar to that of referred pain in patients. In animal experiments, the majority of the newly formed RFs were located distal to the original ones. As exemplified above, this arrangement could provide an explanation for proximal referral (from the distal new RF a neuron can be excited that mediates pain originating more proximally). To what extent these data obtained in animal experiments reflect referral in humans is not clear, because in healthy subjects, muscle pain is predominantly referred distally (see above). However, proximal referral has also been observed in musculoskeletal pain patients (see above) and in volunteers following electrical stimulation of muscle nerve fascicles (Torebjörk et al. 1984).

In animal experiments in which a longer-lasting experimental muscle inflammation is induced, a phenomenon can be observed that resembles pain referral in that new synaptic connections between peripheral nociceptors and dorsal horn neurons are opened. Systematic mapping of rat dorsal horn neurons responding to electrical stimulation of peripheral nerves showed that in the course of a myositis of the gastrocnemius-soleus (GS) muscle, the population of neurons that could be activated by afferents from that muscle increased in size (Hoheisel et al. 1994). Normally, the input from the GS muscle excites neurons in the segments L4 and L5, and practically no neurons in the segment L3. However, in myositis animals there was a rostral expansion of the myositis-induced excitation in the dorsal horn which now also included neurons in L3. The expansion to the rostrally adjacent

segment demonstrates that the changes in dorsal horn connectivity are not restricted to the spinal segment of the lesion.

In rats with a myositis of the GS muscle, L3 neurons not only responded to electrical stimulation of the GS nerve but also acquired mechanosensitive RFs in the GS muscle. In animals with normal GS muscle, such an input to L3 was completely absent. The spread of the excitability to adjacent neuron populations in the dorsal horn might cause the subjective sensation of spreading or radiating pain. In the myositis model, the increase in neuronal excitability expanded into the rostrally adjacent segment; this finding may relate to the clinical observation that muscle pain is often referred (or spreads) to regions outside the segment of the original lesion. Alternatively, an unbalance between the descending inhibitory and facilitatory control may also be hypothesized to presents as facilitation of the relevant neuronal structures for mediating referred pain.

5.7.4 How can Referred Pain occur Without Simultaneous Local Pain?

As pointed out above, there are patients and experimental subjects who report referred muscle pain without local pain. A possible explanation is that – because of the common occurrence of ineffective (silent) synapses in the CNS – there are regions within a muscle that are connected to dorsal horn neurons solely by ineffective synapses. In this case the assumption has to be made that the effective synapses are located on somatotopically inappropriate neurons, i.e., neurons that normally supply regions remote from the lesioned muscle. If a painful lesion occurs in such a muscle region, there will be no acute pain. However, the ineffective synapses can sensitize the somatotopically inappropriate cells. After the sensitization has occurred, the somatically inappropriate neurons will be excited by the lesion in the muscle. Then referred pain occurs in this remote muscle without local pain in the lesioned muscle.

5.7.5 Possible Mechanisms Underlying Changes in Dorsal Horn Connectivity

Theoretically, an increase in neuronal excitability can be due to disinhibition or facilitation of impulse transmission; both processes can take place pre- or postsynaptically (i.e., either the presynaptic terminal releases more transmitter substances or the excitability of the postsynaptic neuron is increased). The process resembles "heterosynaptic facilitation" (Woolf and Wall 1986) which leads to central sensitization. In short, heterosynaptic facilitation means that the excitability of a neuron is increased by an input that originally did not excite the cell.

One possible mechanism of the observed changes is that anatomically existing but functionally ineffective fiber connections between the spinal neurons and the

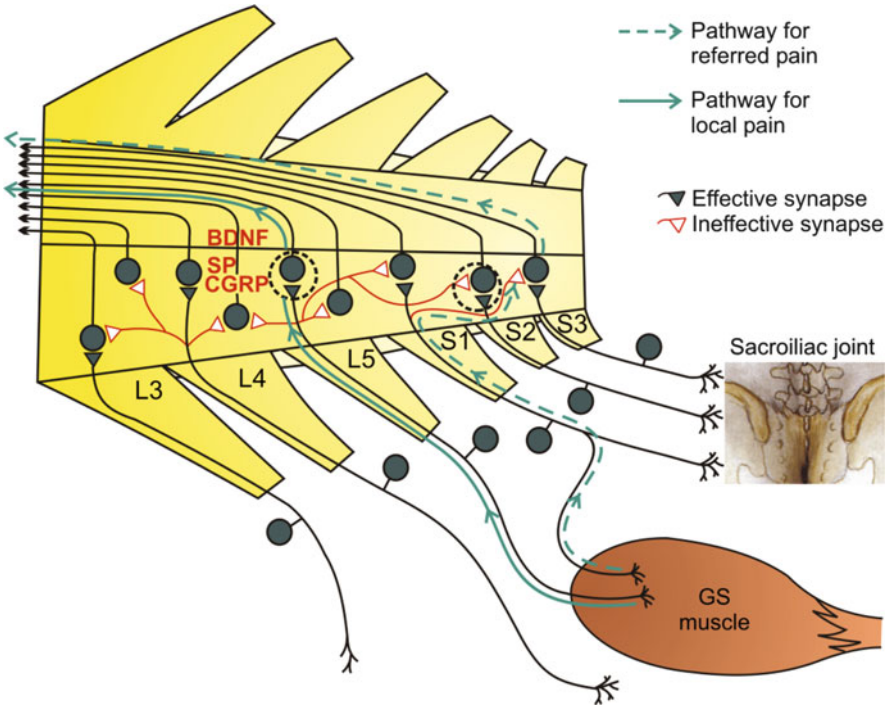

Fig. 5.9 Hypothetical explanation of pain referral by unmasking of synaptic connections. The neuroanatomical model shown may explain referred pain in the sacroiliac joint induced by a lesion in the gastrocnemius-soleus (*GS*) muscle. Such a referral pattern has been described in patients by Travell and Simons (1992). The GS muscle has effective connections (*filled triangles*) to neurons in the segments L5 and S1 in humans. Local pain from the GS is mediated by a pathway that uses these effective connections (*solid green line*). The branches of the afferent fibers from the GS form ineffective (silent) connections with neurons in the segments S2–S3 (*open triangles*). The lesion-induced excitation of nociceptive fibers in the GS, and the resulting activation of microglial cells (not shown), is assumed to release *BDNF* (brain-derived neurotrophic factor), *SP* (substance P) and *CGRP* (calcitonin gene-related peptide) in the dorsal horn. The substances diffuse to the S2 and S3 neurons and increase the efficacy of ineffective connections from the GS muscle to these cells. Now, the S2 and S3 neurons can be activated from the GS muscle (*dashed green lines*). However, the message sent by these neurons to higher nociceptive centers is "pain in the sacroiliac joint"

periphery are opened (unmasked) by the noxious input. Such ineffective fiber collaterals have been demonstrated to exist in a study on mechanosensitive afferents from the skin (Meyers and Snow 1984). In Fig. 5.9, a hypothetical neuroanatomical model is shown which offers an explanation for the observed changes in dorsal horn excitability.

The basic assumption made in Fig. 5.9 is that dorsal horn neurons have two functionally different types of synaptic connections with afferent fibers, namely those with a high synaptic efficacy which are always open (i.e., activity in

presynaptic terminals usually excites the postsynaptic neuron). These connections form the original RF of the neuron. The other connections have a low synaptic efficacy and elicit just small subthreshold potentials in the postsynaptic dorsal horn neuron. For reasons of simplicity, no interneurons have been included in the model; this does not mean that the connections between the ineffective collaterals of the primary afferent fiber and the projecting dorsal horn neuron are monosynaptic.

The model is supposed to explain the referral of pain from a TrP in the GS muscle to the sacroiliac joint in a patient. The wiring demonstrates the necessity of a combination of convergence and divergence to explain the observed effect: the primary afferent fibers originating in the GS muscle and sacroiliac joint show an extensive divergence, i.e., they divide into branches that contact many dorsal horn neurons. On the other hand, the dorsal horn neurons have convergent connections with various primary afferent fibers (mixed ineffective and effective input).

The GS muscle has effective connections with neurons in the segments L5 and S1 in humans. The primary afferent fibers entering these segments also send branches with ineffective synapses to neurons in the segments S2 and S3. These segments normally process information from the sacroiliac joint (under normal conditions the ineffective input from the GS has only a negligible effect on the S2 and S3 neurons). However, if the input from a lesion in the GS is of high frequency or long-lasting, the ineffective connections between the GS afferents and the S2 and S3 neurons can become effective. Now, the nociceptive signals from the GS muscle can excite neurons in the segment S2 and S3. As soon as this happens the patient will feel local pain in the GS (mediated by neurons in L4 and L5) and referred pain in the sacroiliac joint (mediated by neurons in S2 and S3). The referred pain will be felt in the joint because supraspinal centers interpret any activation of the S2 and S3 neurons as pain in the sacroiliac joint independent of how and from where the neurons are excited.

The mechanisms behind the transition from an ineffective to an effective synapse are multifold. In Fig. 5.9, the release of sensitizing or modulatory substances, such as BDNF (brain-derived neurotrophic factor), SP (substance P), and CGRP, from the spinal afferent terminals or glial cells is shown (Li and Zhuo 2001; Bird et al. 2006; Suter et al. 2007). These substances are likely to diffuse to adjacent neuron population (Tobias et al. 2001, Mantyh 2002) and increase the efficacy of synaptic connections. Another possible mechanism has been addressed in Chap. 4, namely the opening of ineffective synapses by subthreshold synaptic potentials. If the nociceptive input from the lesion in the GS is long-lasting, the ineffective synapses on the S2 and S3 neurons probably sensitize the postsynaptic cells. Thus, the formerly subthreshold input may become suprathreshold.

Figure 5.10 shows the application of the hypothetical model of Fig. 5.9 to a clinical case. The patient had a TrP in the soleus muscle, but felt little local pain in that muscle. The main complaint was pain in the sacroiliac joint. In such a case, often pressure on the TrP in the soleus muscle elicits pain in the joint, indicating that the joint pain is referred from the muscle. The putative pathway for the (weak)

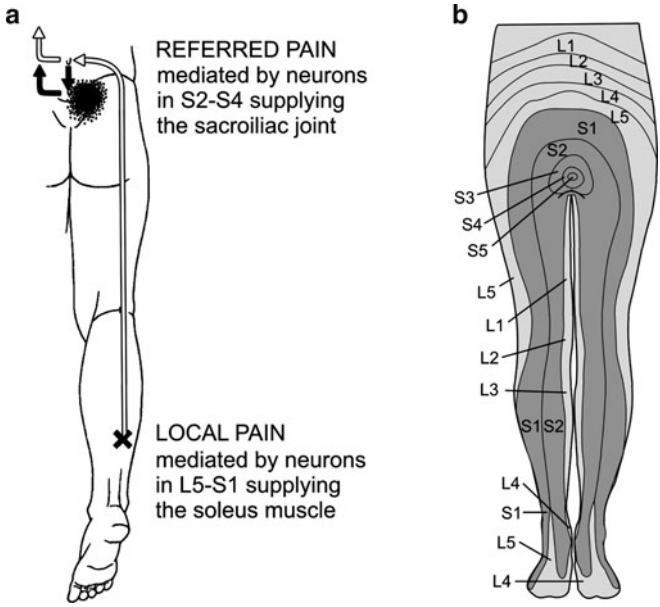

Fig. 5.10 Clinical case of pain referral from a TrP in the soleus muscle to the sacroiliac joint. The patient complained of little pain at the TrP site (local pain) but strong pain in the joint (referred pain). Based on the mechanisms shown in Fig. 5.9, the pain pattern can be explained as follows. **(a)** The local pain at the TrP site is mediated by neurons in the segments L5 and S1, which are somatotopically appropriate for this muscle (i.e., they normally supply that muscle). The nociceptive input from the GS opens the ineffective connections to the neurons in S2–S4. Thus, a second pathway for the referred pain forms, which uses the (somatotopically inappropriate) neurons in S2–S4 (case adopted from Travell and Simons (1992)). **(b)** The panel shows the dermatomes on the back of the leg. Note that, for instance, the receptive fields of neurons in segments S1 and S2 are distributed over the entire length of the leg. In other words: neurons supplying the skin of the calf and sacral region lie in adjacent segments in the spinal cord. Myotomes show a similar segmental arrangement, but such detailed maps are not available

local pain in the TrP region is mediated by neurons in the segments L5 and S1 that normally supply the soleus muscle (Fig. 5.10a). If the nociceptive input from the TrP — which was apparently mainly subthreshold in this case because there was only little local pain in the soleus muscle — is long-lasting, the lesion-induced excitation in the spinal cord spreads and reaches neurons in the sacral cord (S2–S4) that mediate pain in the sacroiliac joint. Viewed like this the long distance between the location of the TrP and the site of the referred pain is no longer enigmatic: the neuron populations supplying the soleus muscle and the sacroiliac joint lie in adjacent segments in the spinal cord. Therefore, a spread of excitation from the segments L5/S1 to S2/S4 is easy to imagine. The proximo-distal distance between local and referred pain on the dorsal surface of the leg is great because in this body region the dermatomes and myotomes are extended in the proximo-distal direction (Fig. 5.10b).

This clinical observation is compatible with the assumption that at the level of the spinal cord the nociceptive information from muscle is fed into somatotopically inappropriate pathways. Similar changes in connectivity have also been described to occur in the thalamus and cortex (Guilbaud 1991), where the subjective (mis) localization of the pain is probably made.

5.7.6 Referred Pain versus Head Zones

An evident manifestation of referred pain is seen in visceral pain conditions, where pain is often felt in structures remote from the affected visceral organs. Classic examples are cases of angina pectoris where pain is felt in the left arm (Procacci et al. 1999), and appendicitis that refers pain to the right lower abdominal quadrant (Stawowy et al. 2002). Muscle pain is often referred across the borders of spinal segments, and therefore differs from the Head zones of the skin which are typically present in the segment of the visceral lesion. The underlying mechanisms are also different: Head zones are assumed to be caused by a pre-existing convergence of cutaneous and visceral afferents on the same dorsal horn neurons. Such an arrangement can function in two ways. Firstly, if both synaptic connections are equally effective and the visceral afferent fibers are normally silent, the neuron is exclusively excited by cutaneous nociceptors. In the presence of a painful visceral lesion the neuron will likewise mediate cutaneous pain, because higher centers interpret

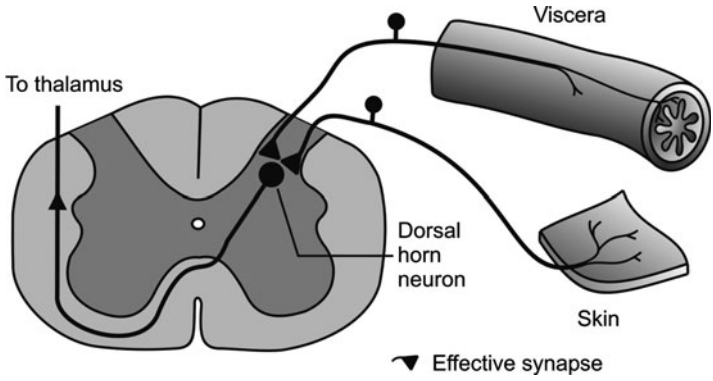

Fig. 5.11 Putative mechanism for the formation of Head zones. A dorsal horn neuron has convergent nociceptive input from both viscera and skin. The neuron is assumed to mediate sensations from the skin (the connection to the viscera is silent under normal conditions). If there is a lesion in the viscera, the visceral nociceptors excite the neuron. The result is subjective pain in the skin, because the higher centers interpret all signals from the neuron as originating in the skin. Note that (in contrast to the convergence-facilitation theory) no neuroplastic change in the spinal cord is required for the formation of Head zones, and that the zones are always in the spinal segment that supplies the painful viscera. Referral to structures supplied by other segments is not explained by this model

all information coming from that neuron as originating in the skin (Fig. 5.11). Secondly, if the connection to the viscera is synaptically less effective than that to the skin, the lesion-induced input from the viscera may render the neuron hyper-excitable, so that it reacts stronger to input from the skin in the same segment. This latter mechanism is in essence the "convergence-facilitation theory" by McKenzie (1909) described above (cf. Fig. 5.8). Since the convergent wiring is assumed to be present on the same neuron, the Head zone is usually located in that dermatome which belongs to the spinal segment that supplies the painful viscera.

In contrast, referral of pain in the sense of this chapter is not due to a pre-existing and effective convergent input from two sources on the same neurons but to neuroplastic changes in the spinal dorsal horn (opening of ineffective or silent synapses which lead to a spread of excitation in the spinal cord as discussed in Chap. 4 (Hoheisel et al. 1994; cf. Figs. 4.15 and 5.9)). If Head zones were really due to neuroplastic central changes it is hard to understand why they do not cross segmental borders but always occur in the segment that supplies the painful viscera.

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Chapter 6
Increased Muscle Tone as a Cause of Muscle Pain

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Abstract The traditional concept that *reflex tone* is the underlying mechanism for tension of a resting muscle is outdated. Sources of muscle tension include mechanisms that are silent in the electromyogram (EMG) (i.e., viscoelastic tone and contracture in the physiological sense) as well as those contractile activities accompanied by EMG signals (voluntary and involuntary contractions, spasm, cramp). Usually, muscle tone is clinically measured as resistance to passive elongation via joint movements. In normal cases at full relaxation, it mainly reflects viscoelastic tone, but may also include extraneous contractile activity. Thixotropy of muscle reflects a decrease of its viscosity and lowered passive resistance by movement. It is a ubiquitous and functionally important phenomenon that is not commonly recognized. Muscle spasm is defined in this chapter as involuntary and long-lasting muscle contraction. It is distinct from spasticity caused by a CNS lesion. The pain–spasm–pain cycle, which is often assumed to be responsible for chronic muscle pain, is a physiologically untenable concept. Tension-type headache (TTH) is a clinical pain condition that can be associated with increased muscle tension in some patients and without evident EMG activity. TTH may also be caused by myofascial trigger points (TrPs). Painful muscle spasm is present in cases of spasmodic torticollis, trismus, nocturnal leg cramps, and stiff-man (preferably, "stiff-person") syndrome.

6.1 Nature of Muscle Tone

Traditionally, muscle tone was attributed to contractions of a small number of motor units in each muscle. The motor unit is all of those muscle cells that are innervated by a single α-motor neuron. The contractions were assumed to be maintained by the activity of muscle spindle afferents that have monosynaptic connections with α-motor neurons, as depicted in Fig. 6.1. The pathway is the same as that for the stretch reflex, and the muscle tone was called *reflex tone* (Sherrington 1915; Davidoff 1992). This type of reflex muscle tone was assumed to be particularly important for antigravity muscles that maintain the erect posture of the body. Discharges in muscle spindles are dependent on the activity of γ-motor neurons, which are influenced by descending (mainly extrapyramidal) motor pathways. Accordingly, the commonly observed increases in muscle tone in stressful situations could be explained by assuming that psychological stressors activated the descending motor pathways.

The original concept of reflex tone posed several inconsistencies. Later, other concepts were offered as an explanation for the resting muscle tone, for instance, the passive elastic properties of muscle tissue (Clemmesen 1951). Nowadays, the

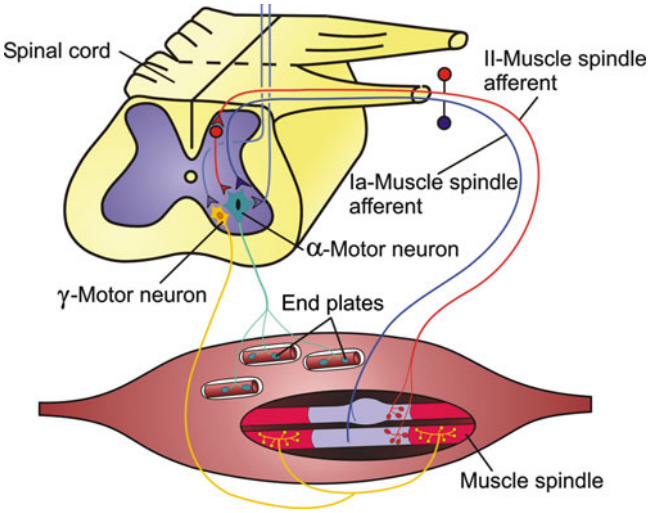

Fig. 6.1 Wiring diagram of the (outdated) reflex tone concept. The continuous afferent input from muscle spindles is assumed to excite a subpopulation of α-motor neurons that cause a contraction of a small number of motor units in each muscle. The afferent arc of the reflex is correct, because the Ia afferents from muscle spindles are known to be tonically active and have monosynaptic connections with α-motor neurons. However, the synaptic connection is not effective enough to drive the motor neuron to firing threshold; it just increases the excitability of the neuron (see Fig. 6.8). A completely relaxed muscle is silent in the surface EMG; this proves that no α-motor neurons or end plates are active

concepts of reflex tone and passive elastic tension should be properly differentiated for the following reasons. First, the reflex tone concept was derived from experiments on decerebrated animals which had markedly exaggerated stretch reflexes. Second, it is well known that in a completely relaxed muscle there is no EMG activity. The latter point is the decisive one, since any α-motor neuron activity and the resulting contraction of motor units should be visible in the EMG if they do occur.

6.2 Components of Muscle Tone

Muscle tone is clinically determined by the resistance of a limb to passive joint movements. It is often overlooked that the muscle tone measured in this way may include two main components: the passive viscoelastic properties of the muscle and soft tissues associated with the muscle (e.g., connective tissue in and around the muscle) and/or any extraneous activation of the contractile apparatus of the muscle.

EMG recordings identify only the electrogenic activity of the motor nerve and the excitation contraction of the muscle cell. In contrast, the viscoelastic tone of myofascial tissue as well as *contractures* (greater overlap of the contractile

apparatus) of the contractile apparatus are not visible in the needle or surface EMG, because both occur without electrical activity of the muscle cell.

The sources of the viscoelastic tone are still largely enigmatic, but are attributed mainly to myosin head cross-bridges to actin filaments and other molecular reactions in the muscle cell (Masi and Hannon 2008). Moreover, the viscoelastic properties of muscle tissue are not constant, but are dependent upon previous movements. These movement-dependent changes of the viscoelastic tone are called thixotropy.

In Fig. 6.2, the viscoelastic tone is presented as a separate entity that is independent of contractile activity. The viscoelastic tone can be present without any contractile activity. However, the contrary is not possible: all active movements are influenced by the viscoelastic properties of muscle tissue. Contractile activity may occur in two different active forms:

1. *Electrogenic contraction*, i.e., muscle tension resulting from electrogenic muscle contraction, either voluntary or extraneous in persons who are not completely relaxed. The term electrogenic refers to the fact that the α-motor neurons and the neuromuscular junction are active under these conditions. Therefore, EMG activity is present.

2. *Electrogenic spasm*, which can be defined as pathological involuntary electrogenic contraction of long duration. Spasm in this sense is also always accompanied by EMG activity.

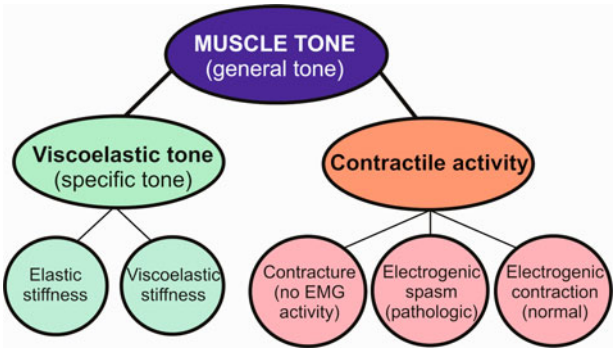

Fig. 6.2 Components of muscle tone. The muscle tone as determined in the clinic by moving joints (the general tone) includes both the viscoelastic tone and possible contractile activity, depending upon the degree of relaxation or reflex muscle activation. The viscoelastic tone is the specific intrinsic tone of a resting muscle. It has two components, elastic and viscoelastic stiffness. Stiffness is generally defined as the resistance of an elastic body to deformation by an applied force (force applied per distance moved). The elastic stiffness can be determined in isolation by moving a joint slowly so that the viscosity of the soft tissues around the joint does not come into play. Contractile activity can occur as electrogenic involuntary spasm or incidental contractions. Electrogenic means that the contraction is elicited by action potentials of the muscle cell membrane, and is therefore associated with EMG activity. Contracture as used in this figure is a pathologic state of muscle, and may cause the sliding-shortening of actin and myosin filaments without electrical activity of the muscle; it therefore lacks EMG activity. Electrogenic spasm is always pathologic, and can be painful or not. Electrogenic contraction includes the normal voluntary activity of a muscle, as well as involuntary contraction of muscles that are not completely relaxed

Contracture is another form of increased resistance to elongation arising endogenously within the muscle fibers without activity in α-motor neurons. These are physical shortenings or contractures in the pathological sense. Thus, contractures of the contractile apparatus are not associated with EMG activity.

For a better understanding of the following sections, some definitions related to muscle tone are given below:

6.2.1 Definitions Related to Muscle Tone

Elastic Stiffness (physics definition): "in an elastic system: the steady force required to produce unit displacement" (Thewlis 1979).

This definition excludes rate of movement as a factor and corresponds to the physics definition of elasticity, which is the resistance encountered by moving something a certain distance (resistance due to *rate* of movement includes *viscous* properties).

Elasticity: "the property whereby a body, when deformed by an applied load, recovers its previous configuration when the load is removed. According to Hooke's law the stress (applied force) is proportional to the strain (resulting movement) within the elastic limit" (Thewlis 1979).

Again, velocity is not a consideration. Elastic stiffness and elasticity are best reflected by the behavior of an ideal spring.

Mechanical Impedance is the resistance to motion produced by the interaction of elasticity, momentum, and viscosity, and concerns rate of movement. To a physicist, it is "the ratio of the (complex) force acting on a given mechanical device to the resulting linear velocity in the direction of the force (Thewlis 1979)." This linear form of the definition can be converted to the rotational form. Then, the force is applied as torque (Walsh 1992). Systems that have impedance show the characteristic of resonance.

Resonance of an oscillatory system is "the marked increase in the amplitude of oscillation . . . when the system is subjected to an impressed (imposed) frequency that is the same (or very close to) the natural frequency of the system (Thewlis 1979)." Resonance occurs at the frequency where resistance to movement is minimal. In mechanical systems, resonance also occurs at the frequency where elasticity balances momentum and the only resistance to motion results from viscosity. At resonance, the effect of inertia balances the effect of elastic stiffness and there is minimum resistance to movement of a muscle (provided only by the damping effect of viscosity). Resistance to motion in a resonant system is considered viscoelastic stiffness. Small changes in viscoelastic stiffness sensitively affect resonant frequency.

Stiffness (the term is used in two definitions): something that is stiff is (1) "not easily bent, rigid, inflexible" and (2) "firmer than liquid in consistency, thick or viscous" (Collins English Dictionary 1991). The first definition concerns simple displacement or deformation and is measured as elasticity. The second definition

is measured as resistance to rate of movement and corresponds to viscoelastic stiffness.

Viscosity is the "resistance to fluid flow, set up by shear stresses within the flowing liquid" (Thewlis 1979).

Thixotropy is a "property shown by many gels of liquefying on being shaken and of reforming on standing (Thewlis 1979)." This decrease of resistance to movement can also occur in response to stirring. Examples are nondrip paints that are less viscous when they are spread with the brush, but become highly viscous — and therefore do not drip — when they are not touched.

Tone (specific, cf. Fig. 6.2): measured as elastic or viscoelastic stiffness in the absence of muscle contractile activity.

Tone (general clinical): measured as elastic or viscoelastic stiffness including any involuntary extraneous muscle contractile activity.

Measurement of overall muscle stiffness includes both major components of muscle tension: viscoelastic tone and contractile activity. Presence of EMG activity identifies the contribution of electrogenic contractions. Muscle *contracture* is more difficult to measure separately, but is a possible component of muscle stiffness. It is important to note that these measurements of myofascial stiffness include the effect not only of the muscle cells, but also of the soft tissues surrounding them.

The physics definition of the above-mentioned types of stiffness must be distinguished from the subjective discomfort associated with movement, which is often symptomatically described as stiffness. An example is the morning "stiffness" felt by patients with rheumatoid arthritis. This symptomatic stiffness is not accompanied by changes in measurable stiffness (Helliwell et al. 1988; Walsh et al. 1989).

From these considerations, the following *definition of muscle tone* can be derived: resting muscle tone (in the specific sense) is the elastic and/or viscoelastic stiffness in the absence of contractile activity (motor unit activity and/or contracture) (Simons and Mense 1998; Masi and Hannon 2008).

6.2.2 Viscoelastic Tone

In clinical practice, muscle tone is usually measured as stiffness, which is the resistance to passive movement. There are two kinds of stiffness that can be measured, namely elastic and viscoelastic. Elastic stiffness is measured in terms of the perceived resistance (tension) to slow passive elongation over the distance moved in order to minimize viscous effects and avoid involuntary reflex contractions. With this technique, the elastic properties of the muscle are estimated, as if the stiffness were caused only by an ideal spring effect. Elastic stiffness of a body segment excludes electrogenic contractile activity, which is identified by EMG monitoring. The presence or absence of EMG activity is fundamentally important to what is being measured and defined.

In contrast, viscoelastic stiffness considers the effect of the speed of movement. Measurements of stiffness that include velocity are more complicated and include

both viscous and elastic components of viscoelasticity. Clinically, the examination will also incorporate inertial (weight) effects. The specific tone as defined and used in this book applies only to viscoelastic tension in the absence of muscle contractile activity. Therefore, when using the terms tone and stiffness, information about the absence or presence of EMG activity should be added.

The origin of muscle tone not dependent on motor unit activity remains largely unknown, and little information is available on this topic in the literature. A model for the frog muscle has been proposed by Campbell and Lakie (1998). They suggested that in resting and relaxed muscle, a small number of cross-bridges between myosin heads and actin filaments are slowly cycling and thus generate tensile force. These cycling cross-bridges may be measurable as viscoelastic tone. They also exhibit thixotropic behavior. This cross-bridge mechanism is independent of electrical activity; therefore, it is clearly distinct from the old concept of reflex tone. The cross-bridge model is still the most widely accepted explanation for thixotropy of muscles (Hagbarth et al. 1985; Walsh 1992). Friction between layers of tissue is likewise being discussed as a possible reason for muscle viscoelasticity by some. However, changes in the viscosity of the sarcoplasm of muscle cells and properties of the titin filaments have been reported to be of greater importance (Mutungi and Ranatunga 1996; Minajeva et al. 2001; Di Cola et al. 2005).

6.2.2.1 Measurements of Muscle Tone

Pendulum Test (Wartenberg 1951). The test is performed with the patient sitting on the edge of a table and the relaxed legs hanging over the edge (Fig. 6.3a). The examiner lifts both legs to the horizontal position (knees straight) and then releases them, observing their movement as they swing freely. The test is still being used clinically, e.g., for assessing the passive stiffness and viscosity in patients (Valle et al. 2006). Normally, a leg swings in smoothly decreasing sinusoidal arcs (Fig. 6.3b). Figure 6.3c shows the over-reactive reflex stretch responses of spastic muscles. The spasticity reduces the number and smoothness of the oscillations and may stop the first swing before it can complete its initial downward phase. In muscular hypotonia (Fig. 6.3d) the decreasing oscillations continue for a prolonged period of time.

The pendulum test has the advantage of simplicity, but it also has several disadvantages or sources of errors:

1. The test provides only one source of force (gravity).
2. Its application is largely restricted to a few muscles around the knee.
3. The mass of the lower leg is variable among subjects.
4. When performed in the usual clinical setting the evaluation is done by simple inspection which is a subjective method and does not detect slight deviations from normal.

Instrumented forms of the test are objective and more quantitative, but are mostly reserved for scientific purposes. Recently, attempts have been made to use a

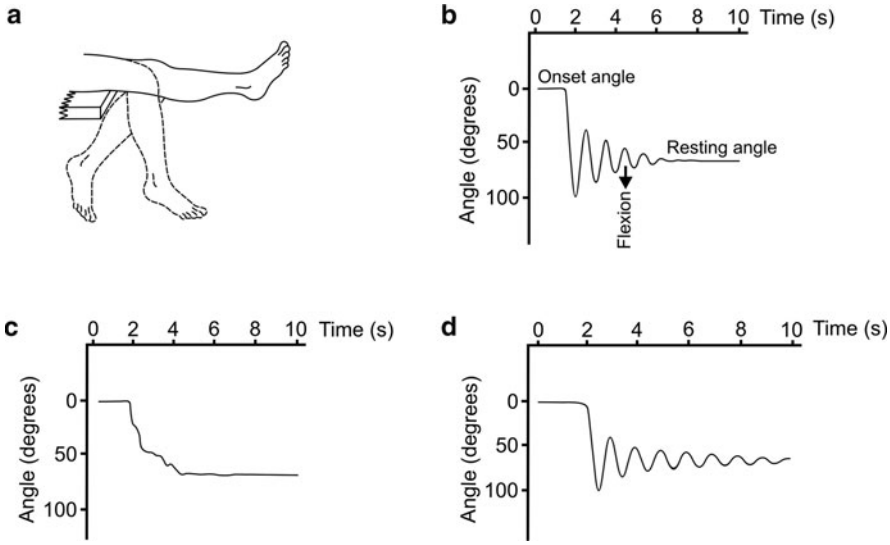

Fig. 6.3 Measurement of muscle tone with the pendulum (Wartenberg) test. (**a**) Shows how the test is performed. The patient sits on the edge of a table with the knees straight. When the lower leg is dropped it swings back and forth, as shown in (**b**) (normal oscillatory movements). (**c**) Reduced oscillations in a patient with Parkinson's disease. (**d**) Prolonged oscillations characteristic of hypotonic or atrophic muscles (e.g., shortly after a stroke). The onset angle of the straight knee is set at zero

modified pendulum test to measure objectively the degree of spasticity at the elbow in stroke patients (Lin et al. 2003).

Compliance: compliance (hardness) can be measured with a simple hand-held compliance meter (Fischer 1987). By pressing on the muscle, the device provides quantitative information about the stiffness of the tissue. However, the results are ambiguous in that they represent a combination of skin, subcutaneous, and muscle compliance. The device can be useful when closely comparative measurements are made, e.g., bilaterally or repeatedly at the same site. A number of more recent computerized devices have been reported (Sakai et al. 1995; Leonard et al. 2003; Arokoski et al. 2005; Ylinen et al. 2006).

Motor-driven compliance meters are more complicated, but offer a much wider range of test conditions and more sophisticated analysis. Such devices can be used to obtain information on additional measures, namely viscosity, damping, resonant frequency, and thixotropy (Viir et al. 2006; Gavronski et al. 2007).

Resonant frequency: muscle can be viewed as an oscillatory system with a given mass (inertia), damping (viscosity), and elastic stiffness. Like all oscillating systems, muscle has a resonant frequency. Resonance occurs at that speed of oscillations where the potential energy stored by the elastic component (maximum at the end of a swing) exactly matches the kinetic energy supplied by the mass component (maximum in the middle of a swing) as they trade energy back and forth. For example, a violin string produces a tone at its resonant frequency, which is tuned by

changing its tension (elastic stiffness). By measuring changes in resonant frequency of a limb or muscle group, relatively small changes in the viscoelastic stiffness of that limb can be detected, the only condition being that EMG activity is absent.

The principle of measuring the resonant frequency of the soft tissues of a limb segment was developed and described in detail by Walsh and colleagues (Walsh 1992), and is shown in Fig. 6.4. The forearm muscles provide elastic stiffness, which corresponds to the elastic part of the viscoelastic component of resistance to movement. The mass of the forearm tissues corresponds to the inertia. The viscous part of the viscoelastic component of the muscles corresponds to the damping of the system. The printed circuit motor applies small amounts of constant-amplitude sinusoidal torque to the hand and the wrist joint, and drives the system at progressively faster frequencies. The motor provides precise control of the force input and rate of oscillation, while the resultant amplitude and acceleration of hand movement is measured by the potentiometer. The EMG electrodes monitor the electrical activity of the forearm muscles to confirm there was no electrogenic contractile component involved in the movement of the forearm muscles.

At slower and faster speeds than resonance frequency, the mechanical impedance to the applied torques increases. In physics terms, impedance is the ratio of the force applied to a point of a structure in relation to the resulting velocity at that point, or, more generally, the mechanical resistance to dynamic forces. At slower speeds, the effect of mass has increasing importance (the mass has to be accelerated at the beginning of each swing). At speeds faster than resonance, the mechanical impedance increases because of increasing importance of the effect of

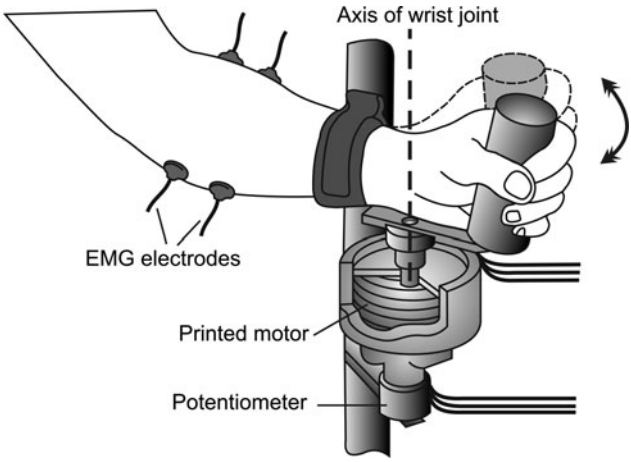

Fig. 6.4 Measurement of resistance to movement and thixotropy of muscle. The wrist is moved by a printed circuit motor shown in cut-away form. Its shaft is aligned with the axis of rotation at the wrist. The forearm is mechanically stabilized to permit precise measurement of hand motion. The printed circuit motor exerts predetermined amounts of torque to the hand and the resulting movement (displacement) at the wrist is recorded by a potentiometer. The induced oscillatory movements have small amplitudes to avoid reflex contractions of the forearm muscles. EMG surface electrodes are used to record any reflex activity that might occur. Modified after Walsh (1992)

viscoelasticity. At resonance, the natural oscillations and the applied sinusoidal torques are in harmony. Then, all of the mechanical impedance comes from viscosity. At this frequency, the mechanical impedance is low, meaning less applied force is needed to cause a structure to move at a given velocity.

The measurements by Walsh and colleagues (Walsh 1992) demonstrated that fully relaxed forearm muscles tested with the above device had a resonant frequency of few Hz (cycles/s). The excursions of the hand were greatest at this resonant frequency and at a given torque, amplitude, and velocity. Another result was that the resonant frequency increased with increasing stiffness of the system. The stiffness was increased simply by voluntary contraction of the forearm muscles.

At resonant frequency, the energy required for moving an oscillating system is minimal. Therefore, birds use their wings at resonant frequency and thus save energy. Wings of smaller mass have a higher resonant frequency; therefore, small birds strike their wings at a higher frequency.

Thixotropy: in addition to muscle, several other materials, such as paint, tomato ketchup, and human blood show the property of thixotropy. Thixotropic substances have a high viscosity when unperturbed that resists first stirring or movement when poured. After initial movement, their viscosity decreases, often precipitously. The resistance to movement depends strongly on the preceding history of movement. The device described above for measuring resonant frequency can be used to also measure the marked thixotropic property of human muscle (Fig. 6.5). At the beginning of the recording (time 1 in upper trace of Fig. 6.5a), the two cycles of increased applied sinusoidal torque immediately caused larger sinusoidal displacements (lower trace of Fig. 6.5a) at the wrist joint. The relation between applied torque and amplitude of the displacement at the wrist is a measure of the viscoelastic stiffness of the forearm muscles. The larger movements persisted after the torque had been adjusted to its original lower level (before time 1 in Fig. 6.5a). The greater amplitude is an indication of a reduction in the resistance to movement of the forearm muscles, i.e., a reduction of viscosity. The reduced viscoelastic stiffness persisted as long as motion persisted. However, when the movements were discontinued for 1 s, the stiffness returned to its previous state. The original stiffness returned very quickly, sometimes within one or a few seconds as in Fig. 6.5, but sometimes it could take much longer, e.g., 2 or 3 min (Hagbarth et al. 1985). During these changes in viscoelastic stiffness, no EMG activity was present, and neuromuscular blocking drugs failed to affect the thixotropic effect (Walsh 1992).

The thixotropic changes observed by Lakie et al. (1984) in forearm muscles appear to be a general phenomenon of all muscles. Hagbarth et al. (1985) observed similar effects in the extensor muscles that move the metacarpophalangeal joint of the index finger. In these experiments, voluntary contraction of the antagonistic flexors produced a reduction in extensor muscle stiffness similar to passive extension of the finger. This suggests that the viscoelastic stiffness of a muscle can be reduced not only by passive or contractile activity of that muscle, but also by contraction of an antagonistic muscle or muscle group.

The movement-dependent changes in viscoelastic stiffness are underestimated or ignored by most examiners, although they are of utmost importance for the

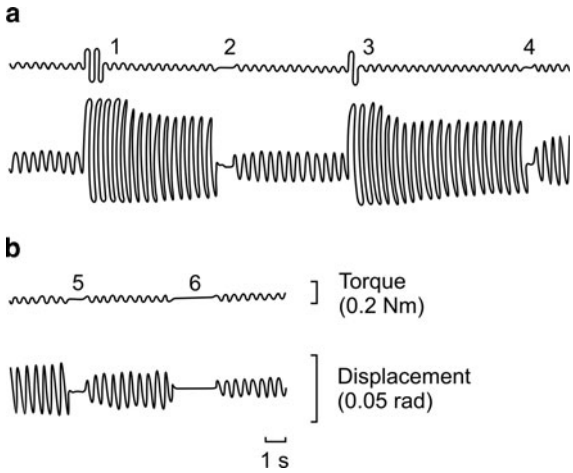

Fig. 6.5 Effect of muscle thixotropy measured with the apparatus shown in Fig. 6.4. The force (torque) applied to the wrist is recorded in the upper trace of (**a**) and (**b**), the wrist movement (displacement) in the lower trace. The relationship between torque and displacement at the beginning of (**a**) is a measure of the initial viscoelastic stiffness of the forearm muscles. At time 1, two cycles of increased torque were applied. As expected, this resulted in larger displacements. However, the larger displacements persisted after return of the torque to its original level, indicating a reduced resistance to movement by the preceding movements. An interruption of passive wrist motion for 1 s at time 2 restored the stiffness to its original level. At time 3 in (**a**), just one cycle of increased torque was applied, and the muscle responded with a decrease in stiffness similar to that at time 1. A very brief, two-cycle interruption of movement at time 4 failed to fully return the musculature to its preceding state of stiffness. When the duration of the movement interruption lasted longer (times 5 and 6), the stiffness progressively returned to the original level. The temporary decrease of muscle stiffness in response to a brief increase in its activity is an example of thixotropy. The data demonstrate that muscle stiffness greatly depends on the movement history of the muscle. Torque is measured in Newton meters (*Nm*), displacement in radians (*rad*), and time in seconds (*s*). Modified after Walsh (1992)

normal functioning of a muscle. For instance, after 10 min of rest, a threefold increase in the thixotropic stiffening has been found that continued to increase at a declining rate up to 30 h later (Lakie and Robson 1988). These data show that thixotropic time constants can cover a considerable range.

The extent to which factors such as age, gender, fatigue, pain, and psychological status might influence thixotropy of human muscle is unexplored.

The practical importance of thixotropy for muscle function is generally underestimated. The well-known practice of athletes to warm up prior to exercise is a direct application of the principle of reducing muscle viscosity by movement. On the other hand, the high viscoelasticity of a resting muscle (e.g., of the erector spinae or triceps surae) can help in keeping an erect posture without unnecessary muscle contractile activity (Masi and Hannon 2008). In this situation, the passive property of muscle thixotropy helps to provide stability in balanced postures to save active metabolic energy.

Moreover, the thixotropic properties of a muscle are essential for assessing the position of a limb. Temperature influences thixotropy, therefore the position sense is impaired in a cool environment. This may be one reason for the poor motor performance of cold muscles (Sekihara et al. 2007).

6.3 Clinical Applications

6.3.1 Stiffness Based on Resonant Frequency

Patients with rheumatoid arthritis have long been known to experience subjective morning stiffness. Attempts have been made to measure increased resistance to passive motion, possibly associated with the subjective sensation, but the studies gave conflicting results with measurements at the metacarpophalangeal joint (Wright and Johns 1960; Yung et al. 1986; Johnson 1989).

Measurements of resonant frequency at the wrist of patients with rheumatoid arthritis, all of whom had early morning stiffness (Walsh et al. 1989), demonstrated that the patients had lower resonant frequencies than controls. This means that — contrary to expectations — the viscoelastic stiffness of their forearm muscles was smaller and not larger compared to controls. However, results were not controlled for mass of forearm muscles. According to the available data, the morning stiffness of rheumatoid arthritis cannot be verified in objective measurements (Helliwell et al. 1988), and therefore appears to have a major subjective component.

As to possible mechanisms of the common symptom of stiffness of old age following periods of fixed postures (e.g., when working at a computer keyboard), some data are available. Measurements of chemically skinned muscle fibers in vitro showed that the stiffness of muscle fibers from older men exhibited increased instantaneous stiffness compared with younger men (Ochala et al. 2007). To what extent these changes might contribute to the subjective sensation of muscle stiffness, however, is unknown.

An interesting field for stiffness research would be the perceived loss of muscle tone as one falls asleep. The question of whether this loss of tone is an example of central nervous influence on viscoelastic stiffness or due to other components could be answered with a combination of EMG monitoring and measurement of the viscoelastic muscle tone. Of course, a major problem would be to make the latter measurements without awakening the subjects.

6.3.2 Thixotropy

From the work of Basmajian and Deluca (1985), it is known that we can stand erect without sustained postural muscle EMG activity. Only small correctional

movements of the erector spinae muscle or upper extremities are necessary to retain balance in equilibrium postures. However, the muscle stiffness decreases immediately when the muscle is moved. Such decreased stiffness then helps further use of the muscle with little extra energy expenditure.

Acute and chronic muscle pain is associated with changes in muscle stiffness (see Chap. 7). In most cases, these changes are probably due to reflex activity. However, the possibility that the changed stiffness is related to altered resting muscle tone or to thixotropic phenomena cannot be discarded at present (Masi and Hannon 2008). Interestingly, changes in thixotropy of the levator palpebrae muscle have been reported to be responsible for the lagophthalmos (incomplete closure of the eyelid) of patients after peripheral facial nerve palsy (Aramideh et al. 2002). In their study, the hypothesis was tested that the lagophthalmos was due to an increased formation of cross-bridges between the actin and myosin filaments, causing increased stiffness of the levator palpebrae muscle, rather than to paralysis of the orbicularis oculi muscle. The results supported the hypothesis that thixotropic behavior of the levator muscle contributes to the lagophthalmos of the patients.

6.3.3 Clinically Relevant Deviations and Normal Muscle Tone

6.3.3.1 Hypotonia (synonym hypotonicity)

Interesting examples of congenital hypotonia are the so-called "floppy" infants. This term describes an abnormally diminished viscoelastic stiffness marked by a decreased resistance to passive stretching that occurs for unknown reasons. A lack of basic activity in α-motor neuron is being discussed by some.

Patients with cerebellar disorders (Ghez and Thach 2000) or the Joubert syndrome (Zaki et al. 2008) are known to have a decreased tonic muscle tension (hypotonia). It is interesting to speculate that the central lesion may directly influence the thixotropic properties of muscle, although at present no solid evidence is available in this regard.

6.3.3.2 Hypertonia

Generally, the term means increased muscle tone for any reason. It includes conditions such as spasticity, rigidity, dystonia, and contracture in the physiological sense (Poewe 1989). Therefore, the mechanisms of the increased tone may be totally different. This generalized terminology may be useful clinically, but can lead to confusion because it is not specific. A novel hypothesis has been proposed that the deforming spinal rheumatic condition, called ankylosing spondylitis, may be predisposed by axial myofascial hypertonicity (Masi and Walsh 2003; Masi et al. 2003, 2005, 2007).

6.3.3.3 Resting Muscle Tone

In his book on muscles and movement, Walsh (1992) reviewed the common misconception that resting muscle tone depends on a low-level tonic discharge of motor neurons to muscles resulting in a low-level tonic contraction. Historically, the misconception is based on findings by the Sherrington school in the early decades of the last century, who equated all forms of postural muscle tone to the stretch reflex. The results published by Sherrington and his pupils had been obtained from midbrain or spinal-transected animals (Sherrington 1915). Therefore, such data based on markedly hyperreflexic animal specimens cannot be applied to human beings with an intact spinal cord (Masi and Hannon 2008).

The numerous EMG measurements that have been made in attempts to find evidence of electric activity in resting muscle have failed long ago (Clemmesen 1951; Ralston and Libet 1953; Basmajian 1957), as reviewed recently (Masi and Hannon 2008). The possibility is unlikely in these studies that activation of a small number of muscle cells has been overlooked. The EMG techniques used were widely applied and sensitive enough to detect meaningful α-motor neuron activity that might be responsible for the tone of a resting muscle. An EMG needle is known to record electrical activity within a diameter of approximately 1 cm in most skeletal muscles. The basis of this consideration is that in most postural muscles, one α-motor neuron activates 500 or more muscle fibers.

Moreover, resonant frequency studies did not show any changes in muscle stiffness before and after deep anesthesia (Lakie et al. 1979). No reduction in tone was observed as a result of surgical anesthesia (Lakie et al. 1980). Therefore, the tone of normal resting muscle is not due to low-level voluntary or CNS-controlled muscle contractile activity, but rather is caused by its intrinsic viscoelastic properties. Clinically, the *elastic* stiffness of a body segment can be examined by moving it slowly so that the speed of movement does not affect the result. The general stiffness – including elastic and viscous factors – can be assessed by moving the segment at different speeds.

Hypo- and hypertonia of a muscle is also assessed clinically by pressing a finger into the overlying tissue to determine how easily it is indented and how "springy" it is. In fact, this procedure assesses the compliance (compressibility) of a muscle being tested, not its extensibility. The speed of application of the pressure is not included in this rather coarse examination. The less easily a muscle is indented, and the more it returns to its original shape, the stiffer (elastic) it is.

A limited range of motion (ROM) of a muscle is estimated clinically by slowly stretching the respective joint until it reaches a point where the tension increases rather suddenly, known as its end-feel. If the ROM is reduced, this point is reached earlier (at a shorter muscle length) than in a normal muscle. This test is not specific; it fails to distinguish among increased viscoelastic tension, spasticity, physiological contracture, and fibrosis. An increased ROM (hypermobility)

must be interpreted with caution, because a decreased muscle tone is not the only explanation. Laxity of ligamentous and capsular connective tissue can have the same effect.

6.4 Contracture

6.4.1 Contractures in the Physiological Sense

The term physiological contracture is used to describe a shortening of the muscle (greater overlap of the myosin and actin filaments) in the absence of electrical activity of the muscle cell membrane (Layzer 1994). For instance, it has long been known that a high concentration of caffeine leads to contractures of muscle fibers. In this case, the normally occurring electromechanical coupling of force generation is replaced by chemomechanical coupling (Oba et al. 1997).

6.4.2 Clinical Usage of Contracture

Clinicians use the term contracture to describe shortening of muscle or connective tissue that may include joint capsules and ligaments and may be associated with an increase in the proportion of myofibroblasts (e.g., in fasciae or joint capsule). These changes occur when the muscle remains in a shortened position for a prolonged period of time (Hildebrand et al. 2004). Like muscle contractures as defined above, this condition also lacks EMG activity, but for a different reason.

Relatively uncommon genetic abnormalities can cause painful EMG-free muscle contracture. The genetic abnormalities result either in excessive release of calcium from the sarcoplasmic reticulum or impaired reuptake of calcium by the reticulum.

Excessive calcium release is the underlying mechanism of *myoedema* and the *rippling muscle syndrome* (Layzer 1994). When a muscle is hit with a rod or small percussion hammer in patients with myoedema, the muscle reacts with an EMG-free mounding. The reason for the mounding is that the mechanical percussion releases calcium which causes nonpropagated local contracture of the muscle – similar to the common postmortem phenomenon.

In contrast to the stationary mounding, the rippling muscle syndrome is characterized by a wave of contraction that spreads across the muscle in both directions after mechanical deformation of the muscle.

Slow reuptake of calcium by the sarcoplasmic reticulum occurs in patients with myxedema due to hypothyroidism. The associated slow relaxation of the muscle often leads to painful muscle spasms during exercise. Likewise, cases of genetic enzyme deficiencies that impair energy metabolism of the muscle may be

accompanied by slow calcium uptake. The calcium ions accumulate in the sarcoplasm of the muscle cell and cause muscle contractures during exercise. These contractures may be painful and are relieved by rest. Examples include deficiencies in muscle phosphorylase, debrancher enzyme, phosphofructokinase, phosphoglycerate kinase, and lactate dehydrogenase. McArdle syndrome with its contractures is a prominent example of a myophosphorylase deficiency (glycogenosis type V; Bruno 2002).

A much more common phenomenon that has to be considered in the differential diagnosis of painful conditions of muscle is the palpable taut bands associated with myofascial trigger points (TrPs). At present, there is no proof that palpable taut bands are muscle fibers in contracture, but clinical observations fit this explanation (see Chap. 2 in the companion volume by Mense and Gerwin (2010)).

6.4.3 Identification of Contracture

Metabolic disorders are likely to cause a more uniformly distributed contracture of the whole muscle and can be measured as an increase in elastic stiffness (force/displacement ratio) or as increased viscoelastic stiffness (increased resonant frequency). Another way of identifying muscle contracture is to measure tissue compliance (the reciprocal of elastic stiffness, i.e., deformation in millimeters/force in kilograms). When interpreting compliance measurements, e.g., with a hand-held compliance meter, the contribution of the skin has to be taken into account (Sakai et al. 1995; Leonard et al. 2003; Arokoski et al. 2005; Ylinen et al. 2006).

6.5 Muscle Spasm

6.5.1 Definition of Muscle Spasm

Spasm is the involuntary, more or less localized, tonic or phasic bracing (contraction) of muscle (Mathies 1988). In contrast to contractures, spasm is accompanied by EMG activity. Pain should not be included in the definition of spasm, as it may not be painful. An abnormally palpable muscle tension or firmness can have many reasons, and likewise, causation should not be part of the definition of spasm.

The term spasticity is appropriate for muscle spasm occurring in hyper-reflexic conditions, such as hemiplegia, brain injury, or spinal cord injury. It is associated with hyperactive stretch reflexes and tendon jerks due to disinhibition of spinal motor neurons (Mattle 1988; Benecke 1989). Rapid passive movements of a limb may elicit clonus, defined as “contractions and relaxations of a muscle occurring in

rapid succession, after forcible extension or flexion of a part" (Stedman's Concise Medical Dictionary 1994). In patients with spinal cord injury, a muscle spasm may be initiated by any afferent input to that portion of the spinal cord, indicating a loss of supraspinal inhibitory influence on the α-motor neurons at the spinal level (Benecke 1989).

Spasticity occurring as a response to rapid stretch is mostly not painful. However, if it is sustained, as in many patients with certain CNS lesions, it is often painful and may require spasmolytic drug therapy, motor point block, or injection of the motor end plate zones with Botulinum A toxin.

Rigidity differs from spasticity caused by disinhibition of upper motor neurons (UMNs) and has a different etiology. The typical example is the rigidity in Parkinson's disease. In this case, rigidity and the flexed posture of the patients are due to a cocontraction of antagonist muscles (Walsh 1992; Vaillancourt et al. 2004). The underlying mechanism is an imbalance between the direct and indirect pathways of the dopaminergic basal ganglia (DeLong 2000; Fahn 2003). Parkinson rigidity can be considered a type of muscle spasm of supraspinal origin.

Parkinson patients often have muscle pain, particularly low back pain. In a recent study, Broetz et al. (2007) reported a prevalence of 74% back pain in Parkinson patients. It is interesting to note that the patients with low back pain did not receive more pain medication than control patients. This suggests that muscle pain in Parkinson patients is often overlooked or ignored. On the other hand, the tonic contraction of muscles held in a shortened position, as occurs in Parkinson patients, would be expected to cause pain.

A muscle cramp can be defined as a sudden, painful, involuntary contraction of muscle (Miller and Layzer 2005). A prominent example is nocturnal leg cramps (Layzer 1994). The mechanism underlying the cramp pain is largely obscure. An old – but still valid – hypothesis is that only parts of a muscle are cramping (Norris et al. 1957). Shearing forces can occur between cramping and normal muscle that are likely to mechanically activate nociceptors.

6.5.2 Measurement of Spasm

Muscle spasm as defined above is associated with electrogenic contractions. Therefore, it can be quantitated in terms of EMG activity, either by needle or surface electrodes. The latter records activity from a relatively large sample of superficial muscle and often also from adjacent muscles. Monopolar needle electrodes monitor a more restricted region of activity within the muscle. Therefore, this technique is subject to greater danger of negative sampling error. The greater spatial resolution of needle electrodes is more likely to miss localized activity outside of its detection range. Coaxial, bipolar, and single-fiber needle electrodes sample successively smaller regions of muscle activity.

Another way of measuring muscle spasm is determining the increased muscle stiffness. Muscle stiffness and its measurement were dealt with under muscle tone.

Muscle stiffness can be used as a measure of spasm only when other sources of increased stiffness have been eliminated.

The most common method of scoring spasticity in the clinic is the modified Ashworth scale which grades resistance to passive movements, but its validity is unclear (Kumar et al. 2006). Spasticity has also been studied in terms of EMG activity produced by reflex responses as a function of flexion or extension of a body segment (Webster 1970), or as the response to various frequencies of applied oscillatory movement (Burke et al. 1971). In these classic studies, the investigators recorded the amount of force required to move the body segment a predetermined distance. A pathological increase in reflex gain is the mechanism underlying the spastic hypertonus of hemiparetic patients rather than a reduction in the threshold of the stretch reflexes (Thilmann et al. 1991).

The severity of spasm can be determined by measuring the overall averaged EMG activity in the relaxed subject. With modern EMG techniques these measurements can be quantified by rectifying the potentials. This process transforms all negative potentials into positive ones and vice versa, which are then averaged. The result is a curve that indicates the amount of spasm as a function of time.

6.6 Clinical Conditions with Painful Increased Muscle Tension

6.6.1 Tension-Type Headache (TTH)

Tension-type headache (TTH) is not the most severe type, but the most common form of headache (Schulman 2001). Many definitions of this type of headache depend primarily on the clinical history with little consideration of physical findings. The *Classification of Chronic Pain* booklet published by the International Association for the Study of Pain (IASP; Merskey and Bogduk 1994) distinguishes "acute tension headache" from "tension headache: chronic form (scalp) muscle contraction headache." The original term put forward by the Ad Hoc Committee on the Classification of Headache (1962) of the International Headache Society was "muscle contraction headache." However, in the more recent classifications, cases are included that do not exhibit increased EMG activity of the pericranial muscles (Headache Classification Committee of the International Headache Society 1988, 1993). The term TTH is now also being used for disorders such as psychomyogenic headache, stress headache, ordinary headache, and psychogenic headache (Ashina et al. 2005; Couppé et al. 2007).

The pathology of TTH is still unsettled, and increased muscle activity is not always demonstrable in the EMG (Couppé et al. 2007). Patients with TTH appear to be more prone to develop pain in response to a static exercise, but this does not mean that the pain of TTH is due to a static contraction of the pericranial muscles (Christensen et al. 2005). On the other hand, in some TTH patients a certain relationship between stiff neck muscles and TTH appears to exist. Sakai et al.

(1995) reported that the trapezius muscle and the posterior neck muscles showed significantly increased stiffness compared to controls. The best documented abnormality found in TTH is tenderness of the pericranial muscles. Lous and Olesen (1982) reported that nearly all patients with TTH had tender pericranial muscles. However, the site of pain complaint was frequently not where the tenderness was observed in the muscles. In general, muscle tenderness, subjective muscle tension, and the severity of headache pain appear to be unrelated to EMG activity (Peterson et al. 1995). In the chronic form, an impaired supraspinal control of nociceptive input is being discussed (Schulman 2001; Ashina et al. 2005).

A possible explanation for the headache in many patients with chronic TTH is myofascial TrPs in pericranial and neck muscles. TrPs in the temporalis, sternocleidomastoid, upper trapezius, and suboccipital muscles have been shown to induce referred pain in the pericranial muscles and thus to produce the clinical picture of TTH (Simons et al. 1999; Fig. 6.6). Poor posture, such as forward head posture, has been shown to be positively correlated with the development of TrPs in the suboccipital muscle and TTH. Patients with chronic TTH and TrPs in the suboccipital muscle reported a greater headache intensity and frequency (Fernández-de-las-Peñas et al. 2006). Therefore, TrPs in overloaded neck muscles may be considered an important causal or aggravating factor of chronic TTH.

The finding that the palpable taut band harboring a TrP in a muscle (see Chap. 2 in the companion volume by Mense and Gerwin (2010)) is not associated with EMG activity may explain why the pericranial muscles feel tense, but are silent in the EMG. The failure of many examiners to find increased EMG activity in apparently tense muscles may be due to this combination.

Because of the high prevalence of TrPs and their relevance for TTH pain, the physical examination of the patient for TrPs in the neck and shoulder muscles should be routine in subjects who complain of headache.

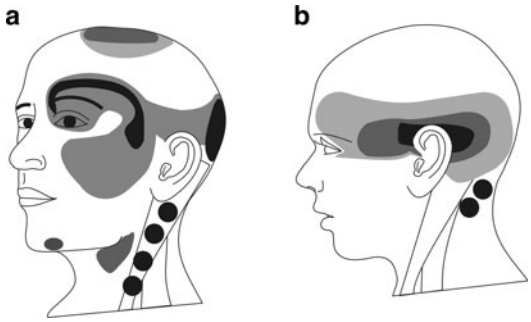

Fig. 6.6 Referred pain from myofascial trigger points, causing symptoms of tension-type headache. The location of the trigger points in the left sternocleidomastoid muscle or suboccipital muscle is marked by *filled circles*. Referred pain patterns are indicated by *gray* and *black areas*. (**a**) Trigger points in the sternal (superficial) division of the sternocleidomastoid muscle. (**b**) Trigger points in the left suboccipital muscles. The grade of shading indicates the intensity of the referred pain. Modified after Simons et al. (1999)

Psychological stress has been shown to aggravate the pain of TTH. In one study (Leistad et al. 2006), TTH patients were tested with cognitive stress, and their pain level and surface EMG were monitored. Subjects with TTH had higher pain responses to stress in temporalis and frontalis muscles than controls, but there was no correlation to surface EMG activity.

The differential diagnosis of chronic TTH included (1) radiculopathy, (2) arthritis (atlantoaxial articulation, subaxial facet joint, temporomandibular joint), and (3) nonarticular pain, such as myofascial TrPs, painful temporomandibular disorders, and fibromyalgia syndrome. A chronic headache can be the first sign of inflammatory processes such as sinusitis, dental abscess, or giant cell arteritis. As mentioned above, poor posture can cause muscle pain when the head is projected forward for long periods of time. A situation where such a posture is common is watching television with a large pillow behind or under the head.

6.6.2 Muscle Spasm

As defined above, muscle spasm is a long-lasting involuntary muscle contraction that can be determined by EMG monitoring of the muscle. This section deals with conditions that are attributed to *painful* muscle spasm. Contractions of a few minutes duration are usually not painful, unlike sustained muscular contractions. A mechanism underlying the pain is that the muscle compresses its own blood vessels if it exceeds a certain level of force (for most muscles, approximately 30% of maximal contraction force). The resulting ischemia is associated with the release of pain-producing substances that sensitize muscle nociceptors. The pain-producing substances that are released under these circumstances include bradykinin, ATP, and H^+-ions. Bradykinin is a well-known inflammatory and nociceptor-sensitizing agent (see Chap. 3); ATP and H^+-ions also proved to be effective stimulants for nociceptive free nerve endings in muscle (Hoheisel et al. 1994; Reinöhl et al. 2003). Another possible explanation for the pain of muscle spasm is that only some fascicles chronically contract which are overloaded under these conditions, although the increased force developed by the muscle as a whole is small.

6.6.2.1 The Misconception of a Pain–Spasm–Pain Cycle

A widely held concept states that muscle pain causes spasm of the same muscle, which in turn causes more pain that perpetuates the spasm. The postulated mechanism is that the painful input from muscle excites the homonymous α-motor neurons (those motor neurons that supply the painful muscle). In turn, the muscle contracts and is responsible for the spasm. When the spasm is strong enough and lasts long enough, it becomes painful and the resulting excitation of the muscle nociceptors perpetuates the spasm (Fig. 6.7a). However, clinical practice shows that

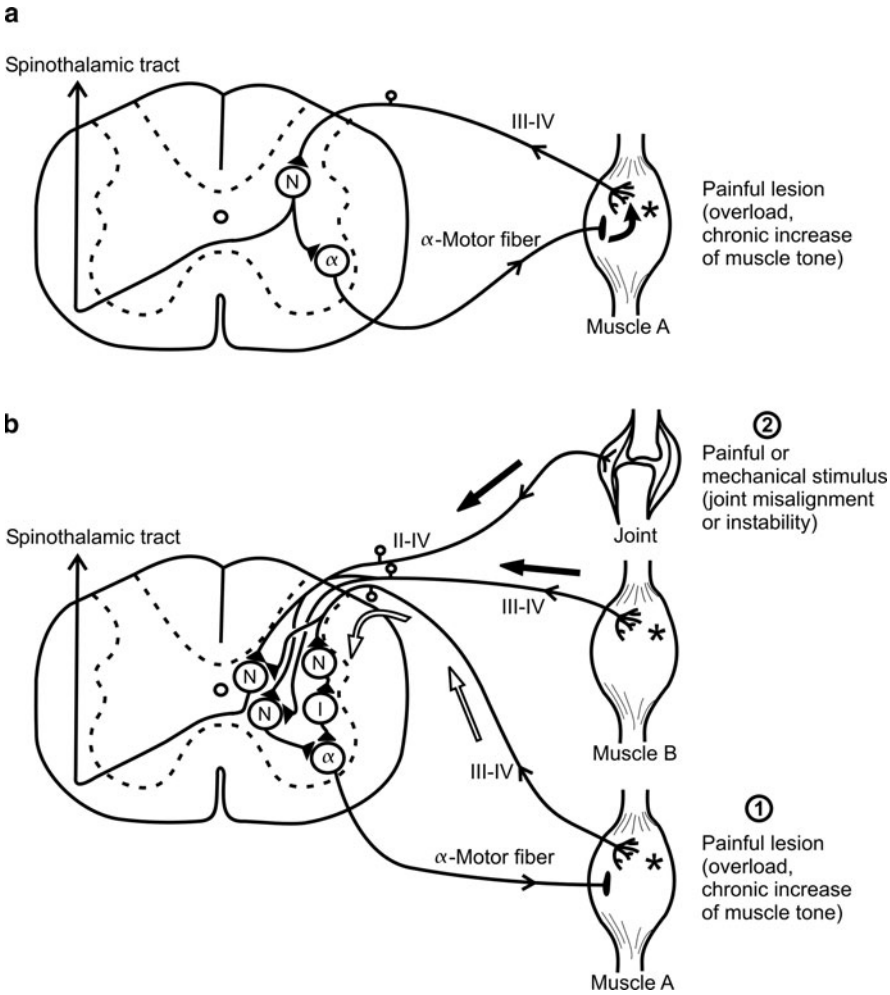

Fig. 6.7 Effects of muscle and joint pain on the contractile status of the muscle. (**a**) Outdated concept of a pain–spasm–pain cycle. A painful muscle lesion (*asterisks*) is assumed to excite nociceptive group III and IV muscle afferents. The nociceptive input activates a dorsal horn neuron (N) that sends a fiber branch into the spinothalamic tract, the main pain-mediating tract. These two statements are correct. Another branch of the neuron N is assumed to excite α-motor neurons that supply the painful muscle. The activated motor neurons cause a tonic contraction of the muscle which compresses the blood vessels and leads to ischemia. Ischemic contractions are painful and excite the muscle nociceptors. Thus — theoretically — a vicious cycle is formed that perpetuates the pain and spasm. According to more recent data, the synaptic connections between neuron N and the α−motor neuron are present, but not effective enough to drive the motor neurons to firing threshold. Moreover, the wiring diagram is greatly oversimplified (see Fig. 6.8). (**b**) Generation of muscle spasm by input from a dysfunctional joint or from another muscle. In this still simplified figure, the input from the nociceptors in muscle *1* reaches the α-motor neuron via an inhibitory interneuron *I* that decreases the excitability of the motor neuron. Thus, the main effect of a painful lesion in a muscle is inhibition of the motor neurons supplying that muscle. However,

(1) commonly, the painful muscle has no EMG activity, and (2) not every electromyographically identified muscle spasm is painful.

The basis of the misconception of a pain–spasm–pain cycle is the misunderstanding of motor reflexes, as properly exemplified by Walsh (1992). The bulk of the available data do not support the concept of a pain–spasm–pain cycle. Muscle pain and increased EMG activity lacked correlation in patients with low back pain as well (Arena et al. 1991; Sherman et al. 1991; Letchuman and Deusinger 1993).

When a patient complains of pain in a muscle that exhibits involuntary EMG activity (spasm), one cannot assume that the spasm is causing the pain. Spasm of sufficient force and long duration can cause pain, and in that case, the amount of spasm and pain will correlate. However, the muscle pain is not causing the spasm. In a study on low back pain patients who had palpable paraspinal muscle "spasm," the low back muscles showed EMG activity nearly continuously during the night (Fischer and Chang 1985). At that time, a pain–spasm–pain vicious cycle was assumed to relate the two findings. Later, the majority of the patients were diagnosed as having myofascial pain due to TrPs. Apparently, TrPs can induce muscle spasm in muscles other than that harboring the TrP (Donaldson et al. 1994).

Data from experiments on animals and human subjects point in the same direction. The pain–spasm–pain concept postulates an excitation of α-motor neurons during pain in the homonymous muscle. To the contrary, recordings from these neurons during painful stimulation of muscle nociceptors showed an inhibition of extensor and an activation of flexor motor neurons (Kniffki et al. 1981). Applied to the pain–spasm–pain concept, these data mean that spasm can occur only in flexor muscles, which of course is not true. In experiments on humans, experimental muscle pain was induced with hypertonic saline, and again there was an inhibition of the homonymous α-motor neurons (Le Pera et al. 2001). Apparently, α-motor neurons are *inhibited* rather than excited by nociceptive input from the homonymous muscle (Fig. 6.7b).

Theoretically, a spasm could also be induced by activation of γ-motor neurons. These motor neurons increase the discharge of muscle spindles which then excite α-motor neurons through the monosynaptic stretch reflex pathway. However, data from animal experiments demonstrate that γ-motor neurons likewise are *inhibited* rather than excited by a painful alteration of muscle (Mense and Skeppar 1991). Burke (1983) likewise discarded the participation of γ-motor neurons in the generation of muscle spasm. When chronic inflammatory muscle lesions were induced in animal experiments, there was often an initial phase of γ-motor neuron excitation

Fig. 6.7 (continued) nociceptive input from a joint that is moved by the muscle (*2*) or from another painful muscle (muscle *B*) may excite the α-motor neuron through an excitatory interneuron *N* and thus cause spasm. Note that also non-nociceptive input from joint mechanoreceptors (group II fibers) can induce spasm. The *open arrows* mark the inhibitory pathway from a painful muscle to the motor neurons of that muscle, *filled arrows* the excitatory pathway from nociceptors in the joint or another muscle. *III–IV*; group III and IV afferent fibers from muscle nociceptors. *II–IV*; group II, III, and IV muscle afferents from joint mechanoreceptors (group II) and nociceptors (group III and IV)

before the inhibition set in (Mense and Skeppar 1991). Therefore, when discussing the effects of a muscle lesion on locomotion, the time course of the motor neuron reaction has to be considered.

One reason for the misunderstanding of muscle spasm and the great popularity of the pain–spasm–pain concept is that it is based on a greatly simplified and outdated schema of the wiring of spinal α-motor neurons. Nowadays, the α-motor neurons are known to be subject to a multitude of excitatory and inhibitory influences from many sources of segmental (muscle, skin, joint) and supraspinal (pyramidal and extrapyramidal tracts) origins (Fig. 6.8). These influences are partly active, partly silent, vary with time, and are variable in strength (discharge frequency). An important aspect of this wiring diagram is that most of the input reaches the α-motor neurons through an *inhibitory* neuron pool. These neurons are part of the

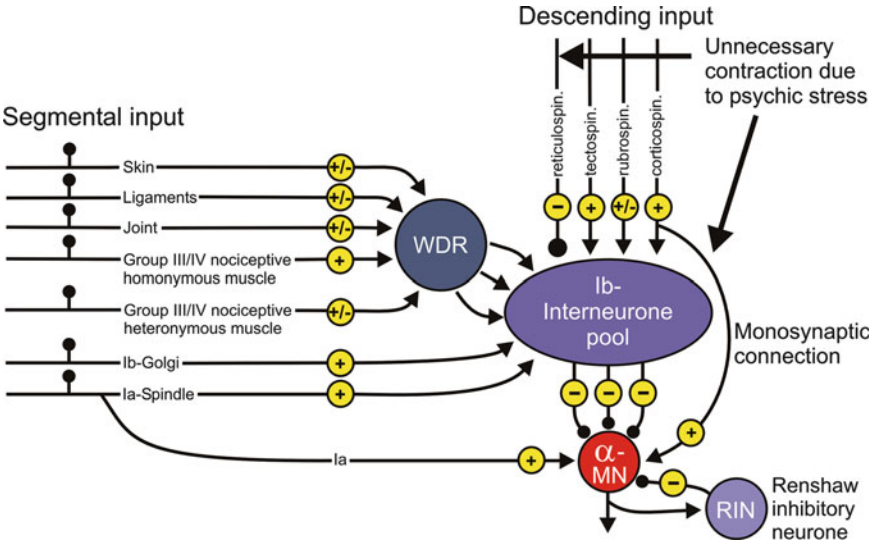

Fig. 6.8 Wiring diagram of α-motor neurons (α-MN) in the spinal cord. There are two main input pathways to the motor neurons, namely segmental connections from the periphery and descending tracts from supraspinal centers. Most inputs reach the motor neurons not directly but via an interneuron pool (the Ib-interneuron pool) that inhibits the α-motor neurons. A plus sign (+) indicates excitatory connections, a minus sign (−) inhibitory ones. Mixed influences are marked +/–. Three pathways are shown that reach the α-motor neuron directly, namely: (1) Ia fibers from the primary endings of muscle spindles (Ia), (2) cortico-spinal fibers that circumvent the Ib pool and excite the α-motor neurons directly (monosynaptic connection): these fibers are part of the pyramidal tract, they might play a role in unnecessary — and often involuntary — contractions under psychic stress, and (3) connections from Renshaw inhibitory neurons (RIN) that are driven by collateral branches of the α-motor fiber. *WDR*; wide dynamic range neuron in the dorsal horn. WDR neurons are thought to be nociceptive. *Group III/IV nociceptive homonymous muscle*; afferents, thin myelinated and unmyelinated nociceptive fibers from the muscle that is supplied by the α-MN shown. This input has mainly inhibitory effects, because it excites the inhibitory Ib-pool via the WDR neurons and thus decreases the excitability of the α-MN. *Heteronymous* muscles are muscles other than that supplied by the α-MN. For further functional details, see text

pathway from the Golgi tendon organs and therefore labeled Ib–interneuron pool after the afferent fibers of the tendon organs.

The segmental input from group III/IV muscle and joint afferents is partly excitatory and partly inhibitory. An inhibitory input to the Ib–interneuron pool leads to a disinhibition of the α-motor neurons, thereby enhancing their excitability, and potentially causing spasm. An interesting input to the Ib–interneuron pool is the descending reticulospinal tract, because it has an inhibitory effect on the interneuron pool. The tract can be activated by psychological stressors. Higher activity in this tract might be one reason for the unnecessary contractions many patients have, particularly when they feel stressed or are pressed in time at the workplace. The purpose of Fig. 6.8 is to demonstrate that a single input has a negligible influence on the excitability of the α-motor neurons. Rather, it is the balance between all these influences that decides if the α-motor neurons increase or decrease their discharge rate (or excitability). Spasm can occur if too many inhibitory input sources act simultaneously on the interneuron pool and lead to a disinhibition of the α-motor neurons.

Taken together, the presented data show that the pain–spasm–pain concept is untenable as an explanation for painful muscle spasm. Lund et al. (1991) replaced it by the pain-adaptation model which is more compatible with the neurophysiology literature. It stresses the common experimental observation that muscle pain generally inhibits the α-motor neurons of the painful muscle(s) and can induce a dysfunction of the motor system by activating the antagonists. Of course, there can be no doubt that many patients suffer from (painful) muscle spasm. However, in most of these cases the origin of the spasm is not the muscle that is in spasm, but other muscles or dysfunctional joints that are moved by the muscle. Interestingly, not only can nociceptive joint afferents be associated with muscle spasm, but also mechanosensitive (non-nociceptive) joint receptors that are connected to the CNS via group II afferent fibers (Fig. 6.7b). For more details on the effects of muscle pain on motor performance, see Chap. 7.

6.6.3 Spasmodic Torticollis

This condition is characterized by tonic (relatively continuous) or phasic (episodic) muscle spasms or tremulous shaking that can be very painful (Deuschl et al. 1992). Such chronic focal dystonia of the head and neck muscles causes various abnormal movements, including rotation (torticollis) or tilting laterally (lateralcollis), forward (antercollis), or backward (retrocollis). Congenital torticollis is rare and is believed to be associated with sternocleidomastoid muscle injury during a difficult delivery (Do 2006). In children, neck muscle contraction may also be secondary to ocular muscle imbalance or deformities of the cervical spine or musculature (Herman 2006).

The adult onset form is much more common and of unknown etiology, although a small percentage of patients have a family history of spasmodic torticollis (Dauer

et al. 1998). Torticollis ranges from mild to severe disease that is difficult to treat. The course is usually slowly progressive for one or more years, then tends to plateau. In about 20%, spontaneous recovery may occur within 5 years of onset, usually in milder cases of younger onset. About one-fifth of cases have evidence of dystonia elsewhere, e.g., eyelids, face, jaw, or hand (Dauer et al. 1998). Interestingly, involuntary movements are improved in sleep (Jahanshahi 2000) or were documented to not occur (Lobbezoo et al. 1996).

Etiology: as indicated above, no one cause of spasmodic torticollis is generally recognized. However, experiments in one controlled study (Grünewald et al. 1997), suggest abnormal perception of motion, but not position, in dystonic subjects. It was hypothesized that the findings were due to a disorder of muscle spindle afferent processing. Lateralization of the intracranial P22/N30 somatosensory evoked potentials (SEPs) by median nerve stimulation were abnormal in 40 patients with spasmodic torticollis compared to 40 healthy volunteers (Kanovský et al. 1997). The findings were interpreted as possibly being due to altered precentral cortex activation in the cervical dystonia patients. Another similar SEP study showed greater decreases in evoked potentials in patients with spasmodic torticollis than in Parkinson's disease, both more so than in normals. The findings suggested lesions involving the basal ganglia or their connections with the supplementary motor area (Mazzini et al. 1994).

In patients who had undergone microvascular decompression for spasmodic torticollis, EMG and nerve conduction velocity measurements of the sternocleidomastoid muscle were studied (Saito et al. 1993). Responses of the motor spinal accessory nerve (SAN) from electrical stimulation at the neck were compared to stimulation at the intracranial portion of the SAN. The abnormal findings in nine of 12 patients with unilateral symptoms were interpreted as resulting from a cross-transmission. The abnormal locus was believed to be more central than at the vascular compression of the SAN in the neck, and was hypothesized to be in its motor nucleus (Saito et al. 1993).

The pattern of EMG findings in 35 patients with spasmodic torticollis was analyzed in another study (Ando et al. 1997). In 12 patients, abnormal spontaneous muscle discharges were recorded only from the sternocleidomastoid muscle and the trapezius muscle on the same side, which share motoneuron innervation with the ipsilateral SAN. The findings suggested hyperexcitability of the unilateral accessory nervous system (Ando et al. 1997). Visuospatial functions were also evaluated in 18 patients with spasmodic torticollis and in 18 matched controls (Leplow and Stubinger 1994). The results were attributed to a discrete dysfunction of the striatal–frontal circuits, at least in a subgroup of patients.

In rotational spasmodic torticollis, determined by the direction of chin deviation, the most commonly involved muscles were the contralateral sternocleidomastoid and/or the ipsilateral splenius, based on polymyographic recordings (Deuschl et al. 1992). The contralateral splenius was also overactive in about one third of such patients, but rarely the contralateral trapezius. Retrocollis was usually due to bilateral splenius activity. Laterocollis was due to overactivity of all recorded muscles on the ipsilateral neck. Thus, surface EMG monitoring is useful in making

a more specific, functional diagnosis and for guiding treatment (Deuschl et al. 1992).

Acute torticollis in children often results from a reflex muscle spasm due to an inflammatory process (Brendenkamp and Maceri 1990). Common causes are upper respiratory infection, sinusitis, otomastoiditis, cervical adenitis, and retropharyngeal abscess or cellulitis. Torticollis was also associated with subluxation of the atlantoaxial joint in four patients (Brendenkamp and Maceri 1990).

Treatment: drugs and/or physiotherapy do not provide sufficient relief in the majority of patients with spasmodic torticollis (Crowner 2007). The most satisfactory nonsurgical treatment is currently injection of the spastic muscles with Botulinum A toxin (Botox; Thiel et al. 1994; van Herwaarden et al. 1994; Benecke and Dressler 2007; Chapman et al. 2007; Pappert et al. 2008) or Botulinum B toxin (BtB) for secondary failures to Botulinum A toxin (Ferreira et al. 2007). Although effective, this therapy is expensive and provides only temporary correction for most patients (Tassorelli et al. 2006). Failing that, selective microvascular denervation surgery may be successful in this condition (Jho and Jannetta 1995; Münchau et al. 2001; Cohen-Gadol et al. 2003). Microvascular decompression has been reported as a relatively effective and benign procedure. In a series of 20 patients, no mortality was reported in 22 operations (Jho and Jannetta 1995). Of the 17 patients who were followed for at least 5 years, 65% were reported cured and 20% improved with minimum spasm (Jho and Jannetta 1995).

Most patients have less pain following BTX injection as well as improvement in posture (Wöber et al. 1999; Naumann et al. 2002; Comella and Thompson 2006). Injection with BTX similarly improved a series of patients with tardive dystonia ($N = 7$) and idiopathic cervical dystonia ($N = 149$), treated with a series of BTX injections over 5 years (Brashear et al. 1998).

Not all patients respond positively to botulinum toxin type A (BtA or BTX) injection or become resistant to it (Greene et al. 1994; Naumann et al. 2002), and botulinum toxin serotype B (BtB) has been reviewed as alternate therapy (Costa et al. 2005). Ten percent to 15% of patients with torticollis developed BTX resistance on repeated injections. At least 4% of 559 patients treated with BTX developed antibodies (Greene et al. 1994; Tintner and Jankovic 2001). Responding patients require retreatment within weeks to several months, depending upon how thoroughly endplate function is destroyed and how quickly the muscle fibers are reinnervated.

BTX acts by inactivating acetylcholinesterase (AChE) release and destroying the neuromuscular junction (Comella et al. 2000). Transient side effects include fatigue, dysphagia, neck weakness, hoarseness, and local pain (Naumann et al. 2002; Comella and Thompson 2006). It follows that more specific injections of the neuromuscular junctions of the spastic muscle yield more effective results and fewer side effects (Tintner and Jankovic 2001).

Significantly improved clinical results were obtained when multiple points rather than single points were injected in each muscle (Borodic et al. 1992). A significantly greater number of patients experienced marked improvement when needle EMG guidance and clinical examination were used to assist

localization of the injection rather than clinical examination alone (Comella et al. 1992). The involved muscle was localized with EMG assistance by having the patient voluntarily contract the respective muscle to be injected (Comella et al. 1992). A needle specifically for this purpose is manufactured by Nicolet Biomedical Instruments (P.O. Box 4287, Madison WS 53711-0287, USA).

In one patient with index finger distal phalanx spasticity, BTX injection results were improved when the incriminated muscle was more precisely located by monopolar needle stimulation (Roggenbuck and Yablon 1995). Since motor endplates are the desired targets of BTX injection, additional specificity would also be expected in spasmodic torticollis by their more accurate localization. The endplate zone (previously called the motor point) can be located by electrical stimulation or by EMG monitoring. Superficial muscles may be stimulated through the skin (Kimura 1989) or the neuromuscular junction may be localized by systematic needle EMG searching (Ottaviani and Childers 1995). In addition, the initial negative polarity of motor unit action potentials may be identified by precise needle EMG placement (Buchthal et al. 1955). The latter localization may be observed after asking the patient to do a minimal voluntary contraction. A steep and purely negative onset of the motor unit action potential is only recorded within 1 mm of the endplate (Buchthal et al. 1955). All other motor unit potentials monitored farther from the endplate have a positive-first deflection.

6.6.4 Trismus

Trismus is defined as a firm clenching of the jaw due to tonic spasm of the muscles of mastication (McDonough 1994). Lockjaw is an example of trismus caused by tetanus infection. In practice, the term is commonly applied to restricted opening of the mouth not only because of muscle spasm, but also because of fibrotic contractures and/or adhesions. Restricted mouth opening from fibrotic contractures induces a sharply defined highly reproducible barrier, and reaching the barrier may not be painful. The muscles are likely to be relatively slack unless they are in spasm. When the opening is restricted by muscles in spasm, serious attempts to open the mouth and to chew are usually painful. In this case, the muscles always show evidence of EMG activity and exhibit uniform tension. When the mouth is opened passively, the endpoint caused by spasm is painful, not as clearly defined, and more variable than that of fibrosis.

Trismus due to muscle spasm may be the result of trauma such as mandibular fractures (Throckmorton et al. 2004) or of acute inflammation due to tissue injury during surgical procedures (Troullos et al. 1990). Muscle spasm may also occur after sustained opening of the patient's mouth for dental treatment (Jaeger 1994). All of these muscle stresses may activate myofascial TrPs that contribute to the patient's pain and delay return of normal function (see Chap. 2 in the companion volume by Mense and Gerwin (2010)). Medications such as Compazine and Stelazine or other major tranquilizers may cause muscle spasm (Jaeger 1994).

Widespread injection of the spastic muscles with 0.5% or 1% procaine or lidocaine produces temporary relief by blocking neural transmission. The muscles tend to relax as the initiating stimulus that caused the reflex spasm subsides. Jaw use within pain-free limits is then strongly encouraged. As the painful active movements of the jaw decrease, gradual *active* stretching with simultaneous application of counter-stimulation or injection (as described above) facilitates restoration of normal function. Neglect can lead to permanent restriction of mouth opening (Jaeger 1994).

6.6.5 Unnecessary Muscle Tension

Unnecessary or extraneous muscle tension is a confusing intermediate status between muscle contraction that is beyond voluntary control (spasm, see Sect. 5.1) and viscoelastic tension that shows no EMG activity (see Sect. 5.2). Chronically unintentional muscle contraction can itself cause pain at times and can seriously influence other sources of muscle pain such as TrPs. Unwitting muscular contraction that is amenable to voluntary control (sometimes requiring biofeedback assistance) is commonly identified clinically as muscle tension (Rachlin 1994).

Misunderstanding of muscle tension is aggravated by confusion in terminology and the fact that this increased motor unit activity is unintentional and not purposely induced by the person. However, with conscious effort and appropriate assistance or guidance, the contractions can be behaviorally decreased. False assumptions as to the central nervous system level of the origin of muscle tension further cloud the issue (see Sect. 5.2)

Another reason why this concept of muscle tension is a gray area is that some patients with appropriate help and training have been able to exercise a degree of "voluntary" influence over an organic brain dysfunction affecting motor control. Patients with spastic torticollis, which originates in motor control pathways of the brain, were significantly improved either by EMG feedback training or by relaxation training with graded neck exercises (Jahanshahi et al. 1991).

Another study (Harver et al. 1992) showed that children could be trained to establish a predetermined baseline level of EMG activity using biofeedback techniques. This was done because their usual baseline fluctuations were annoyingly large for experimental purposes before training.

Three sources of unnecessary muscle activity (tension) are well recognized: (a) psychological distress or anxiety, (b) overload from sustained contraction or repetitive activity, and (c) inefficient (untrained) use of muscles.

6.6.5.1 Psychological Distress

Emotional distress and anxiety are normally expressed through increased muscular activity. We say someone is "uptight," reflecting an apparent increase in muscular

tension. Activity of the facial muscles often reveals a person's emotional reaction to a situation. This kind of muscular activity that is not primarily for intentional motor purposes has been the focus in use of EMG feedback techniques.

6.6.5.2 Chronic Muscle Overload

Common causes of chronic muscle overload are poor posture, positioning, or workstation arrangement, and inappropriate patterns of muscle use. These factors are now recognized as sources of chronic musculoskeletal pain (Middaugh et al. 1994). Controlled quantitative studies have been performed on type I muscle fiber size from trapezius muscles of subjects with work-related localized myalgia (Larsson et al. 2001; Andersen et al. 2008). An increase in hypertrophied type I fibers with poor capillarization was found in patients with trapezius myalgia in the more recent study (Andersen et al. 2008), but not in the earlier report (Larsson et al. 2001). Muscles are intolerant of sustained contraction or of monotonously repetitive movements. Muscle function decompensates when the demands of such activity induce fatigue and exceed muscle tolerance, often painfully. With the advent of computer terminals, individuals spend long hours in nearly the same position doing the same thing repetitively. Until recently, little attention was paid to such resultant muscle pain.

The discipline of ergonomics is dedicated to providing a work situation that provides optimal trunk and limb support and placement of work materials. A goal of ergonomics is to minimize unnecessary motor activity, especially repetitive and sustained muscle contraction. Unnecessary muscle overload is not spasm by definition, but is a potent potential cause of painful muscles.

The nomenclature of the literature concerned with the problem of muscle overload in the work place concentrates on the stress condition, without an adequate understanding of the classification and causes of the pain (Hagberg 2005). For the most part, three issues are addressed: the cumulative nature of the stress or trauma, the repetitive nature of the activity, and the degree of overuse. The need to reduce stress is appropriately emphasized. However, to most authors, the mechanism by which the stress causes the pain remains enigmatic. The immediate problem in these overload conditions concerns *muscle dysfunction* that is objectively demonstrated by surface EMG recordings (Headley 1997). The muscles were rarely examined for the loci or source of pain.

A review of 56 papers published between 1990 and 1995 and indexed in MEDLINE showed that 28 (one half) were concerned with the repetitive nature of the activity, most commonly identified as the group of *repetitive strain injur*y (Guidotti 1992). Other variants included: *repetitive motion injury*, *studies of repetitive motion*, *repetitive strain disorder*, *repetitive motion disorder*, and *repetitive use injury*. The mushrooming of occupational computer use has brought with it a virtual epidemic of repetitive strain injury of the upper quarter of the body (Thompson and Phelps 1990).

A second group of 20 papers emphasized the cumulative nature of the problem which was identified 18 times as *cumulative trauma disorder* (Childre and Winzeler 1995), once as *cumulative stress disorder*, and once as *cumulative trauma illness*.

The third group of seven papers referred to the *overuse syndrome* while one author called it *overuse injury syndrome* (Fry 1993).

Most of these authors concentrated their diagnostic attention on neurological causes, tendinitis, biopsychosocial dysfunction, and central disturbance of nociception, but rarely on muscles. With this variety of terms, and unresolved cause of the pain, it is little wonder that skepticism exists for their causation of work-related upper extremity disorders (Szabo 2006). In a 1995 questionnaire survey, half of the responding doctors indicated that no genuine organic condition corresponded to their understanding of "repetitive strain injury" (Diwaker and Stothard 1995). Based on the diverse definitions offered by the responding physicians, the authors of the survey concluded that so many completely different meanings are applied to this condition that it is medically (and legally) meaningless. A systematic literature review concluded that little is known about the effectiveness of conservative treatment options for repetitive strain injury and that more high-quality trials are needed (Konijnenberg et al. 2001).

There are a number of separate (but often related) causes for the pain. Causes include fatigue due to demands that exceed the tolerance of that muscle, sustained contraction with hypoxia, and unrecognized TrPs which are initiated and aggravated by these conditions. Acute pain that persists eventually becomes chronic pain that is processed in the brain differently. Acute pain activates sensory centers in the brain and has little effect on emotion, whereas chronic pain has a strong action on centers concerned with emotion (Hsieh et al. 1995), in this case suffering. Functional imaging of brain responses to pain is profoundly complex and is not yet well understood (Peyron et al. 2000). Prevention of the pain in the first place, or early and effective intervention, can pay big dividends to the sufferer and to the medical care system. Much can be gained by concentrating on why the muscles are hurting and by dealing with such causes of the pain.

6.6.5.3 Inefficient Use

Inefficient (unnecessary) use of muscles is best illustrated by the differences in the way a novice and a skilled athlete use muscles to perform the same activity. At any given moment during a movement, the skilled athlete uses *only* those muscles that are required. As soon as a muscle is no longer needed, it immediately relaxes. Muscles that need not be involved remain relaxed. The result is a smooth, rhythmic, graceful, and efficient movement. The novice, on the other hand, recruits muscles unnecessarily. This produces wasteful cocontraction of antagonists and allows muscles to continue to contract when no longer needed. The additional muscular activity contributes to stiffer and awkward movements. The difference in the use of muscles becomes readily apparent when one observes a mixed group of amateur skaters at a rink.

One form of inefficient use of muscles is the failure to relax fully following voluntary contraction. Subjects with work-related trapezius myalgia retained a significantly higher level of muscle tension between contractions compared to normal controls (Elert et al. 1993). Abnormal failure to relax was seen in 25 female cleaners suffering from chronic myalgia of the trapezius muscle (Larsson et al. 2000).

6.6.6 Nocturnal Leg Cramps

The topic of nocturnal leg cramps, sometimes called calf cramps or systremma, was previously reviewed (Layzer 1994; Travell and Simons 1992; Butler et al. 2002; Coppin et al. 2005), so it is summarized briefly here. Clinically, these cramps most commonly occur in the gastrocnemius muscle (also in other leg muscles) and have a spontaneous onset when sitting quietly or sleeping. The contraction, which is palpable or visible, is very painful and may leave soreness and swelling. It tends to be restricted to one muscle or one functional muscle group. Contraction may wax and wane in different parts of the muscle. Cramps are likely to occur when the muscle has remained in the shortened position for some time. Cramps can be induced by voluntarily contracting the muscle in a shortened position.

Studies suggest that common leg cramps result from excitation of motor unit action potentials, possibly caused by spinal motor neurons (Jansen et al. 1999) or, in the older theory, by stimulation originating in the intramuscular portion of motor nerve terminals (Denny-Brown 1953). The latter is the anatomical site of myofascial TrPs (Simons 1996). Sometimes cramps are associated with fasciculations and lower motor neuron disease. Most people with frequent fasciculations have frequent muscle cramps, but the reverse is not true. Also, fasciculations are not characteristic of TrPs. Leg cramps may also result from changes in extracellular fluid produced by rapid dehydration (e.g., diuretic therapy), by hemodialysis, and by electrolyte imbalance (Layzer 1994).

Effective relief is usually obtainable by passively stretching the muscle. However, active stretching of the cramping muscle by voluntarily contracting its antagonist is usually more effective because of the added effect of reciprocal inhibition. Many individuals are helped by walking for relief. Frequently, muscles prone to this type of cramping have identifiable latent or active TrPs. When the TrPs are inactivated (see Chap. 2 in the companion volume by Mense and Gerwin (2010)) and suppressed by *daily*, slow stretching exercises, the cramps are less likely to recur and often cease.

A variant of muscle cramps is the cramp–fasciculation syndrome (CFS), which is believed to result from peripheral nerve hyperexcitability (Harrison and Benatar 2007). Fasciculations and evoked potentials were abolished by regional application of curare (which inactivates the motor endplates), but not by nerve block. *Carbamazepine* therapy was considered helpful (Tahmoush et al. 1991).

6.6.7 Stiff-Man (stiff-person) Syndrome (Moersch-Woltman syndrome)

This rare disorder of motor function, characterized by involuntary stiffness, has been reviewed (McEvoy 1991; Layzer 1994; Vogels et al. 2003). The term "stiff-man" is a misnomer, since women have long been recognized to be equally affected (Editorial 1967). The currently preferred label is stiff-person syndrome (Vogels et al. 2003). Abnormally increased brain stem excitability and reflexes with exaggerated startle have been reported to occur in this condition (Molloy et al. 2002; Khasani et al. 2004). Diagnostic criteria include: (1) slowly progressive stiffness of the axial and proximal limb muscles, (2) intermittent painful muscle spasms that are spontaneous (or triggered by sensory stimulation, emotion, movement, or passive stretching of the muscle), (3) presence of positive EMG activation potentials (including at rest), and (4) suppression of EMG activity by sleep, anesthesia, myoneural block, or nerve block (Young 1966; Editorial 1967; Layzer 1994; Vogels et al. 2003). Muscle histology is normal. Symptoms begin with intermittent aching and tightness of axial limb muscles, followed by continuous board-like stiffness that interferes with mobility. The muscle spasms can become severe enough to fracture the neck of the femur (Cohen 1966). Despite this, in one patient the condition was still diagnosed as psychogenic.

Stiff-person syndrome is of spinal or brainstem origin (Molloy et al. 2002; Khasani et al. 2004) and shows evidence of being an *autoimmune disease* (McEvoy 1991; Layzer 1994; Vogels et al. 2003). The standard treatment for this condition has been benzodiazepines (McEvoy 1991).

6.6.8 Muscle Stiffness of Aging

Muscle stiffness is increased with aging, having been confirmed in calf muscles of women (Gajdosik et al. 2004). The stiffness is not painful by itself, but reduces the pain-free ROM and the maximum rate of movement, most noticeably following prolonged inactivity. Many elderly citizens increasingly restrict their activity to stay within the comfort — nonpainful — zone, and therefore show the characteristic slow, stiff gait. It is a common, non-life-threatening condition that has been neglected as a subject of research.

This condition must be distinguished from the pain of a progressive peripheral joint osteoarthritis, silent ankylosing spondylitis, progressive osteopenia, and capsular contraction of the ligaments about a peripheral joint, to name a few. A careful history, physical examination, and laboratory assessment will identify the characteristic features of these conditions.

The best management of stiffness in the elderly is an individualized balance between proper diet, physical exercise, and adequate rest. Physical exertion must be adequately planned, because unaccustomed muscular activity is potentially

damaging. Some of the sedating muscle-relaxant medications presented above can be used at night to enhance sleep.

6.7 General Remarks on Medications

This section deals with medications for a group of disorders whose common theme is muscle spasm but, in reality, the separate entities are more different than similar. Since the pathophysiological mechanisms responsible for these conditions are apparently very different, it should come as no surprise that a single treatment is not effective for all conditions. In fact, the drugs typically considered to be muscle relaxants are often of little benefit in true muscle spasm, except that they provide the sedation which allows centrally mediated relaxation.

The current treatment of choice for spasmic torticollis is Botulinum A toxin injections strategically placed in skeletal muscle, as discussed above. Trismus is often successfully treated by local injections of anesthetic agents such as lidocaine or procaine into affected skeletal muscle. Unnecessary muscle tension, which includes the effects of psychological distress, muscle overload, and inefficient use may involve the use of sedative hypnotic drugs to relieve psychological tension and facilitate sleep. Importantly, emphasis should also be placed on posture principles, taking breaks to stretch fatigued muscles, and recognizing the signs of mechanical muscle pain before the symptoms become chronically fixed.

The medications to be presented in the following list have been advocated for the relaxation of skeletal muscle in situations such as surgery, assisted ventilation, or ambulatory muscle spasm.

Skeletal muscle-relaxant drugs can include centrally and peripherally acting agents. The peripherally acting agents tend to be in the neuromuscular blocking group while the more centrally acting agents (i.e., muscle relaxants) are more frequently orally administered sedatives.

Most of the peripherally acting agents (an exception is dantrolene sodium) are highly polar and poorly absorbed from the gastrointestinal tract. They are undependably distributed from intramuscular injection so they are usually administered intravenously. They can be divided into depolarizing agents (e.g., succinylcholine) and nondepolarizing agents (e.g., tubocurarine chloride, gallamine triethiodide, vecuronium bromide). These agents are used primarily as part of an anesthetic program during surgery or for immobilization during intubated passive respiration. Only one of the peripherally acting agents (Botulinum A toxin) will be profiled.

The centrally acting agents are widely marketed as muscle-relaxant drugs, but actually exert their benefits more through sedation than by direct relaxation of contracted skeletal muscle.

D-Botulinum A toxin

The mechanism of action has been described above. Transient side-effects include fatigue, dysphagia, neck weakness, hoarseness, and local pain. Since BTX acts by permanently inactivating ACh release and destroying the neuromuscular

junction, it follows that the more specifically the neuromuscular junctions of the spastic muscle are injected, the more effective the injection will be, and the fewer the side effects.

Quinine sulfate

Quinine is believed to increase the tensile response of muscle to a single maximum stimulus, but it also increases the refractory period of the muscle by a direct action on the muscle fiber. Quinine has been used to manage night-time leg cramps, but controlled clinical trials have failed to prove it significantly better than placebo. The United States Food and Drug Administration no longer considers it useful for that indication.

A classical unwanted side effect is cinchonism (SYN quininism) manifested by tinnitus, headache, nausea, and visual disturbances. Quinine is contraindicated in pregnancy because of potential teratogenic effects.

Clonazepam

The mechanism of action is uncertain but the drug's anxiolytic or sedating effects may contribute to muscle relaxation. There is evidence that benzodiazepines cause skeletal muscle relaxation by facilitating the inhibitory action of gamma-aminobutyric acid in the brain or spinal cord. The duration of muscle relaxation after a single dose may be up to 8 h.

The most frequent untoward effects associated with short-term use are sedation, abnormal mentation, nightmares, dysarthria, and extrapyramidal reactions. Chronic usage can contribute to dependency, and acute discontinuation of large dosages can lead to seizures.

Levodopa–carbidopa

Parkinson's syndrome is known to result from a decrease in dopamine effect in the central nervous system, particularly in the striatum. In contrast to dopamine itself, levodopa readily crosses the blood–brain barrier and is enzymatically converted to dopamine. Carbidopa inhibits the peripheral decarboxylation of levodopa without affecting its conversion to dopamine in the central nervous system. Thus, carbidopa increases the amount of levodopa available to the brain. Some of the effects of carbidopa may relate to central serotonin functions. The mechanism of the levodopa–carbidopa effect on nocturnal myoclonus is not known.

The most prominent central side-effects are involuntary movements such as bruxism, grimacing, chewing, protrusions of the head, or rhythmic motions of the head. Psychological manifestations may include affective manifestations, alterations in mood, and behavioral disturbances. Most of the side-effects of levodopa are reversible with dosage reduction. The combination of carbidopa with levodopa reduces the frequency of systemic adverse effects, but does not reduce central adverse effects of levodopa. Rapid reduction of dosage should be avoided because it can induce a neuroleptic malignant-like syndrome.

Diazepam

The mechanism responsible for the antianxiety effects of the benzodiazepines is primarily related to its effects on the brain. The mechanism by which the

benzodiazepines influence skeletal muscle spasm may be more localized in the spinal cord. There is also evidence that they may have some direct effects at the myoneural junction.

The most common adverse effect is sedation, but amnesia, headaches, vivid dreams, dysarthria, paradoxic agitation due to disinhibition, dry mouth, and other anticholinergic effects also occur. Chronic dosage can cause dependence, so the dosage should be tapered rather than suddenly discontinued.

Cyclobenzaprine hydrochloride

The pharmacological action of this sedating central nervous system depressant resembles the tricyclic antidepressants. The mechanism of its influence on skeletal muscle is central. It has no direct local action on skeletal muscle. Like the tricyclic antidepressants, this agent is serotonergic, noradrenergic, and anticholinergic.

The main adverse effects are drowsiness, dry mouth, and dizziness. As with other agents with anticholinergic activity, caution should be used with angle-closure glaucoma and urinary retention.

Carisoprodol

Carisoprodol acts primarily on the central nervous system because it has little or no direct action on skeletal muscles. It may disconnect central pain perception without interfering with peripheral pain reflexes.

The main adverse effect is drowsiness, but other central nervous system effects may include irritability, headache, affective symptoms, vertigo, and tremor.

Baclofen

Baclofen is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The mechanism of its action is incompletely understood. There is evidence that it inhibits afferent signal transmission in the spinal cord, because there is very little penetration of the blood–brain barrier. It has antinociceptive properties and inhibits motor neuron-related muscle spasticity. Indications for use of oral baclofen include muscle spasticity of spinal cord origin associated with multiple sclerosis and other cord injuries.

The most common adverse effect is drowsiness, so operation of mechanical equipment may be hazardous. Caution should be exercised when treating patients with seizure disorders. Withdrawal of this drug too rapidly can cause hallucinations, seizures, and recurrence of muscle spasms.

Dantrolene sodium

This drug directly affects skeletal muscle by inhibiting the release of calcium from the sarcoplasmic reticulum. Beneficial effects often take 1 week before becoming evident.

There are serious adverse effects associated with long-term therapy with dantrolene, including development of a seizure disorder, fatal hepatotoxicity, and serositis (pleural effusions, pericarditis). The hepatotoxicity can be idiosyncratic and irreversible. Therefore, careful monitoring of the liver function tests should be performed and the dosage modified on the basis of the findings.

Methocarbamol

This drug is a central nervous system sedative with skeletal muscle relaxant effects. The mechanism of action on skeletal muscle is unknown; there is no direct effect.

The most frequent problems with the drug are drowsiness, dizziness, and light-headedness.

Orphenadrine citrate

This drug has central atropine-like sedating effects on central motor centers or on the medulla.

The main side-effects are those associated with anticholinergic actions such as dry mouth, urinary retention, blurred vision, and drowsiness.

Valproic acid

This drug is an anticonvulsant, but has been observed to reduce the chorea and tardive dyskinesia in patients on antipsychotic drug therapy. It probably influences skeletal muscle spasticity in a manner similar to baclofen.

The most common problems are gastrointestinal intolerance and hepatic failure resulting in death. It can be sedating, or lead to anxiety, confusion, depression, or agitation.

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Chapter 7
Reorganized Motor Control Due to Muscle Pain

Thomas Graven-Nielsen and Lars Arendt-Nielsen

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Abstract It has become evident that muscle pain interferes with motor control strategies, and different patterns of interaction are reported during rest, static contractions, and dynamic conditions. A reorganized motor control system with functional adaptations of the muscle coordination and strategies is a key factor in musculoskeletal pain conditions; its relevance in the transition from acute pain to chronic pain is most likely underestimated. The interaction between muscle pain and motor control depends on the specific motor task. Muscle pain causes no increase in muscle activity assessed by electromyography at rest, reduces maximal voluntary contraction (MVC) levels, and shortens endurance time during submaximal contractions. Moreover, muscle pain causes an adaptive change in the

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coordination during dynamic exercises. In some cases, increased muscle activity reflecting reorganized muscle coordination and strategy is also a component of the functional adaptation to muscle pain. In general, the "vicious cycle" hypothesis is not supported by these findings. More relevant is an adaptive model predicting reduced agonistic muscle activity eventually advanced by changed antagonistic muscle activity. The quantitative motor control assessment procedures provide additional clinical information, and give further support for optimizing prevention procedures and treatment regimes and for musculoskeletal pain.

7.1 Introduction

Pain from deep tissues is generally accepted to constitute a special diagnostic and therapeutic challenge, and insight into the peripheral and central neurobiological mechanisms is necessary to improve diagnosis and management strategies. It is clear that muscle pain has functional implications when it comes to motor performance. From daily life it is well-known that pain from joints and muscles affects our motor performance or causes facial expressions — the painful limb or area is protected by voluntary or reflex-based movements with reduced amplitude or strength. Related to the influence of pain on the motor performance is the opposite scenario, that manual work can induce musculoskeletal pain. Within occupational health, it is still not clear why some workers develop musculoskeletal pain and others do not develop pain, even though they are exposed to the same conditions. It is likely that the interactions *pain–motor function* and *motor function–pain* are closely related; at least, a poor motor function will be detrimental and augment occupational pain conditions.

Human experimental pain models applied to healthy volunteers provide a potential strategy to investigate functional aspects of deep-tissue pain. Experimental muscle pain research involves two separate topics: (1) standardized activation of the nociceptive system, and (2) quantitative assessment of the evoked sensory and motor responses. In this situation, healthy volunteers transiently become patients with a well-defined muscle pain where the sensory manifestations and sensory-motor interaction can be assessed. Several techniques have been used to induce human muscle pain (for review see Graven-Nielsen (2006)), and this chapter describes the basic effects of experimental muscle pain on muscle coordination. It is important to recognize that the mutual link between experimental muscle pain and changes in motor control cannot be directly transferred to the clinical conditions with chronic muscle pain. Nevertheless, several groups of patients suffering from chronic muscle pain such as low back pain, fibromyalgia and myofascial temporomandibular pain demonstrate similar changes in the muscle coordination as found with experimental muscle pain. One important advantage with experimental muscle pain studies is that the cause–effect relationship is known, i.e., the effects of pain on movement coordination can be described by electromyographic (EMG), kinematic, and force recordings. Thus, the use of experimental muscle pain can elucidate basic biological motor-control mechanisms, which are affected by muscle pain. An involvement of

these mechanisms is likely in chronic muscle pain conditions, in parallel with the mechanisms responsible for the transition from acute to chronic pain.

7.2 Relevant Pain Modalities

The sensation of acute deep-tissue pain is the result of activation of group III (Aδ-fiber) and group IV (C-fiber) polymodal muscle nociceptors (see Chaps. 2 and 3). Algesic (pain-producing) substances and strong mechanical stimuli can excite the nociceptors, in contrast to muscle stretch, muscle contraction or normal movements.

Exercise-induced muscle pain by concentric muscle work is normally short-lasting, and a result of impaired blood flow during work. Therefore, it may resemble the condition of ischemic muscle pain. As an example, muscle pain was induced during cycle ergometry of various loads (O'Connor and Cook 2001). Eccentric muscle work causes delayed onset of muscle soreness, with peak soreness after 24–48 h. Delayed-onset muscle soreness (DOMS) has been widely used to explore pathophysiological components of the musculoskeletal system and gender-related issues (Dannecker et al. 2003). A model of deep tissue hyperalgesia based on DOMS in wrist extensors with characteristics similar to tennis elbow pain has been described (Slater et al. 2005). The mechanism underlying DOMS is not clear, but is probably related to ultrastructural damage resulting in the release of algesic substances. This may produce an inflammatory reaction, as anti-inflammatory drugs (NSAID) appear to have an effect on this type of muscle soreness.

Exogenous and endogenous algesic substances have been used to induce experimental muscle pain in humans (Graven-Nielsen 2006). The hypertonic saline model in particular has been used extensively to characterize the sensory and motor effects involved in muscle pain, as the quality of the induced pain is comparable to acute clinical muscle pain, and shows localized and referred pain characteristics (Kellgren 1938). The work of Kellgren (1938) and Lewis (1938) in the late 1930s introduced the method of muscle pain induced by hypertonic saline. In most of the earlier studies, manual bolus injections of hypertonic saline have been used (Fig. 7.1). Later, the model was improved by computer-controlled infusions of hypertonic saline, which give a more standardized model and allow induction of tonic muscle pain by continuous infusion. Saline-induced muscle pain intensity is dependent on volume, concentration and infusion rate. The quality of saline-induced muscle pain is typically described as "aching, cramping, boring, drilling, taut, tight, spreading and radiating." The saline-induced pain model has been used extensively in studies on the influence of muscle pain on motor performance; no side-effects associated to hypertonic saline have been reported (Graven-Nielsen 2006). Recent animal studies have shown no cause of muscle toxicity by this method (Svendsen et al. 2005), and underpin its use for human experimentation.

Animal studies have shown a robust excitation of group III and IV afferent fibers (Fig. 7.1) by hypertonic saline (Cairns et al. 2003; Hoheisel et al. 2005) in contrast to the thick, fast afferent fibers (Cairns et al. 2003). Iggo (1961) reported, however, that afferent fibers other than group III and IV (e.g., related to muscle spindles) were

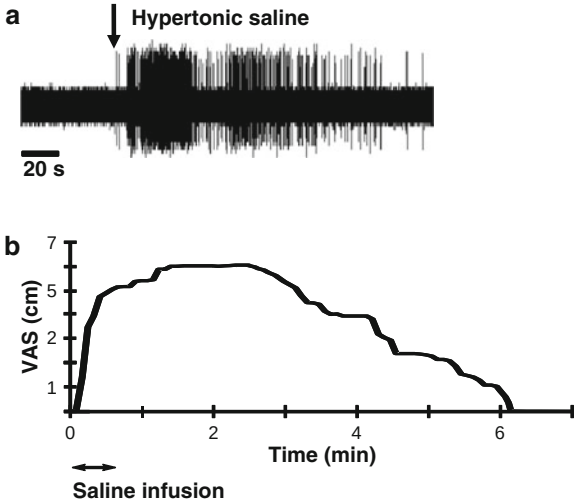

Fig. 7.1 Experimental muscle nociception by hypertonic saline. (**a**) Neuronal activity of a muscle nociceptor recorded in a rat after application of hypertonic saline (5%, 25 μl). Recording provided with the courtesy of S. Mense. (**b**) Mean visual analog scale (VAS) scores (N =10) after injections of hypertonic saline into the tibialis anterior muscle. In the period with muscle pain, motor control parameters can be assessed

excited by hypertonic saline, although no specific details were given. Afferent fibers excited by hypertonic saline showed an inverse relationship between the nerve conduction velocity and saline-evoked cumulative afferent discharges (Cairns et al. 2003) substantiating the predominant excitation of thin-caliber afferents. Other algesic substances (e.g., capsaicin, glutamate, acidic buffers) have also proven reliable for induction of experimental muscle pain (Graven-Nielsen 2006).

7.3 Pain–Motor Interaction

In line with the classical sensory afferent fibers involved in motor control, e.g., tendon organs and muscle spindles (Fig. 7.2), there is dense connectivity from group III and IV afferents to the motoneurons in the ventral horn (Schomburg et al. 1999), and recently it was reported that group III afferents with nociceptive properties in particular had the strongest influence on the reflex control (Schomburg and Steffens 2002).

It is well-accepted from daily life activities that muscle pain interacts with movement performance. Muscle hyperactivity sustained by a vicious cycle due to ischemia was one of the first theories explaining the cause of muscle pain (Fig. 7.3; Travell et al. 1942). Until recently, the part of the model suggesting that muscle pain will induce ongoing muscle activity has not been systematically investigated. Hyperactivity was also proposed in the reflex-spasm and stress-causality models (deVries 1966; Cohen 1978). In addition, a physiological model based on animal data suggests muscle hyperactivity due to facilitation of the γ-motoneurons by

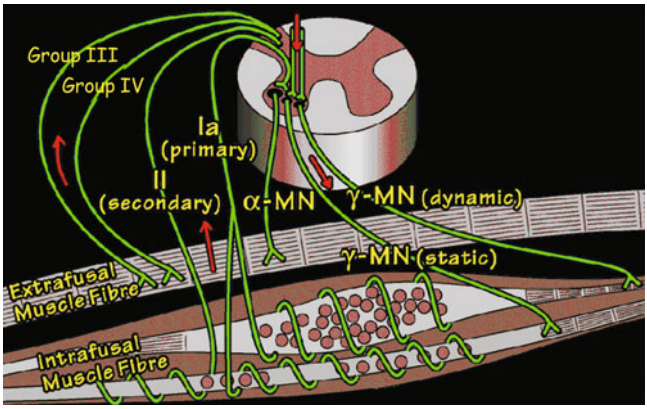

Fig. 7.2 Proprioceptive receptors (e.g., muscle spindles) have mono- and polysynaptic effects on motor neurons or interneurons and in turn affect the motor control. Deep-tissue nociceptors, group III and IV afferent fibres, have central terminals in the spinal dorsal horn, and in addition to the ascending nociceptive activity they have multiple connections in the central nervous system via second-order neurons, among others modulation of alpha and gamma motor neurons

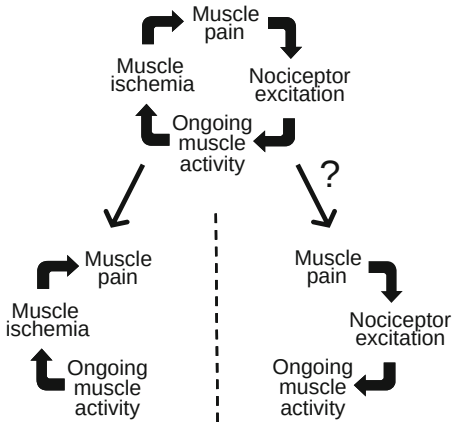

Fig. 7.3 The vicious circle postulates ongoing muscle activity, caused by muscle pain. Ongoing muscle activity will cause ischemia and over time also deep-tissue pain. The second part of the model assumes that ongoing muscle activity is evoked by muscle nociception which, however, is questionable

muscle pain (Schmidt et al. 1981; Johansson and Sojka 1991). It has been suggested that such facilitation causes a reflex-mediated spread of muscle stiffness and a possible initiation of a vicious cycle. Recent animal data, however, do not indicate facilitation of the muscle spindle activity (Ro and Capra 2001; Masri et al. 2005) but rather a change in spindle sensitivity affecting the proprioceptive function.

Lund et al. (1993) proposed the pain-adaptation model to explain the link between activity in nociceptive afferents, a central pattern generator, the motor function and coordination of muscles. This pain-adaptation model predicts increased muscle activity in antagonistic phases and decreased muscle activity in agonistic phases during muscle pain. Such a coordination may produce a decrease in movement amplitude and velocity. The pain-adaptation model includes an inhibitory

and excitatory facilitation of motoneurons according to the functional phases (agonist or antagonist) of the painful muscle, indicating the need for assessing the functional effect of muscle pain in the various functional phases of dynamic contractions, as well as in contractions without movements (static) and in resting conditions.

7.4 Resting Muscle Activity and Muscle Pain

Ashton-Miller et al. (1990) reported a small increase (<1% of EMG from maximal voluntary contraction (MVC)) in the resting activity of the sternocleidomastoid muscle after injecting 5 ml hypertonic saline (5%) into this muscle. Pain in this muscle may, however, be associated with changes in facial expression, and the observed increase in EMG activity was likely due to cross-talk from, for example, the platysma muscle. Increased resting muscle activity after saline-induced muscle pain is found compared with baseline recordings, but not compared with a sham pain condition where subjects recalled a painful condition without having the actual pain stimulation (Stohler et al. 1996). This indicates that hyperactivity is not present due to the muscle pain per se. In another study, a transient increase in the resting EMG activity during i.m. infusion of hypertonic saline was recorded in contrast to the infusion of isotonic saline (Svensson et al. 1998b). Importantly, on-going muscle pain did not produce sustained increased EMG activity. Moreover, experimental muscle pain does not cause any changes in the resting EMG activity between repeated MVC (Graven-Nielsen et al. 1997; Fig. 7.4). In contrast, glutamate-induced muscle pain caused increased resting activity in neck and facial muscles, which might suggest a difference between pain modalities or muscles (Svensson et al. 2004). Recent data suggest that increased resting muscle activity during glutamate–muscle pain is found predominately when induced in fatigued muscle (Torisu et al. 2007), and this seems to be expressed more in males than in females (Torisu et al. 2006).

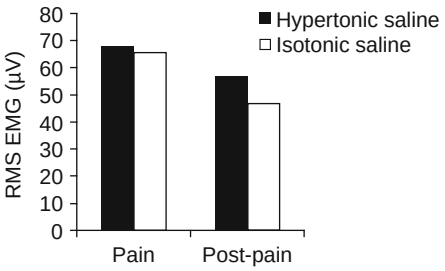

Fig. 7.4 Average resting EMG levels (root mean square values) recorded from m. tibialis anterior between maximal voluntary contractions after injections of isotonic (0.9%) and hypertonic saline (5%, 0.5 ml, $N = 9$). During pain, there was no significant spontaneous activity compared to the control injections or compared to the postpain recordings. Based on data from Graven-Nielsen et al. (1997)

In contrast to the experimental studies, both increased and unchanged resting EMG activities have been reported in musculoskeletal pain patients. Elert et al. (1989) reported an increase in the resting EMG activity between contractions in fibromyalgia patients. Others report no increase in the resting muscle EMG activity in fibromyalgia (Zidar et al. 1990), temporomandibular disorder (Bodéré et al. 2005), chronic neck pain due to trapezius myalgia (Larsson et al. 1999), and low back pain patients (Collins et al. 1982; Ahern et al. 1988). Observation of muscle spasms in the referred pain area from muscle pain evoked by trigger point activation has also been reported (Travell et al. 1944). In addition, saline-induced muscle pain produced apparently increased resting muscle activity in muscles away from the painful muscle (Simons et al. 1943; Bogduk and Munro 1979), but this finding was not constant, based on limited material, and thus difficult to interpret. In DOMS, spontaneous muscle activity (deVries 1966) and unchanged (Howell et al. 1985; Bobbert et al. 1986) resting muscle activity was found at the time of maximal soreness.

The evidence for any increased human EMG activity during muscle pain is weak, which is in strong contrast to the increases in EMG activity in animal studies (Sessle 2000). Nevertheless, the strongest responses in animal studies are seen in jaw-opening muscles and weaker effects in the jaw-closing muscle, which might be interpreted as a reflex reaction in order to avoid movements.

7.5 Static Muscle Activity and Muscle Pain

MVC during saline-induced muscle pain is significantly lower than in a control condition (Fig. 7.5; Graven-Nielsen et al. 2002, 1997; Wang et al. 2000a). The attenuation of MVC force during experimental muscle pain was not associated with changes in contractile properties of muscle fibers, but with a pure central effect; i.e., a motor control modulation (Graven-Nielsen et al. 2002; Farina et al. 2005a). A clinical demonstration of the observed decrease in muscle strength during voluntary isometric contractions of a painful muscle has also been made in musculoskeletal pain patients. In fibromyalgia patients, it is suggested that the reduction in strength is due to a deficient central activation of motor units, because supramaximal stimulation of the ulnar nerve shows no difference in the strength of the adductor pollicis muscle between patients and a control group (Bäckman et al. 1988). Attenuated MVC is also found in localized pain conditions, e.g., in lateral epicondylalgia the reduced strength of patients is recorded in their sore arm compared to asymptomatic arms in controls (Slater et al. 2005). Increased muscle activity during static contractions in trapezius myalgia patients has also been reported (Larsson et al. 1999).

During a static contraction (e.g., 80% of the MVC before pain), experimental muscle pain causes a significant reduction in the endurance time (Ciubotariu et al. 2004). The different findings between the submaximal contraction, where the required force can be obtained during pain, and the maximal contraction force

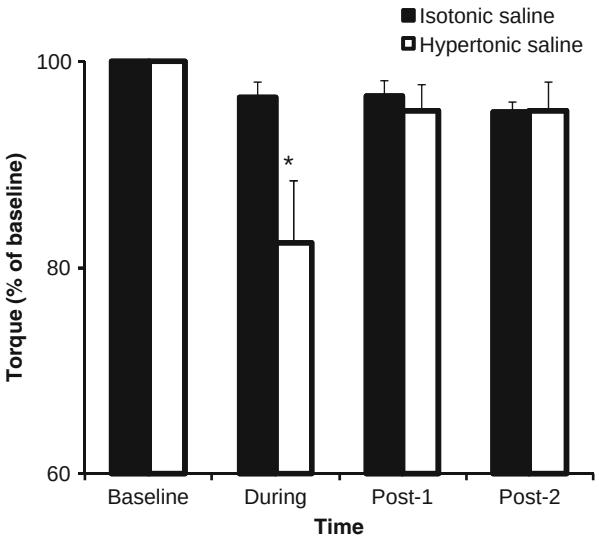

Fig. 7.5 Mean (+ SE) maximal voluntary knee extension torque recorded before and after infusion (during, 10 min and 30 min postinfusion) of isotonic and hypertonic saline into m. rectus femoris. Significantly decreased torque compared with both prepain and postpain recordings and compared with the recording immediately after infusion of isotonic saline is indicated (*asterisk*). Based on data from Graven-Nielsen et al. (2002)

which is reduced by muscle pain may be explained by changes in the descending neural drive to motor neurons. The descending neural drive cannot be voluntarily increased during MVC, and therefore an inhibitory mechanism controlling the motor neurons might explain the decreases in MVC. When submaximal contractions are performed, the voluntary neural drive may be increased and thus compensate for potential inhibitory mechanisms. In addition to the shorter endurance time, experimental muscle pain also delays the recovery phase after fatiguing contractions (Ciubotariu et al. 2007), obviously making the combination of fatigue and pain a detrimental condition.

In accordance with experimental findings (Graven-Nielsen et al. 1997), a decreased endurance time is reported in muscle pain patients performing a submaximal contraction compared with age- and sex-matched control subjects (Clark et al. 1984; Elert et al. 1993; Bengtsson et al. 1994;Gay et al. 1994). If submaximal contractions during muscle pain are obtained by increased voluntary neural drive, the decreased endurance time may alternatively be due to a more pronounced central fatigue (James et al. 1995). In clinical studies, various physiological factors within the muscle (e.g., microcirculation) could influence endurance time, but this is not likely to occur in healthy volunteers exposed to experimental muscle pain.

Decreased surface EMG activity is detected for contraction levels above 25% MVC (Falla et al. 2007a), but at low contraction levels, attenuations are also detectable by slow firing of single motor unit activity (Sohn et al. 2000; Farina

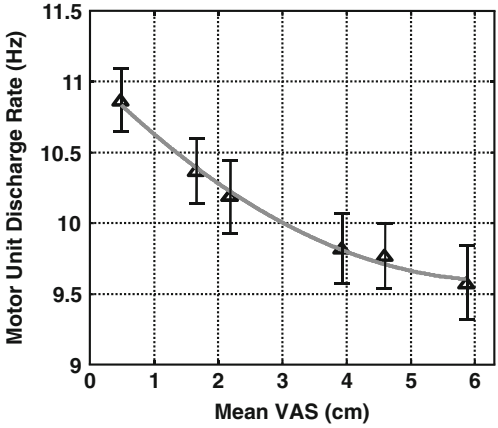

Fig. 7.6 The correlation between average (± SE) firing rate of single motor unit recordings (m. tibialis anterior) and VAS scores from six standardized low-intensity contractions after injection of different volumes of hypertonic saline inducing different levels of pain. A close relation between pain intensity and motor unit decrease is seen. Based on data from Farina et al. (2004)

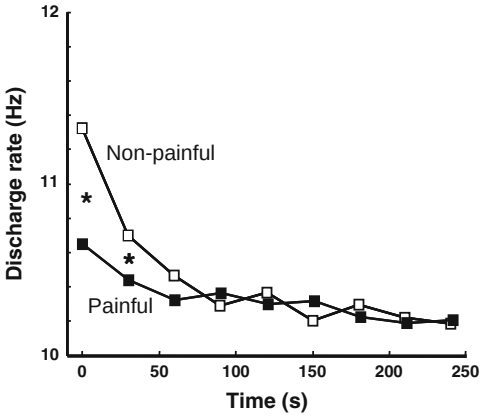

Fig. 7.7 Mean discharge rate at different time instants during a prolonged contraction at 25% of the maximal dorsiflexion torque with injections of hypertonic and isotonic saline. Experimental muscle pain significantly reduced the initial motor unit discharge rates compared to the control condition (*asterisks*). Based on data from Farina et al. (2005b)

et al. 2004). The reduced motor unit firing is correlated to the amount of induced pain (Fig. 7.6). Reduced motor unit firing over time is also detected in nonpainful but fatiguing contractions (Fig. 7.7), and interestingly the initial firing rate is reduced to the same level as during fatiguing contractions, suggesting that the muscle nociceptive activity is strongly associated with the reduced motor unit firing during fatigue (Farina et al. 2005b).

An important observation is that the muscle pain during static contractions does not only decrease the muscle activity of the painful muscle, but also attenuates the synergistic muscles (Ciubotariu et al. 2004; Falla et al. 2007a). The spatial distribution of muscle activity can be assessed by surface matrix EMG electrodes, and the trapezius muscle activity was found to be completely reorganized and reduced by experimental muscle pain (Madeleine et al. 2006). To produce the required force, the generalized inhibition calls for a changed muscle coordination and eventual overload of otherwise nonpainful muscles. As motor unit firing rate is an

important determinant of the force generated in a muscle, it is unclear how constant force can be maintained despite the decrease in motor unit firing rate during muscle pain. Changes in motor unit twitch properties have been suggested as a compensatory mechanism for the decreased motor unit firing during pain. Indeed, increased twitch force of low-threshold motor units has been reported during experimental muscle pain (Sohn et al. 2004; Farina et al. 2008). In contrast, the muscle membrane properties seems not to be affected by experimental muscle pain, as both motor unit conduction velocity (Farina et al. 2005b) and M-wave (Farina et al. 2005a) are unchanged. Interestingly, the peak twitch force remained increased also in postpain conditions, where the motor unit firing rate returned to normal (Farina et al. 2008). This strongly suggests that the facilitated twitch force is not the mechanism compensating for the decline in motor unit firing rate. Another likely mechanism for the maintenance of force is that the nervous system may increase the activity of muscles with a synergistic action to compensate for decreased force production by a painful muscle. However, a recent study actually reported that motor units in synergistic muscles neighbouring a painful muscle show reduced firings, (Fig. 7.8; Hodges et al. 2008). Thus, increased firing of low threshold motor units in synergistic muscles does not account for maintenance of force during painful constant force contractions. Possible recruitment of additional higher threshold motor units during pain is an attractive mechanism for explaining the maintained force with reduced motor unit firing, but this needs to be further investigated.

The widely used model based on saline injections has been shown not to affect the contractile apparatus (Graven-Nielsen et al. 2002). In contrast, DOMS (DOMS) is probably based on ultrastructural damage affecting the contractile properties, resulting in loss of force. Inhibition of motor cortex and/or spinal motoneurons may contribute to the loss of force, especially in the first 24 h (Prasartwuth et al. 2005). In a recent study, eccentric contractions caused reduced EMG amplitude during sustained contractions which was not seen before DOMS, suggesting a change in

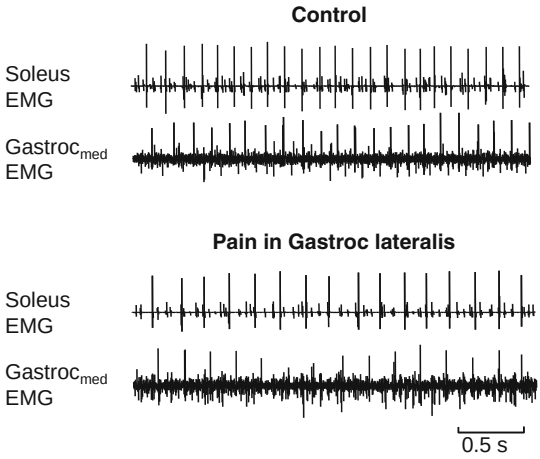

Fig. 7.8 Motor unit recordings from the soleus and medial head of gastrocnemius muscle before and after induction of experimental pain in the lateral head of the gastrocnemius muscle by hypertonic saline. During pain, the instantaneous firing rate is significantly reduced in synergistic motor units. Based on data from Hodges et al. (2008)

the contractile properties (Hedayatpour et al. 2008). Other studies show no change (Bajaj et al. 2002; Pearce et al. 1998), increased (Kroon and Naeije 1991), and decreased (Nie et al. 2007) EMG activity of static contractions in DOMS. Therefore caution is needed in conditions including changes of the contractile properties as well as modulation of motor control parameters by nociception.

7.6 Dynamic Muscle Activity and Muscle Pain

In experimental and clinical low back muscle pain, low back muscle activity was recorded during gait on a treadmill; during pain, the low back muscle activity was: (1) increased in phases where the EMG activity is normally silent, and (2) not affected or decreased in the phases with strong EMG activity in control subjects (Arendt-Nielsen et al. 1996). During gait, muscle pain causes typically decreased EMG in the agonistic phase and increased EMG in the antagonistic phase of the leg muscle activity (Graven-Nielsen et al. 1997). Another example is found in trunk flexion–extension movements, where the antagonist phase, normally silent in pain-free controls, showed increased activity in low back patients (Sihvonen et al. 1991). This indicates that the pain modulation of muscle activity is dependent on the specific muscle function (agonist/antagonist phases), which has also been reported in several previous clinical studies (Lund et al. 1993). The functional consequence of this is reduced movement amplitudes as found in experimental and clinical musculoskeletal pain conditions such as low back pain (Arendt-Nielsen et al. 1996). This reorganized motor control may protect the painful muscle by reducing the muscle activity and contraction force. However, other strategies might be adopted, as individual combinations of increased, decreased and cocontraction activity of trunk flexors and extensors have been reported to maintain spine stability in conditions of experimental low back pain (Hodges et al. 2006). Decreased activity in both the agonistic and antagonistic muscles during muscle pain has been found, without impairing the movement amplitude or acceleration significantly (Ervilha et al. 2004a). The initial (100 ms) agonistic EMG burst activity in particular was decreased, illustrating that the motor strategy was reorganized by muscle pain (Fig. 7.9). Another example of changes in motor planning is illustrated by reduced feed-forward responses of the abdominal muscles in conditions of pain induced in the lower back muscles, which might compromise the spinal stability (Hodges et al. 2003). Finally, gait initiation is also dependent on specific motor control strategies which have been perturbed by experimental muscle pain (Madeleine et al. 1999). Abnormal motor planning is highly important in occupational settings, where such a change may need compensatory action from other muscles to fulfil the required movement and thereby possibly contribute to the development of musculoskeletal pain problems. Increased trapezius activity during contractions has been found during biceps muscle pain, which might illustrate a compensatory action (Ervilha et al. 2004a). Moreover, reorganization of trapezius muscle activity during repetitive shoulder flexion has been found as activity of the upper trapezius

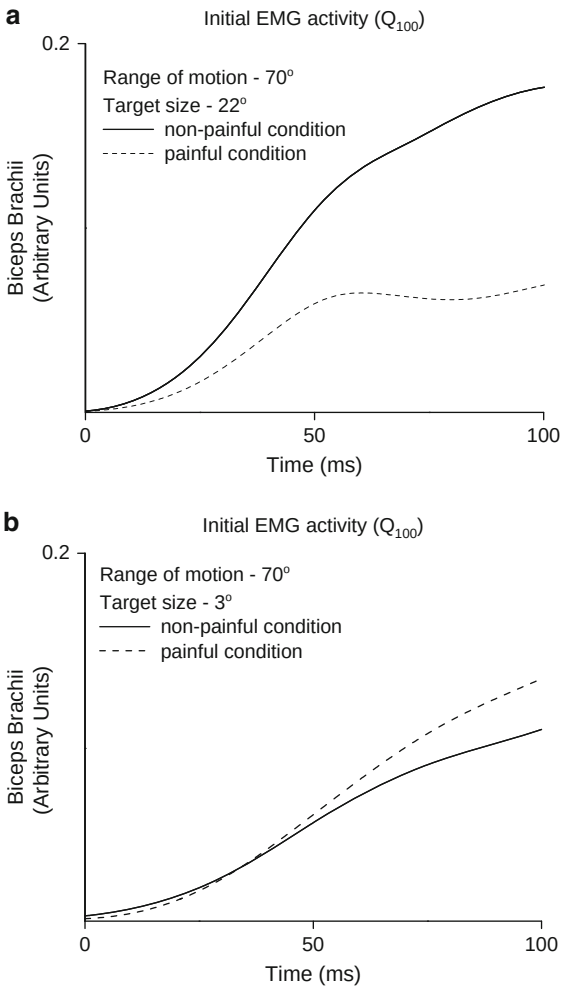

Fig. 7.9 The effect of muscle pain on the motor control scheme is depending on many variables. The motor control strategy is defined by the required task and typically reflected in the initial muscle activity. Two specific strategies are illustrated for pointing movements to a wide (**a**) and narrow (**b**) target size. Pointing to a wide target during muscle pain results in reduced muscle activity in the initial phase (100 ms), which is then later voluntarily adjusted to the same activity level with and without pain (not shown) to fulfil the requirements. In contrast, another strategy is applied when pointing to a narrow target, where there was no significant modulation of the muscle activity by muscle pain (Ervilha et al. 2004b). Therefore, the effect of pain is strongly dependent on the strategy and degrees of freedom accepted within the specific strategy

(where pain was induced) decreased, and the lower trapezius showed compensatory actions by increased muscle activity (Falla et al. 2007b).

Muscle pain can have a strong biomechanical impact on the other skeletal structures. Recently, the functional significance of muscle pain on knee joint control during gait was assessed by three-dimensional gait analyses during experimental pain induced in the vastus medialis muscle. Muscle pain modulated the function of the quadriceps muscle, resulting in impaired knee joint control and joint instability during walking (Henriksen et al. 2007). These changes are similar to those observed in patients with osteoarthritic knee pain. The loss of joint control may leave the knee joint prone to injury, potentially participate in the chronicity of musculoskeletal problems, and may have clinically important implications for the rehabilitation and training of patients with knee pain of musculoskeletal origin.

7.7 Motor Neuronal Excitability During Muscle Pain

The central mechanisms potentially involved in the decrease of muscle activity during pain may be numerous. The H-reflex is not affected, whereas the stretch reflex is facilitated during experimental muscle pain (Truini et al. 2006; Matre et al. 1998; Svensson et al. 1998a; Wang et al. 2000b). Recent microneurography recordings from spindle afferents showed no increased discharge activity during experimental pain, suggesting that muscle pain does not cause a reflex increase in fusimotor drive, in contrast to the hyperactivity theory (Birznieks et al. 2008). Increased stretch reflexes might be related to more pronounced stiffness in the painful motor system, and result in impaired motor performance. The long-latency inhibitory reflex (silent period) is disinhibited (i.e., net facilitation) during experimental muscle pain (Wang et al. 1999). There is no consistent relationship between the findings describing muscle pain induced reflex facilitation and decreased muscle activity during muscle pain. Most experimental studies assessing the effect of muscle pain on excitatory and inhibitory reflexes have, however, not assessed the potential effect of postsynaptic modulation by nociceptive activity, since the motor unit firing rate or global muscle activity were kept constant before assessing the reflex. A recent study has demonstrated facilitated homonymous recurrent inhibition of the soleus muscle during experimental muscle pain with a close relationship

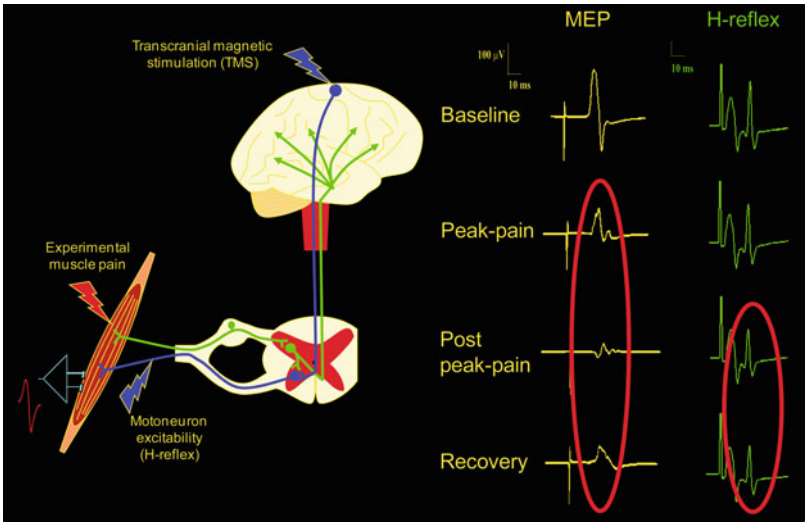

Fig. 7.10 Potential interactions between muscle nociception and motor control can be evaluated by neurophysiological techniques. For example, during experimental muscle pain the motor neuron excitability can be assessed by the H-reflex, and measurements of the transcranial magnetic evoked potentials (*MEP*) indicate the cortical motoneuronal excitability. Le Pera et al. (2001) showed reduced transcranial magnetic motor evoked potentials from the abductor digiti minimi muscle during muscle pain, and with a time lag the spinal motoneurons also showed reduced excitability assessed by the H-reflex. Decreased potentials are *encircled*

between the temporal aspects of the pain and efficacy of recurrent inhibition (Rossi et al. 2003). The functional effects of facilitated recurrent inhibition are complex (Katz and Pierrot-Deseilligny 1999), but reduced muscle activity during muscle pain might reflect facilitated recurrent inhibition by muscle pain.

The complex changes in the motor neuronal system are further illustrated by differential effects of muscle nociception on spinal and cortical motor neurons. In a recent study, muscle nociception facilitated spinal motor neurons innervating elbow flexor and extensor muscles, and at the same time depressed motor cortical neurons projecting to these muscles (Martin et al. 2008). In line with this, a previous study showed reduced motor transcranial magnetic evoked potentials from the abductor digiti minimi muscle during muscle pain, and with a time lag the spinal motor neurons also showed reduced excitability assessed by the H-reflex (Fig. 7.10; Le Pera et al. 2001). The variety of reflex changes caused by muscle pain substantiates the complex interaction between pain and reflexes probably due to the highly flexible and plastic motor control system.

7.8 Conclusion

Motor control reorganization is a fundamental factor in muscle pain conditions, and is probably crucial in understanding mechanisms translating acute pain to chronic pain conditions. The interaction between muscle pain and motor control depends on the specific motor task. Muscle pain causes no increase in EMG activity at rest, and reduces MVC and endurance time during submaximal contractions. Moreover, muscle pain causes a change in the coordination during dynamic exercises. The functional adaptation to muscle pain may also involve increased muscle activity reflecting reorganized muscle coordination and strategy. Overall, these findings do not support the "vicious cycle" hypothesis, but rather an adaptive model predicting reduced agonistic muscle activity eventually advanced by decreased antagonistic muscle activity.

The presented experimental pain techniques are needed to translate basic findings into the clinical manifestations and mechanisms. Motor control assessment procedures can provide complementary clinical information, and give qualified clues to revise and optimize treatment regimes.

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Glossary

The glossary contains the terms and definitions as used in the book. Some of the terms were adopted from Stedman's Concise Medical Dictionary (2nd edn., J.T. McDonough (ed), Williams and Wilkins, Baltimore, 1994), from the Classification of Chronic Pain (2nd edn., H. Merskey and N. Bogduk (eds), IASP Press, Seattle, 1994), from Dorland's Illustrated Medical Dictionary (31st edn., AW. Block et al. (eds), Saunders Elsevier, Philadelphia, 2007) and from Loeser and Treede (2008) Pain 137:473–477.

A band The (anisotropic) dark band that can be seen running across muscle fibers in the light microscope. It is formed by the aligned myosin filaments of many myofibrils, and causes the visible striations of skeletal muscle fibers. The A band contains mainly myosin filaments, and has a zone of overlap with actin filaments.

Abduction A movement which draws a limb away from the median plane of the body.

Acetylcholine (ACh) The neurotransmitter of the neuromuscular endplate (junction between a motor fiber and a muscle cell).

Acetylcholinesterase (AChE) An enzyme that specifically degrades (through its hydrolytic activity) ACh, producing choline and an acetate group.

Acetylsalicylic acid (ASA) Aspirin, one of the nonsteroidal anti-inflammatory drugs.

Acid-sensing ion channels (ASICs) A family of receptor molecules that are sensitive to a drop in pH, and open at various pH values.

Action potential A propagated change of the membrane potential of a nerve or muscle cell. If the membrane is depolarized (its inside made more positive) to threshold, a sudden influx of sodium ions occurs that makes the membrane

potential transiently positive. It becomes negative again through an outflux of potassium ions.

Activation Stimulation of a receptor or neuron so that it starts firing action potentials or increases its discharge frequency.

Active TrP (trigger point) A myofascial trigger point that produces pain spontaneously, or with activity.

Acute pain Pain caused by a short-lasting noxious (painful, tissue-threatening) stimulus acting on normal nociceptive structures. Acute pain does not lead to long-lasting changes in the nervous system, i.e., after the end of the acute pain, the nociceptive system returns to its normal state of excitability.

A-delta (A-δ) fiber A thin *myelinated* nerve fiber that conducts action potentials at a velocity of approximately 2.5–30 m/s in man.

Adenosine triphosphatase (ATPase) An enzyme that splits adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and phosphate (P) plus energy.

Adenosine triphosphate (ATP) A molecule that provides energy for energy-dependent cell processes by splitting into adenosin-diphosphate (ADP) and energy. ATP is also assumed to be a cotransmitter in sympathetic efferent neurons.

Adhesions Inflammatory bands which bind surfaces together that are covered by mucous membranes.

Adventitia Connective tissue surrounding blood vessels and some inner organs.

Affect An emotional state, incorporating feelings and mood.

Afferent fiber or nerve cell A neuron that conducts action potentials from the periphery to the central nervous system (primary afferent fiber) or to higher centers within the central nervous system (secondary or higher order afferent neurons). Often 'sensory' is used as a synonym for afferent.

Afferent unit An afferent (sensory) fiber including the receptive ending in the body periphery, cell body in the spinal or cranial ganglia, and central terminal in the spinal cord or brain stem.

Afterdischarge A discharge of neurons outlasting the duration of the stimulus. Afterdischarges in nociceptors are likely to be the cause of painful aftersensations following strong painful stimuli.

Agonistic muscle activity Muscle activity producing the movement.

Algesic substance A substance that causes pain and/or increases the sensitivity of pain receptors (e.g., bradykinin, serotonin, high concentrations of potassium ions, protons).

Algogenic (or algesic) Pain-producing.

Algometer (algesiometer) A hand-held device used to exert a defined pressure on the muscle and to determine the pressure pain threshold.

Algometry (measurement of pain) In practice, algometry is the measurement of tenderness in response to a force applied perpendicularly to the skin.

Alleles One of the variant forms of a gene at a particular locus, or location, on a chromosome. A single allele for each locus is inherited from each parent.

Allodynia A condition in which normally nonpainful stimuli are perceived as painful (decreased pain threshold: for instance, tactile stimuli evoke pain.)

Amino acid transmitters Neurotransmitters that consist of amino acids such as glutamate and aspartate.

Aminoacyl tRNA-synthetases (aaRS) These are enzymes that promote binding of specific amino acids to their cognate tRNA to form an aminoacyl-transferRNA (tRNA). This is an important step for protein synthesis.

AMPA channels Also called non-NMDA channels. AMPA is alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate, a neurotransmitter that binds to and opens a specific channel in the nerve membrane (together with kainate). The AMPA channels are mainly permeable to sodium ions.

Amygdala Short form for corpus amygdaloideum, a nucleus in the brain. The amygdala is a major nucleus for the processing of stress and fear reactions.

Amyopathic dermatomyositis/hypomyopathic dermatomyositis Skin rash typical for dermatomyositis, but with no or mild muscle weakness.

ANA Anti nuclear autoantibodies.

Analgesia Absence of pain in response to a stimulus which would normally be painful.

Anaphylaxis The immediate transient kind of immunologic (allergic) reaction characterized by contraction of smooth muscle and dilation of capillaries due to release of pharmacologically active substances such as histamine, bradykinin, and serotonin.

Antagonistic muscle activity Muscle activity counteracting and stabilizing the movement.

Anterograde transport Intraaxonal transport in the distal direction (away from the cell body of a neuron) of substances synthesized in (or injected into) spinal or cranial ganglion cells.

Antidromic An impulse propagation against the normal direction. Mainly used for action potentials in sensory fibers when they propagate toward the body periphery.

Anti-Jo-1 Anti-histidyl-tRNA synthetase; myositis-specific antibody.

Anti-Mi-2 Anti-SFN2-superfamily nuclear helicase; myositis-specific antibody.

Anti-SRP antibody Antisignal recognition particle; myositis-specific antibody.

Antisynthetase syndrome Clinical phenotype, associated with antisynthetase antibodies, characterized by myositis, interstitial lung disease, Raynaud's phenomenon, mechanic's hands and nonerosive arthritis.

Aponeurosis A fibrous sheet or expanded tendon, giving attachment to muscular fibers, and serving as the means of origin or insertion of a flat muscle (Sted.)

Arteritis Inflammation involving an artery (Sted).

Arterioles Small arterial vessels of a size between arteries and capillaries. In contrast to capillaries, the wall of arterioles contains a thin layer of smooth muscle cells.

Association cortex Those parts of the cortex that are not specialized, in the sense that they process sensory or motor information directly. In the association cortex, information processing at a higher level takes place, and for this purpose information from many different cortical areas as well as previous experiences are used.

Atrophy (of a muscle) A wasting of tissue, e.g., from disuse.

Autoimmune disease A disease arising from and directed against the individual's own tissues (Sted).

Autonomic nervous system Those efferent parts of the nervous system that are not under voluntary control. It consists of two main parts: sympathetic and parasympathetic nervous system. Some authors distinguish a third part, the enteric system that is located in the walls of hollow inner organs.

Axial muscles Head and trunk muscles that are situated in the central part of the body.

Axodendritic synapse A contact between the axon of one neuron and the dendrite of another nerve cell.

Axon A process of a neuron that conducts action potentials away from the cell body. The axon is the output portion of a neuron.

Axon reflex The invasion of nonexcited branches of a receptive ending by antidromic action potentials arising in other excited branches of the ending or in the axon. Antidromic action potentials propagate against the normal direction of conduction. The invasion is followed by the release of neuropeptides from the retrogradely invaded branch of the nociceptor. The

neuropeptides influence the microcirculation in the vicinity of the ending. The flare reaction (reddening of the skin) around a lesion is assumed to be due to the axon reflex.

Axotomy The transection of nerve fibers or a nerve.

Basal ganglia Originally, all of the large masses of gray matter at the base of the cerebral hemisphere; currently, the corpus striatum (caudate and lentiform nucleus) and cell groups associated with the corpus striatum (Sted).

Benign Denoting the mild character of an illness, or the nonmalignant character of a neoplasm (Sted).

Bidirectional referral The term describes the situation that for example, pressure on the original lesion evokes referred pain, *and* that also pressure on the area of referral evokes pain from the original lesion. See 'unidirectional referral.'

Biofeedback A training technique that enables an individual to gain some element of voluntary control over autonomic (or other involuntary) body functions (Sted). In EMG feedback training, the patient sees or hears the EMG of the affected muscle, and thus receives information (feedback) about the contractile state of the muscle he/she is trying to relax or activate.

Blood Oxygenation Level Dependent (BOLD) Brain cells need oxygen to function. Red blood cells in the brain thus go from an oxygenated state (lots of oxygen bound to the hemoglobin of the red blood cell) to a deoxygenated state (less oxygen bound) during functional activation of the brain. This changes the magnetic properties of the blood, which can be measured with fMRI. The effect of the change of magnetic properties of the blood cells is called the BOLD response. Simplistically speaking: the more energy a certain brain area needs because of its activity, the higher the BOLD response in this area.

Botulinum A toxin (D-Botulinum A toxin (BTX)) The toxin of the bacterium clostridium botulinum, which can be present in improperly preserved food. It acts by preventing ACh release and destroying the neuromuscular junction, thereby inducing a selective and reversible muscle weakness of up to several months when injected intramuscularly in minute quantities. The toxin is used in the therapy of spasticity.

Bradykinin (BKN) A molecule composed of nine amino acids (a nonapeptide). One of the so-called vasoneuroactive substances; it dilates blood vessels and sensitizes or excites nociceptors. BKN is cleaved from a precursor protein (kallidin) in the blood plasma.

Bradykinin receptors (B1 and B2) In intact tissue, BKN excites or sensitizes nerve endings by the activation of the bradykinin receptor molecule B2, whereas under pathological conditions (e.g., inflammation) the receptor B1 is

the predominant BKN receptor. The de novo synthesis of the B1 receptor is a neuroplastic change in the *peripheral* nervous system.

Brainstem The mesencephalon plus rhombencephalon (other definitions also exist). The rhombencephalon includes the pons, cerebellum, and medulla oblongata (syn.:hindbrain) (Sted).

Branched fiber theory of referral Referral due to branching of a primary afferent fiber, the branches supplying two separate regions or tissues.

Brodmann area A region of the cortex characterized by a particular cytoarchitecture, i.e., size, arrangement, and density of nerve cells.

Bruxism A clenching of the teeth, resulting in rubbing, gritting, or grinding together of the teeth, usually during sleep (Sted).

Bullous rash Fluid-filled blisters larger than 1 cm. A skin symptom that can be seen in dermatomyositis.

cAMP Adenosine 3′,5′-cyclic monophosphate (Sted), an intracellular second messenger that is part of the cascade of events that transforms the action of neurotransmitters or other substances into metabolic changes in the affected cell.

C fiber An *unmyelinated* nerve fiber that conducts action potentials at a velocity of less than 2.5 m/s in man.

Calcitonin gene-related peptide (CGRP) A neuropeptide composed of 37 amino acids.

Calcium pump An energy-dependent transport mechanism that transports Ca^{2+} across a membrane. For instance, it returns Ca^{2+} ions into the sarcoplasmic reticulum of a muscle cell to terminate muscle contraction following their release to activate the contraction.

cAMP response element binding (CREB) protein A transcription factor that binds to certain DNA sequences called cAMP response elements (CRE) and thereby increases or decreases the transcription. It thus controls the expression of certain genes. Phosphorylation of CREB (addition of a phosphate (PO_4) group to the molecule) can turn the transcription factor on or off.

Candidate gene A gene thought most likely to be responsible for a given effect.

Capillary The smallest blood vessel. Here, the exchange processes between blood and tissue take place. Capillaries consist of an inner layer of endothelial cells and a basal lamina. They lack a muscle layer.

Capsaicin The active ingredient of chilli pepper which causes the burning sensations after ingestion. It is a powerful stimulating agent for afferent C fibers that possess the molecular TRPV1 receptor. Its stimulating action is often followed by reduced sensitivity of C nociceptors, i.e., by desensitization.

Carrageenan A sulphated polysaccharide derived from Irish moss; it is used in animal experiments to induce a sterile inflammation.

Catastrophization Psychological response where a person interprets events in the worst possible way.

Catecholamines Pyrocatechols with an alkylamine side chain; for example, epinephrine, norepinephrine (Sted), dopamine.

Caudal Relating to the tail end of an organism.

Causalgia A syndrome of sustained burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes.

Cellulitis Inflammation of cellular or connective tissue.

Central nervous system (CNS) The brain and the spinal cord.

Central pain Pain initiated or caused by a primary lesion or dysfunction in the central nervous system, e.g., spinal cord injury, CNS ablative surgery, stroke lesion in the thalamus.

Central sensitization Mechanisms that lead to increased excitability of nociceptive neurons at the spinal (and higher) levels. The central sensitization can last for long periods of time following an acute painful stimulus.

Cerebral ventricles Normal cavities in the brain which are interconnected and filled with cerebrospinal fluid. The third ventricle is located in the midline diencephalon; its lateral walls are partly formed by the thalamus and hypothalamus.

c-fos Cellular (c) oncogene that controls the growth of osteosarcoma (os). It is one of the immediate early genes IEGs) that are expressed in neurons within a few hours following stimulation.

c-Fos The transcription factor (protein) synthesized by the c-fos gene. C-Fos is widely used as a general neuronal activity marker, particularly for nociceptive neurons.

Chronic pain That pain which persists past the normal time of healing; in clinical practice a period of 3 months is recognized as a convenient dividing line between acute and chronic pain. Chronic pain is characterized by suffering rather than painful sensations.

Cinderella hypothesis It postulates that during monotonous work at low force level, just a few — and always the same — type I motor units are activated, which have the lowest activation threshold and therefore are the first to be recruited and the last to be derecruited. These muscle fibers do most of the work, and are likely to be overloaded.

Cingulate cortex or gyrus A gyrus on the medial aspect of a hemisphere located directly above and running parallel to the corpus callosum.

Colic Spasmodic pain in the abdomen (Sted).

Collateral A side-branch of an axon.

Complex regional pain syndrome (formerly called reflex sympathetic dystrophy) Forms of pain (e.g., causalgia, Sudeck syndrome) that are associated with signs of sympathetic disturbances, and therefore suggest an involvement of the sympathetic system.

Compliance The compressibility of, for example, a muscle that can be assessed clinically by pressing a finger into it or by squeezing it between the fingers to determine how easily it is indented and how "springy" it is.

Compound action potential Summed action potentials of many fibers in a nerve which are excited simultaneously, e.g., by an electrical stimulus.

Concentric (shortening) contraction A reduction of muscle length produced by generation of muscle force. An example is the quadriceps femoris muscle extending the knee during walking uphill.

Contractile activity Forms of activation of the contractile apparatus of a muscle: (1) electrogenic contraction or stiffness (muscle tension coming from voluntary muscle contraction accompanied by observable EMG activity and seen in normals who are not completely relaxed; the term electrogenic refers to propagated action potentials originating in the α-motor neurons and transmitted by the neuromuscular junctions), (2) electrogenic spasm that specifically identifies pathological involuntary electrogenic contraction, and (3) contracture in the physiological (dynamic) sense arising endogenously within the muscle fibers, independent of EMG activity.

Contraction knot The salient histopathological feature of a myofascial trigger point. It exhibits localized (segmental) contractions of only part of an individual muscle fiber.

Contraction-sensitive receptor A muscle receptor that responds strongly to physiological contractions. Probably, the receptors are identical to the "ergoreceptors" that mediate circulatory and respiratory adjustments during muscle work.

Contracture (1) In the clinical (static) sense: shortening of muscle caused by remodeling of connective tissue that may include joint capsules and ligaments and reduction in the number of sarcomeres. These changes occur when the muscle remains in a shortened position for a prolonged period of time. Like the contracture in the physiological sense, this condition lacks EMG activity, but for a different reason. (2) In the physiological (dynamic) sense or rigor: an activation of the contractile mechanism of a muscle (sliding of actin and

myosin filaments) unaccompanied by electrical activity of the muscle cell, i.e., in the absence of EMG activity.

Convergence A neuroanatomical connection implying that inputs from many sources make synaptic contacts with a single neuron in the central nervous system.

Convergence-facilitation theory of pain referral A theory put forward by McKenzie which assumes that a continuous impulse traffic from one peripheral source can enhance the responses of a CNS neuron to the input from a second source.

Convergence-projection theory of pain referral A theory put forward by Ruch which assumes that afferent connections from two input sources contact the same dorsal horn neuron. The main difference to the convergence-facilitation theory is that no change in responsiveness of the dorsal horn neuron or in the efficacy of the input connections is necessary.

Cortical reorganization A functional or structural change in the primary sensorimotor areas of the cortex that can also occur in the adult nervous system, but was long thought possible only in the developing organism.

Cramp Painful muscle spasm associated with EMG activity, such as nocturnal leg cramp. Sometimes, EMG-free contracture (as observed in McArdle disease) is also called cramp, but actually is a dynamic contracture in the physiological sense.

Cranial Relating to the head end of an organism.

Cranial nerve A peripheral nerve whose fibers originate and terminate in supraspinal portions of the central nervous system (brainstem and diencephalon). The cranial nerves are numbered with the Latin numerals I–XII. For instance, cranial nerve X is the vagus nerve.

Curare A plant extract that produces paralysis of skeletal muscle by blocking the receptor molecule for acetylcholine in the postsynaptic portion of the neuromuscular endplate.

Cyclooxygenase (COX) An enzyme that synthesizes prostaglandins from arachidonic acid. Some of the prostaglandins (e.g., PGE2) sensitize nociceptors.

Deafferentation Abolition of the influence of afferent fibers (or afferent activity) from central nervous neurons. Dorsal root avulsion is an example of traumatic deafferentation.

Deep somatic tissues All subcutaneous tissues that are not viscera, namely tendon, fascia, muscles, ligaments, and joints.

Demyelination Destruction of the myelin sheath of thick nerve fibers caused by degenerative and metabolic diseases (e.g., multiple sclerosis or diabetes).

Dendrite A process of a central neuron where most of the synaptic contacts with axons of other neurons are located. A dendrite is the input region of a neurone.

Dermatographia Wheal and flare response elicited by gentle cutaneous stimulation.

Dermatome The area of skin supplied by cutaneous branches from a single spinal nerve (Sted).

Descending antinociceptive (pain-inhibiting) system A network of neurons that originates in the mesencephalon and medulla, and inhibits the activity of spinal nociceptive neurons via descending axons.

Descending facilitation Pain-enhancing activity of a network of spinal nociceptive neurons that originate in the mesencephalon and medulla, and influence spinal neurons via descending axons. These pain-facilitating neurons are intermingled with the pain-inhibiting neurons of the antinociceptive system.

Descending inhibition A network of neurons that originates in the mesencephalon and medulla oblongata and inhibits spinal nociceptive neurons (syn.: descending antinociceptive system).

Desensitization A reduction in sensitivity of a neuron to a chemical stimulus, caused by the same or another stimulant. An example is the desensitization of receptors caused by capsaicin after initial excitation.

Diffuse noxious inhibitory controls (DNIC) The term refers to a phenomenon where a painful stimulus in one area of the body is inhibited by a second painful stimulus that is applied to any part of the body, distinct from the excitatory receptive fields of the neurons of the first stimulus.

Diffusion Tensor Imaging (DTI) DTI determines the mobility of water in the brain tissue as a function of the direction the water molecules can move. It enables the measurement of the restricted diffusion of water in tissue in order to produce images of neural tracts or nerve fiber bundles.

Disinhibition The abolition of an existing inhibition of a neuron. In terms of discharge frequency of an active neuron, disinhibition is equivalent to activation.

Distal Situated away from the center of the body, or from the point of origin; applied to the extremity or distant part of a limb or organ (Sted).

Divergence A neuroanatomical connection implying that a single afferent fiber has synaptic contacts with more than one central nervous neuron.

Dolorimeter A device for measuring the intensity of a painful stimulus.

Dorsal horn The dorsal portion of the gray matter in the spinal cord. Here, sensory neurons — including nociceptive ones — are located.

Dorsal root Fiber bundles that enter the spinal cord at the dorsolateral circumference of the spinal cord. It contains primary afferent fibers.

Dorsal root ganglion An accumulation of sensory nerve cell bodies forming part of a dorsal root. The cell bodies in the ganglion have a central process that terminates in the spinal cord, and a peripheral one that forms one or several receptive nerve endings.

Dry needling A technique of stimulating a myofascial trigger point with a needle inserted through the skin and into a trigger point, to induce a local twitch response and inactivate the trigger point.

Dysesthesia An unpleasant abnormal sensation, whether spontaneous or evoked (IASP).

Dysfunctional endplate It releases spontaneously much more ACh than a normal endplate. This leads to a depolarization of the postjunctional membrane (the muscle cell membrane), which releases Ca^{2+} from the sarcoplasmic reticulum. A local contracture of the muscle fiber under or in the vicinity of the endplate ensues.

Dystonia An abnormal tonicity in any of the tissues (Sted).

Eccentric (lengthening) contraction A passive increase in muscle length, with muscle force resisting the lengthening of the muscle by external forces. In eccentric contractions, the force developed by the muscle is smaller than the external force causing the lengthening. An example is the contraction of the quadriceps muscle during walking downhill.

Ectopic Out of place (Sted). With regard to neuronal activity, the term means that the discharges originate at an abnormal location, i.e., not at the receptive ending (in the case of an afferent fiber) or in the soma of a motor neuron, but in a CNS tract, peripheral nerve or dorsal root. Neuropathic pain is often associated with ectopic discharges.

Edema An accumulation of an excessive amount of watery fluid in cells, tissues or serous cavities (Sted).

Elastic stiffness In physics, it is the steady force required to produce unit displacement in an elastic system. In skeletal muscle, it is the elastic part of the viscoelastic component of resistance to movement. It is clinically tested by performing slow movements (where the viscosity does not influence the measurement).

Electroencephalography (EEG) EEG measures the electrical activity or brain wave patterns of the brain. The electrical activity is measured by surface electrodes on the scalp and amplified for observance via a computer. The

resulting image reflects the summation of the activity of millions of individual neurons.

Electrogenic contraction A contraction elicited by electrical activity of the motor nerve and muscle cell (in contrast to a contracture, which occurs without electrical activity in both structures).

Electrogenic spasm The pathological involuntary electrogenic contraction of long duration. Muscle spasm in this sense is always accompanied by EMG activity.

Electromyography (EMG) A procedure whereby the electrical activity of muscle is displayed visually and audibly. Electromyography can be performed with needle electrodes inserted through the skin into the muscle, or by placing disk electrodes on the skin (surface electromyography).

Elevation Lifting a part of the body.

Emotional–affective component of pain The pain component that is identified with suffering.

Endogenous Originating or produced within the organism (Sted).

Endomysium A thin layer of loose connective tissue around a single muscle cell (a muscle fiber).

Endorphin An endogenous opioid with morphine-like actions. It is an inhibitory transmitter of the descending antinociceptive system.

Endplate potential (EPP) A short-lasting positive change (depolarization) of the normally negative membrane potential of a muscle cell. The EPP is caused by the binding of ACh to the ACh receptors; it is normally suprathreshold, i.e., it reaches threshold and makes the muscle cell fire an action potential (to be distinguished from a miniature endplate potential).

Endplate zone (now also called the motor point) That part of a skeletal muscle where the endplates are located.

Enkephalin An endogenous opioid with morphine-like actions, it is derived from endorphin by splitting. Morphine mimics the action of endorphin and enkephalin.

Enthesitis Painful inflammation of the insertion region of a muscle provoked by muscle stress (Sted).

Enthesopathy A disease process occurring at the site of insertions of muscle tendons and ligaments into bones or joint capsules (Sted).

Ephapse Synapse-like close apposition between neighboring fibers in a damaged nerve or neuroma which may provide direct electrical coupling leading to cross-talk between the fibers.

Epicondylalgia Pain in an epicondyle of the humerus or in the tendons or muscles that originate there.

Epimysium The tight connective tissue that encloses a whole muscle. In many muscles, it forms a dense fascia in which the muscle contracts without deformation of the skin.

Epitendineum (peritendineum externum) Dense connective tissue surrounding a tendon. It contains blood vessels, lymphatic vessels, and nerve fibers.

Ergonomics A scientific discipline dedicated to providing a work situation that provides optimal trunk and limb support and placement of work materials. A goal of ergonomics is to minimize unnecessary motor activity, especially repetitive and sustained muscle contraction.

Ergoreceptor A non-nociceptive muscle Group IV (or III) receptor that is activated during physiological contractions. It is assumed to mediate respiratory and circulatory adjustments during physical work.

Evoked potential A change in voltage usually recorded from the somatosensory cortex surface following stimulation of a peripheral nerve or another sensory input. The potential consists of several waves which are named according to their polarity (N for negative, P for positive) and their latency (time between onset of the stimulus and occurrence of the potential) in msec.

Excitatory amino acids Amino acids that act as neurotransmitters. They activate cell membrane receptors and initiate neuronal activity. Glutamate is an example of an excitatory amino acid.

Excitatory postsynaptic potential (EPSP) A short-lasting depolarizing potential in a postsynaptic neuron. It is evoked by opening ion channels that are permeable to small positively charged ions (cations, mainly Na^+ and/or Ca^{2+}). The depolarization renders the cell more positive. The normal EPSP is subthreshold, i.e., it is too small to initiate an action potential.

Extrapyramidal reactions Motor reactions that are due to activation of the extrapyramidal motor pathways (pathways outside the pyramidal tract). Disturbances of these pathways express themselves not in paralysis but in the way movements are performed.

Facet joints The small joints connecting the vertebrae.

Fascia A sheet of fibrous tissue that envelops the body beneath the skin; it also encloses muscles and muscle groups, and separates structural components of a muscle.

Fascia innervation To date, little information is available about the innervation of fascia. This is an important gap in our knowledge, because fascia is an important component of the musculoskeletal system and likely to contribute to many types of pain that are subsumed under the label "muscle" pain.

Fascicle A bundle of nerve or muscle fibers that are enclosed in perineurium or perimysium respectively.

Fasciculations Involuntary contractions, or twitchings, of groups (fasciculi) of muscle fibers, a coarser form of muscular contraction than fibrillation (Sted).

Fibrillation Involuntary contraction of individual muscle fibers.

Fibromyalgia (FM) or fibromyalgia syndrome (FMS) The classification criteria for fibromyalgia were published in 1990 by the American Rheumatological Association. The patient must have wide-spread pain of at least 3 months duration. Widespread pain means that over time at least three of the four body quadrants must be involved. That is ensured by finding 11 of the 18 predetermined sites to be tender.

Fibrosis Formation of fibrous tissue as a reparative or reactive process (Sted).

Fibrositis The term "fibrositis" is unsuitable as a label for fibromyalgia, because the suffix "itis" implies an inflammatory process for which there is no evidence.

Filament (1) One of the contractile proteins of the muscle (actin and myosin). The filaments consist of a chain of amino acids. The myosin filament has so-called heads which attach to the actin filaments during contraction and make repeated flexing movements to cause sliding of the filaments. (2) In neurophysiological animal experiments, a filament is a thin bundle of nerve fibers dissected from a nerve for recording the impulse activity in single fibers.

First and second pain First and second pain occur when a fast, short lasting stimulus acts on a cutaneous nerve or innervation territory of a skin nerve, for instance an electrical stimulus or a sudden blow to a skin region. The first pain has a sharp, pricking character, whereas the second pain arrives later and is felt as dull or aching.

Flare A redness of the skin extending beyond the local reaction to the application of an irritant or a noxious stimulus; it is assumed to be due to vasodilation caused by the release of histamine from mast cells, and of neuropeptides (CGRP and SP) from sensory nerve endings.

Flexion (or flexor) reflex A reflex leading to the contraction of a flexor muscle. Usually, the reflex occurs in response to a painful stimulus to the skin. The effect of the reflex is to move the limb away from the source of pain.

Forward flexion test In this test, the patient bends forward either while standing or while sitting. The examiner places the thumbs on the underside of the posterior superior iliac spine (PSIS), and notes the movement of the PSIS on each side as the patient bends. Normally, the two PSIS move symmetrically.

Free nerve ending The main type of receptive ending of small-diameter afferent fibers (Aδ- and C fibers). The name is derived from the fact that under the light microscope the endings lack an identifiable structural specialization. Functionally, they are nociceptors, thermoreceptors, and mechanoreceptors.

Functional magnetic resonance imaging (fMRI) Magnetic resonance imaging (MRI) uses magnetic fields to create images of the human brain. Functional MRI measures the BOLD response of the brain in response to a stimulus and then analyzes the resulting images with special software.

Funiculus Synonymous for column in the central nervous system. The largest subdivision of the white matter in the spinal cord (e.g., dorsal funiculus between the two dorsal horns.)

Fusimotor system The gamma motoneurons and muscle spindles. Gamma motoneurons control the muscle spindle sensitivity.

Gamma-amino-butyric acid (GABA) An inhibitory neurotransmitter in the CNS.

Gate-control hypothesis A spinal mechanism for the modulation of pain which assumes that impulse activity in small-diameter (nociceptive) fibers elicits pain (opens the gate), whereas activity in large-diameter (non-nociceptive) fibers inhibits pain (closes the gate).

General muscle tone This muscle tone is detected clinically as elastic or viscoelastic stiffness, including any involuntary contractile activity that may occur during the passive movement of a limb.

Genotype Genetic make-up of a person.

Glial cells There are three main types in the CNS: (1) *astrocytes*, which contribute to the development of the blood brain barrier and form glial scars after CNS lesions, (2) *oligodendrocytes*, which build myelin sheaths around myelinated central nervous axons, and (3) *microglia*, that differ from the first two in that they are immunocompetent cells, move to the site of a lesion, and can perform phagocytosis of necrotic cells. They are the macrophages of the CNS, and are involved in central sensitization.

Glycolysis The anaerobic conversion of glucose to lactic acid; it yields much less energy per molecule glucose than does oxidative metabolism.

Golgi (tendon) organs Corpuscular receptors that measure the tension of a muscle. They are arranged in series with the extrafusal muscle fibers (fibers outside muscle spindles); their predominant location is the transition zone between muscle and tendon. The afferent fiber is the Ib fiber. Golgi organs are excited by both muscle contraction and muscle stretch, i.e., during all situations that increase the tension of the muscle.

Gottron's papules Violet-reddish small papules symmetrically distributed over the extensor side of finger joints or elbows.

G-protein coupled receptor A guanosine triphosphate (GTP)-coupled receptor molecule that is not associated with ion channels, but transfers signals across the postsynaptic membrane by activating a chain of molecules in or close to the membrane. These receptors bind modulators such as substance P, and control intracellular signal cascades that influence second messengers (e.g., cAMP).

Gray matter The tissue component of the CNS that contains the cell bodies of the neurons together with other structures. The processing of impulse activity takes place in the gray matter.

Group I–IV fibers Nomenclature for afferent fibres that originate in deep somatic tissues (muscle, tendon, joint). The term "group IV fibers" is synonymous with C fibers from the skin; they comprise unmyelinated muscle afferent (sensory) fibers that conduct action potentials at a velocity of less than 2.5 m/s (conduction velocities given for humans). Group III are synonymous with Aδ-fibers; they conduct at a velocity of 2.5–30 m/s. Group II fibers and cutaneous Aβ-fibers are largely identical (conduction velocity 30–70 m/s). Group I fibers comprise the primary endings from muscle spindles (Ia-fibers) and Ib-fibers from Golgi tendon organs (conduction velocity 70–110 m/s). There are no cutaneous and visceral afferent fibers that have such a high conduction velocity. The denominations using Roman numerals are based on the diameter of the nerve fibers, those using Arabic letters on the conduction velocity.

Gyrus One of the prominent, folded elevations that form the cerebral hemispheres. Each gyrus is separated from the next by a sulcus.

H (Hensen) band The pale middle zone of the A band of a muscle sarcomere. It marks that region of the A band where only myosin (and no actin) filaments are present.

H-reflex A reflex (Hoffmann reflex) occurring after electrical stimulation of sensory muscle afferents (Ia afferents from primary endings of muscle spindles).

Half-life (or half-time) The time for half of a substance to be converted or disappear from the tissue.

Hamstring muscles They include the semimembranosus, semitendinosus, and biceps femoris muscles. The tendons of these muscles attach to the ischial tuberosity.

Haplotype The term is a contraction of the term "haploid genotype." In genetics, a haplotype is a combination of alleles at multiple loci that are transmitted together on the same chromosome.

Head zone A hypersensitive or painful region in the skin caused by a painful lesion in viscera. The underlying mechanism is pain referral from the viscera to

the skin via dorsal horn neurons which have convergent connections with skin and viscera, but only mediate sensations from the skin.

Heliotrope rash Reddish-violet rash symmetrically distributed over eyelids, often with edema.

Hemiparesis Slight paralysis affecting one side of the body (Sted).

Hemiplegia Paralysis of one side of the body (Sted).

Herniated disk A protrusion of the soft center of a vertebral disk into the vertebral canal. The protrusion can compress the spinal cord or nerve roots, and cause pain and other symptoms.

Heterosynaptic facilitation Increase in responsiveness of a central neuron by an input that does not excite the cell, meaning that the input excites another neuron, which in turn facilitates the cell under study.

High-threshold mechanosensitive (HTM) receptor A mechanoreceptor with a high stimulation threshold in the noxious range, and an increase in response magnitude within the noxious range. The term is often used to describe nociceptors that have not been tested with chemical or thermal stimuli. Probably, HTM receptors in muscle mediate the pain caused by mechanical traumas.

High-threshold mechanosensitive (HTM) deep neurons Dorsal horn neurons that have response characteristics similar to the HTM receptor, i.e., a high threshold in the noxious range, increase in response magnitude within the noxious range, and input from deep somatic tissues. These cells are assumed to be nociceptive.

Hippocampus The convoluted structure that forms the caudal medial margin of the cerebral hemisphere. The hippocampus is a part of the limbic system.

Histamine A biological amine derived from histidine by decarboxylation. It stimulates gastric secretion, constricts bronchial smooth muscle, and dilates blood vessels. It is stored in mast cells, and can be released from these cells under pathophysiological circumstances (Sted.), e.g., by substance P liberated from nociceptive nerve endings.

HLA Human leukocyte antigen. It has the same function as MHC (major histocompatibility complex), namely presenting antigens to immune cells in humans. There are several classes: HLA class I (A, B and C) and class II (DR, DP and DQ).

HLA DRB1*0301, DQA1*0501, HLAB7, DQA1*01, DRB1*07, DQA*0201 HLA-genes associated with inflammatory myopathies.

Holster sign Erythema over hips.

Homonymous Having the same name (Sted). When used with regard to muscle reflexes, it means that the receptor eliciting the reflex and the contracting motor units are located in the same muscle.

HRCT High resolution computerized tomography.

Hyperalgesia The condition in which painful stimuli are perceived as more painful than is usually the case. Many cases of hyperalgesia have also features of allodynia. Loeser and Treede (2008) propose to use hyperalgesia as an "umbrella term" for all cases of increased pain sensitivity, because it is often difficult to know if a stimulus is capable of activating nociceptors.

Hyperesthesia An increased sensitivity to stimulation, excluding the special senses.

Hyperexcitability An abnormal increase in responsiveness of a central neuron to synaptic input. Hyperexcitability is assumed to be the cause of various forms of pain such as phantom pain and hyperalgesia.

Hyperpathia A painful syndrome characterized by abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.

Hypertonia (synonym hypertonicity) An abnormally increased muscle tone for any reason. Such conditions may include those that do not show electrogenic EMG evidence of muscle contractions (such as tension-type headache and low back pain), and those that do involve active muscle contractions (such as spasticity, rigidity, dystonia). Contracture in the physiological sense may manifest hypertonicity, but without EMG activation

Hypertonic saline A salt solution that has a higher osmotic pressure than serum. In pain research it is used as a painful chemical stimulus (usually 5–6% NaCl).

Hypoalgesia Diminished pain in response to a normally painful stimulus.

Hypochondriasis A false belief that one is suffering from some disease.

Hypoesthesia Decreased sensitivity to stimulation, excluding the special senses (IASP).

Hypothalamus The ventral region of the diencephalon forming the walls of the ventral half of the third ventricle. It controls the autonomic nervous system and, through its vascular and neuronal connections with the lobe of the hypophysis, is involved in endocrine mechanisms.

Hypothenar The fleshy mass at the medial side of the palm (Sted).

Hypotonia (synonym hypotonicity) An abnormally diminished viscoelastic stiffness marked by a decreased resistance to passive stretching. It may relate to thixotropy. It is characteristic of so-called "floppy infants."

Hypoxia A reduction in the level of oxygen pressure in body tissues.

I band The pale isotropic area of a muscle sarcomere. The band is adjacent to the Z disk and contains only actin filaments. It forms the light regions of the striation pattern of a skeletal muscle.

Ia fiber An afferent (sensory) fiber with origin in a primary ending of a muscle spindle. Ia fibers have monosynaptic excitatory connections with the α-motor neurons of the homonymous muscle.

Ib fiber An afferent (sensory) fiber originating in a Golgi (tendon) organ. Ib fibers have disynaptic inhibitory connections with the α-motor neurons of the homonymous muscle.

Idiosyncrasy An unusual individual mental, behavioral, or physical characteristic.

ILD Interstitial lung disease.

Immediate early gene (IEG) A gene that is expressed in neurons within a few hours following stimulation by peripheral input. An IEG can produce a transcription factor (a protein) which moves to another area of the chromosome and induces the synthesis of other molecules such as neuropeptides.

Immunoreactive A tissue component (antigen) that is stained histologically with labeled antibodies.

Immunoreactivity The staining produced in histological sections using labeled antibodies to visualize antigens in the tissue.

Inclusions in muscle fibers Accumulations of proteins in muscle fibers that can be visualized as particles by electron microscopy.

Ineffective synapse Also called silent or sleeping synapse. Action potentials arriving at the presynaptic bouton of an ineffective synapse have very little influence on the postsynaptic neuron; they just elicit a very small EPSP which does not affect the overall excitability of the neuron.

Infliximab treatment Immunomodulating treatment by blocking the action of TNF (tumor necrosis factor alpha).

Inhibitory postsynaptic potential (IPSP) A short-lasting hyperpolarization of the membrane of the postsynaptic neuron caused by a small amount of inhibitory neurotransmitter (e.g., GABA or glycine). The IPSP shifts the membrane potential away from threshold. This reduces the excitability of the cell.

Innocuous stimulus A weak stimulus that is not normally painful. In skeletal muscle, small deformations of the tissue or contractions under physiological conditions are innocuous.

Input convergence Connections of various afferent fibers with the same central neuron. This is a normal feature of the wiring in the CNS.

Insula An oval region of the cerebral cortex; it is buried in the depth of the sylvian (lateral) fissure (Sted). Recent research indicates that the insular cortex is involved in pain sensations.

Integration of neuronal activity The processing of simultaneous excitatory and inhibitory synaptic potentials in a neuron. As a result of the integration, the neuron may become more or less active (or stay the same).

Interleukin-1 (IL-1) A polypeptide hormone that is synthesized by monocytes, and acts on the hypothalamus to induce fever, and on the muscle to promote protein degradation (Sted). IL-1 is an important signal for cell-to-cell communication in pathophysiologically altered tissue.

Interneuron A nerve cell that is interposed between two others and has no long axons in ascending or descending tracts; for instance, the activity from group II muscle spindle afferents is transmitted to α-motor neurons by interneurons with short axons.

Intracerebroventricular (injection) An injection into one of the cerebral ventricles.

Intrafusal muscle fiber A muscle fiber inside a muscle spindle. Intrafusal muscle fibers contract in response to activity in efferent γ-motor fibers and change the sensitivity of the spindle to stretch.

Intrathecal (i.t.) Into the subarachnoid space. The term usually refers to administration of a drug into the space around the spinal cord which contains the spinocerebral fluid.

IVIg Intravenous immunoglobulin.

Intrinsic Inherent. Applied to neuronal activity: discharges that occur in neurons in the absence of a recognizable external stimulus.

In vitro From Latin "in the glass." An experimental set-up (organ bath) for studying isolated organs or cells that are immersed in or superfused with artificial extracellular fluid, and kept alive by gassing the fluid with a mixture of oxygen and carbon dioxide.

Ion channel A large channel protein present in the membrane of nerve cells. The protein consists of several subunits that — in the open state — form a pore-like opening through which ions can flow. The channel protein can either be opened by a change in the membrane potential or by binding to a neurotransmitter molecule (e.g., glutamate).

Ionotropic receptor A receptor molecule consisting of large proteins that form a channel or pore that spans the entire width of the axonal membrane. Usually

the channel is closed; after binding a specific stimulating molecule (its ligand), the channel opens and ions flow across the membrane according to their concentration difference inside and outside the membrane (Na^+ and Cl^--ions will enter the ending, K^+-ions leave the ending or neuron).

Iontophoresis (or ionophoresis) The transport of charged molecules by electric current.

Irritable bowel syndrome Troublesome constipation interspersed with painful cramping and diarrhea, often accompanied by tenderness to palpation in the left upper quadrant or the whole left side of the abdomen. The syndrome is seen in many patients with fibromyalgia.

Ischemia A reduction in blood flow in an organ or a part of an organ.

Isometric contraction An increase in force without length change. An example is activation of the masseter muscle when the maxillary and mandibular teeth are in contact. The teeth are not compressible; therefore, the contraction is largely isometric.

Isotonic contraction A reduction in muscle length without change in the force exerted. Isotonic contractions are rare in normal life, because almost all movements are associated with a change in force. Pure isotonic contractions can be performed on an exercise machine that provides constant resistance through the range of movement.

Kinesiology The science or the study of movement, and of the active and passive structures involved (Sted).

Kyphosis Dorsal flexion of the spine.

Lacrimation The secretion of tears, especially in excess.

Lamina Latin for layer. In the book, the term is used for the layers of the dorsal horn of the gray matter of the spinal cord.

Latent (silent) connections Ineffective synaptic connections in the CNS which may become effective under pathological conditions.

Latent Trigger Point A trigger point that does not spontaneously cause pain, and does not cause pain with activity. It is painful when the trigger point is mechanically stimulated, as by palpation or needling. Latent trigger points often cause motor dysfunction (stiffness and restricted range of motion) *without pain* in contrast to the pain-producing active TrPs.

Lentiform nucleus or lenticular nucleus The nucleus comprises the putamen and the globus pallidus within the basal ganglia. It is a large, cone-shaped mass of gray matter (mainly neuronal cell bodies) just lateral to the internal capsule.

Leukotrienes (LTs) Substances released from damaged tissue by activation of the enzyme lipoxygenase. Some LTs promote inflammatory processes and lead to hyperalgesia (e.g., LT B_4), others (e.g., LT D_4) have been shown to depress the activity in muscle nociceptors.

Levator ani syndrome (also known as levator syndrome and proctodynia) Episodic rectal pain, caused by spasm of the levator ani muscle. The etiology is unknown.

Light dermatitis Photosensitivity of skin, erythematous rash on UV-light exposed skin.

Local muscle pain Pain caused by excitation of muscle nociceptors (in contrast to other forms of muscle pain that are due to, for example, lesions of the muscle nerve or alterations of central neurons mediating muscle pain).

Local twitch response A contraction of the taut band of a trigger point in response to mechanical stimulation (snapping palpation or needle penetration) of the trigger point region. The twitch is confined to the taut band, and is unique to the trigger point.

Lockjaw An example of trismus, e.g., caused by tetanus infection.

Locomotor muscle A skeletal muscle that is mainly used for body movement. In contrast, postural muscles are mainly used for maintaining body posture.

Long-term depression (LTD) Also called depotentiation. It is a long-lasting decrease in neuronal excitability which can be induced be low-frequency stimulation.

Long-term potentiation (LTP) The process of inducing a long-lasting increase of neuronal excitability by a short-lasting high-frequency input. LTP represents a neuroplastic change in the CNS which is an important component of hyperalgesia. In the hippocampus, LTP is considered to be the basis of learning processes.

Lordosis Ventral flexion of the spine.

Low-threshold mechanosensitive (LTM) receptors Mechanoreceptors with a low stimulation threshold in the innocuous range. Probably, LTM receptors in muscle mediate subjective sensations of pressure or tension.

Low-threshold mechanosensitive (LTM) deep neurons They have a mechanical threshold in the innocuous range, and respond strongly to weak deformation of muscle and other deep tissues.

Lumbago Pain in mid and lower back (a descriptive term not specifying cause; Sted).

Luxation Complete dislocation of a joint.

Magnetic resonance elastography A new technique that can differentiate tissues of varying densities. The technique involves the introduction of cyclic waves into the muscle, and then using phase contrast imaging to identify tissue distortions.

Magnetic resonance spectroscopy (MRS) A technique that monitors biochemical changes in specific regions of the brain, and can characterize the amount of metabolites present within a predefined brain region.

Magnetoencephalography (MEG) MEG is a brain imaging technique that measures the magnetic fields produced by the electrical activity of the brain (see EEG).

Malignant In reference to a neoplasm: having the property of locally invasive and destructive growth and metastasis (Sted).

Mast cells Free tissue cells that are frequently located in the connective tissue around blood vessels. They contain and release (among other substances) histamine and serotonin. Substance P depletes the substances stored in mast cells.

Masticatory muscle pain (MMP) A term used to describe pain with origin in the masticatory muscles, including tendons and fasciae.

Masticatory muscles Muscles involved in chewing (temporal m., masseter m., medial and lateral pterygoid m., digastric m.)

Mechanical impedance The resistance to motion produced by the interaction of elasticity, momentum, and viscosity, and incorporates rate of movement. Systems that have impedance show the characteristic of resonance.

Mechanic's hands Symptom of *antisynthetase syndrome* characterized by scaling, fissuring and hyperkeratosis of the distal skin pads on lateral aspects of the fingers and thumbs.

Mechanoreceptor Large myelinated sensory fibers (A-beta from skin or group I–II from muscle) which when activated transmit information concerned with touch, pressure or proprioception.

Medulla oblongata The caudalmost part of the brainstem, just rostral to the spinal cord.

Membrane potential The difference in electric charge between the two sides of a cell membrane. The resting membrane potential of most muscle and nerve cells is around −90 mV (inside negative).

Meningitis Inflammation of the membranes of the brain or spinal cord.

Mesencephalon (syn.: midbrain) It is characterized by the lamina tecti dorsally and the crura cerebri ventrally. Important cell groups include the red nucleus,

the substantia nigra, and the periaqueductal gray matter. The mesencephalon is located between the hypothalamus (rostrally) and the pons (caudally).

Metabotropic receptor A receptor molecule located on the outer surface of a cell membrane. Binding of the proper molecule (the ligand) to the receptor activates a G protein (guanine nucleotide-binding protein) on the inside of the membrane. G proteins can regulate intracellular metabolic cascades. For instance, they change of the state of activation of intracellular second messenger systems such as phospholipase C (PLC), cyclic adenosine monophosphate (cAMP), and protein kinases (PKs). One sequel of the activation of these messengers, particularly the PKs, is the phosphorylation of ion channels leading to a higher excitability of the neuron.

Metenkephalin An endogenous opioid that is used as an inhibitory neurotransmitter by neurons of the descending antinociceptive system.

MHC Major histocompatibility complex; a large cluster of genes. MHC class I antigens are present on most nucleated cells with exception of muscle cells and nerve cells, and function as antigen presenting molecules. Class II MHCs are mainly found on immune cells surface and perform important function of antigen presentation.

Microneurography A technique of recording impulse activity from single nerve fibers in humans by inserting thin needle electrodes through the skin into a peripheral nerve.

Miniature endplate potential (MEPP) Small spontaneous synaptic potentials (depolarizations) of the muscle cell membrane under the neuromuscular endplate in the absence of electrical activity of the α-motor neuron. Miniature endplate potentials are always subthreshold for the muscle cell; they are caused by random release of single packets of acetylcholine from the presynaptic nerve terminal.

Mislocalization of pain False localization of the pain source by a patient. The pain is felt remote from the real site of the lesion. An example is referred pain from a trigger point.

Mitochondrium A cell organelle (structure within the cytoplasm) that supplies the cell with energy; it contains the enzymes of the citric acid cycle.

Mixed pain The term is mainly used for a combination of neuropathic and nociceptive pain, i.e., for pain due to a lesion of the central or peripheral nervous system combined with pain caused by excitation of nociceptive nerve endings.

Modulation The term is mostly used for a change in the activity discharge of a neuron under the influence and in the presence of a modulating factor (e.g., a sensitizing substance). This definition implies that the neuron regains its original properties if the modulating factor is no longer present.

Monosynaptic A neuronal connection that includes no interneurons, i.e., one neuron has direct synaptic contacts with a second neuron.

Morning stiffness The stiffness felt by patients with rheumatoid arthritis. It is not accounted for primarily by changes in measurable stiffness, and relates more to subjective discomfort associated with movement than to a change in soft-tissue viscoelastic properties. The common stiffness of old age following periods of a fixed position (when traveling) may well be another example of such a subjective stiffness and reduced pain-free range of motion.

Motoneurons Neurons located in the central nervous system controlling striated muscles (α-motoneuron) or intrafusal muscle fibers of muscle spindles (γ-motoneurons).

Motor (neuromuscular) endplate The structure that links a terminal nerve fiber of the α-motor neuron to a muscle fiber. It contains the synapse where the electrical signal of the nerve fiber is converted to a chemical messenger (acetylcholine), which in turn initiates another electrical signal (the action potential) in the cell membrane of the muscle fiber.

α-motor fiber A thick myelinated nerve fiber of a motor neuron that supplies striated muscle.

γ-motor fiber A thin myelinated motor nerve fiber that supplies the muscle fibers within a muscle spindle (the intrafusal muscles). Excitation of the γ-fibers leads to contraction of the intrafusal muscle fibers and thus changes the sensitivity of the spindle.

Motor point That part of a skeletal muscle where the endplates are located. Now used as synonymous with the endplate zone. Previously defined as the region where the motor nerve entered the muscle.

Motor unit A motor unit includes one α-motor neuron and all of the muscle fibers that it supplies.

MRI Magnetic resonance imaging.

Mucosa (short for tunica mucosa) Mucous membrane lining the inner wall of the intestines and other inner organs.

Multireceptive neurons Nerve cells with convergent input from various receptor classes such as mechanoreceptive and nociceptive. By some authors, these cells are called wide-dynamic range (WDR) neurons.

Muscle compliance The reverse of stiffness, being the ease of deformation with compression.

Muscle contracture A form of physical shortening and increased resistance to elongation arising endogenously within the muscle fibers or the muscle's

surrounding fascial network. Contracture in the physiological sense may manifest hypertonicity, but without EMG activation.

Muscle fatigue A progressive reduction in force of maximum voluntary contraction of a muscle, accompanied by a progressive reduction in median frequency of the EMG and an increasing EMG amplitude, and associated with an increasing sense of muscle tiredness.

Muscle fiber Synonymous for muscle cell. A muscle fiber contains many nuclei and can extend over the whole length of a muscle.

Muscle spasm Spasm is a contraction of striated muscle that cannot be released voluntarily. If the contraction is painful, it is called cramp. Spasm and cramp in the sense of this definition are associated with EMG activity.

Muscle spindles Complex receptive structures that measure the length of a muscle and the rate of length change, i.e., their discharge rate increases with increasing muscle length and with increasing velocity of the length change. They consist of several specialized muscle fibers (the so-called intrafusal muscle fibers; the name is derived from their location inside the spindle-shaped connective tissue sheath). The discharge frequency of muscle spindles decreases during contraction of the muscle, because they are arranged in parallel to the extrafusal muscle fibers, and are relaxed by the contraction.

Muscle stiffness A term commonly used to describe discomfort with movement of a joint.

Muscle tension An increase in resistance to passive joint movement commonly defined as muscle tone or muscle spasm. It depends on two factors: (1) the basic viscoelastic properties of the soft tissues, and/or (2) the degree of the activation of the contractile apparatus of the muscle.

Muscle tone The resting tension of a muscle, clinically determined as resistance to passive movement. Muscle tone has two components: (1) the viscoelastic component; it is independent of nervous activity and reflects the passive physical properties of muscle tissue (tension of elastic fibers, osmotic pressure of cells), and (2) the contractile component. Its presence can be detected in the electromyograph (EMG).

Muscle twitch A single (or short-lasting) activation of the contractile apparatus of a muscle, e.g., by a short electrical stimulus or during a monosynaptic reflex.

Myalgia Pain in a muscle or muscle group.

Myasthenia gravis A chronic progressive muscular weakness, beginning usually in the face and throat, unaccompanied by atrophy; it is due to a defect in myoneural conduction. Syn: Goldflam disease (Sted).

Myelinated nerve fiber A process of a neurone that is surrounded by a myelin sheath. Myelin consists of multiple layers of the membrane of Schwann cells (in peripheral nerves) or of glial cells (in the central nervous system).

Myoadenylate deaminase deficiency (MADD) MADD is the most common metabolic myopathy. It is a muscle disease which interferes with the muscle cell's processing of ATP, the major energy molecule of the cell

Myoedema An EMG-free mounding of the muscle following percussion caused by nonpropagated local contracture of the muscle. It is seen in some individuals with normal muscle relaxation, and is a common post-mortem phenomenon.

Myofibril The contractile element of a muscle cell. Each myofibril consists of a chain of sarcomeres, which are the basic contractile units and contain the actin and myosin filaments.

Myofascial pain syndrome A painful condition caused by active trigger points. Myofascial pain syndrome can be regional, caused by a grouping of muscles that are related to each other functionally, or it can be widespread involving several regions.

Myofascial trigger point A region or zone of exquisite tenderness on a hard or taut band of muscle. The trigger point has the property of referring pain to a distant site, called referred pain.

Myogelosis and "muscle indurations" Painful condition of muscle characterized by a localized tender spot in palpable ropiness of the muscle. A myogelosis is likely to be a myofascial TrP or — if it is a large one — an aggregation of several TrPs.

Myotome The muscles supplied by muscular branches from a single spinal nerve.

Nausea Sick at the stomach; an inclination to vomit (Sted).

Necrosis Death of tissue cells due to pathologic changes.

Neoplasia The pathologic process that results in the formation and growth of a neoplasm.

Neoplasm An abnormal tissue that grows more rapidly than normal, shows lack of structural organization, and usually forms a distinct mass of tissue which may be either benign or malignant (Sted).

Nerve fiber An axonal process of a neurone together with its sheath. A nerve fiber consists of an axon (a cylinder of excitable nerve membrane filled with cytoplasm (the axoplasm)) plus a sheath of Schwann cells. Unmyelinated fibers are not naked axons, they are covered by a single layer of Schwann cells. In myelinated fibers, the sheath also consists of a single layer of Schwann cells,

but here each cell is wrapped around a section of the axon in multiple turns, and the cytoplasm of the Schwann cell is squeezed out so that the membranes of each turn contact each other. This densely packed spiral of Schwann cell membrane is the myelin. In thin myelinated fibers, the myelin consists of a few spiral turns; in thick myelinated ones, the number of turns can amount to several dozen.

Nerve growth factor (NGF) NGF is primarily known as a neurotrophic substance that promotes the development of the nervous system, particularly nociceptive and sympathetic neurons. The neurotrophin is unique in that it has a stimulating action exclusively on HTM, presumably nociceptive, muscle receptors.

Nerve entrapment This occurs when a peripheral nerve suffers from chronic compression along its normal anatomical course. Nerve entrapment can be caused by constricting myofascial taut bands.

Neurite Synonymous for axon; at the neurite, the action potentials originate and leave the neuron.

Neurobiology A term including neuroanatomy, neurophysiology, and neuropharmacology.

Neurogenic inflammation A sterile inflammation caused by antidromic neuronal activity in a spinal nerve or parts of it. The antidromic activity releases endogenous substances with vascular and cellular actions (e.g., substance P, CGRP) from the endings of the nerve fibers. Antidromic means that in afferent (sensory) fibers the propagation of the action potentials occurs in the efferent direction, i.e., toward the body periphery.

Neurokinin A (NKA), neurokinin B (NKB) Peptides that together with substance P form the tachykinin group.

Neurokinin-1 (NK-1) receptor A receptor molecule in the membrane of nerve cells which binds substance P and mediates its intracellular effects.

Neuroma The proliferative mass of Schwann cells and axons that develops at the proximal end of a severed or injured nerve (Sted). In addition to Schwann cells and sprouting axons, a neuroma also contains fibroblasts and fibrocytes.

Neuromuscular junction The region in the muscle where the motor nerve terminal contacts the muscle cell membrane, separated by the synaptic space.

Neuron A nerve cell.

Neuropathy A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, neuropathy multiplex; if diffuse or bilateral, polyneuropathy (IASP).

Neuropeptide A molecule consisting of a chain of amino acids, which is found in the cytoplasm of neurons and other cells. A prominent example of a neuropeptide is substance P (SP) that consists of eleven amino acids. Neuropeptides are considered to be neuromodulators (substances that *modulate* the neuronal activity produced by neurotransmitters), and are not themselves neurotransmitters (substances that elicit and transmit neuronal activity).

Neuroplasticity The capability of the CNS to react to a (short-lasting) input with a long-lasting deviation from normal synaptic function. Nociceptive input from muscle is known to be particularly effective for inducing neuroplastic changes in the CNS.

Neurosis A psychological or behavioral disorder in which anxiety is the primary characteristic; in contrast to the psychoses, the neuroses do not involve gross distortion or disorganization of personality.

Nitric oxide (NO) A small gaseous neuromodulator that is synthesized by the enzyme NO-synthase in neurons. NO diffuses through all cell membranes. Therefore, its action is not restricted to the neuron where it has been synthesized. It can also be produced by endothelial and microglial cells. It has a strong dilatory action on blood vessels.

NMDA (N-methyl-D-aspartate) receptor One of the receptors of glutamate. It is associated with an ion channel that is mainly permeable to Ca^{2+} ions.

Noceffector The term was coined by Kruger (1988) for nociceptors in the tooth; it emphasizes the efferent function of the receptor. Efferent function means that the receptor is involved in the maintenance of the tissue under normal and pathological circumstances by releasing substances stored in the ending. Under pathophysiological circumstances, the effector role of a nociceptor is reflected in the neurogenic inflammation.

Nociception Events in the peripheral and central nervous system that are associated with the processing of electrical signals elicited by tissue-threatening stimuli. Most of these events also occur under anesthesia, and can be studied in experiments on anesthetized animals.

Nociceptive neuron A nerve cell that signals the presence of tissue-threatening stimuli. Excitation of nociceptive cells elicits pain if the frequency of the induced activity is high enough and the pain-inhibiting mechanisms are not highly active. New definition: a central or peripheral neuron that is capable of encoding noxious stimuli. Nociceptive central neurons are (1) wide-dynamic range (WDR) neurons that have a low stimulation threshold and reach maximal discharge frequencies during noxious stimulation, and (2) nociceptive specific (NS) neurons that have a high threshold and respond only to noxious stimuli.

Nociceptor A free nerve ending that is specifically activated by noxious (tissue-threatening, subjectively painful) stimuli. A nociceptor is capable — by its response behavior — of (1) distinguishing between innocuous and noxious stimuli, and (2) signaling the intensity of a noxious stimulus. New definition: a sensory receptor that is capable of transducing and encoding noxious stimuli (Loeser and Treede 2008).

Nocturnal leg cramps (synonyms: calf cramps or systremma) An involuntary, sustained tightening (contraction) of one or more leg muscles (usually the calf) associated with hardening of the muscle, strong pain, and inability to control the affected muscles.

Nonarticular rheumatism A commonly used, but not clearly defined, general term for soft-tissue pain syndromes that are not associated with a specific joint dysfunction or disease. It is generally considered as synonymous with soft-tissue rheumatism.

Nonspecific low back pain Low back pain due to painful disorders of the soft tissues (muscles, fascia, ligaments) of the low back. In these cases, specific causes of low back pain such as displacement of intervertebral disks, spondylolisthesis, bony metastasis, and abscess are not present.

Nonsteroidal anti-inflammatory drug (NSAID) A nonsteroidal drug, e.g., aspirin, that inhibits inflammatory processes. Aspirin blocks the enzyme cyclooxygenase which synthesizes proinflammatory prostaglandins.

Noxious stimulus A tissue-threatening, subjectively painful stimulus. Nociceptors respond in a specific way to noxious stimuli. New definition: an actually or potentially tissue-damaging event.

NT-3 or Neurotrophin 3 NT-3 is a neurotrophic factor, in the NGF (nerve growth factor)-family of neurotrophins. It is a protein growth factor which helps to support the survival and differentiation of existing neurons in the CNS, and encourages the growth and differentiation of new neurons and synapses. NT-3 is seen as preventing central sensitization.

Nucleus (1) The structure in a cell that contains the genetic information (genes). (2) An aggregation of neuronal cell bodies within the CNS, typically belonging to the same sensory or motor system.

Nucleus raphe magnus (NRM) An aggregation of neuronal cell bodies in the midline region of the ventral medulla oblongata. The NRM is an important nucleus of the descending antinociceptive system.

Occlusal appliance A plastic-like device manufactured on the order of a dentist to prevent wearing away of the teeth due to clenching or grinding. Occlusal appliances are often prescribed as part of the therapy of masticatory muscle pain. The mechanism of action is unclear.

Occupational myalgia Muscle pain induced by muscular activity at work that is at or near the muscles' tolerance (because of intensity of work or frequent repetition of monotonous movements). Often the muscle activity has activated myofascial TrPs. Other terms used to describe this condition are repetitive strain injury and cumulative trauma.

Opening of new connections in the CNS Rewiring of CNS connections due to the fact that ineffective synapses become effective.

Opiate Any derivative or preparation from opium (Sted).

μ-opiate agonist An agonist that acts on the μ receptor molecule for opiates.

Opioid Any (synthetic) narcotic that resembles opiates in action but is not derived from opium (Sted).

Overload Putting too much strain on a muscle, or placing a muscle in an awkward position that requires sustained contraction in order to maintain that posture, are the most common examples of overuse. Muscle overload is one of the most likely mechanisms for the formation of TrP.

Oxidative metabolism Energy-yielding degradation of metabolites (glucose, fat, protein) that requires consumption of oxygen.

p-pond (1 p is the force a mass of 1 g exerts under the influence of earth's gravity).

P2X3 receptor A subtype of the purinergic receptor family that is activated by adenosine triphosphate (ATP) and its derivatives. As an energy-providing molecule, ATP is present in every tissue cell. It is released from the tissue during trauma and other pathologic changes that are associated with cell death.

Pacinian corpuscle (PC) Receptor sensitive to mechanical vibrations. It does not respond to static pressure; it requires dynamically changing mechanical stimuli, and is best excited by vibrations of relatively high frequency (close to 300 Hz).

Paciniform corpuscle A rapidly adapting mechanoreceptor with a morphology similar to that of a Pacinian corpuscle. Compared to the Pacinian corpuscle, the paciniform corpuscle is smaller and has fewer laminae in its capsule. In skeletal muscle, it is often supplied by a group III fiber.

Pain components (1) Sensory-discriminative component. (2) Affective–emotional component. (3) Vegetative (autonomic) component. (4) Motor component. (5) Cognitive component. (6) Psycho-motor component.

Pain definition An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP; Merskey and Bogduk 1994).

Pain matrix. The term includes all structures of the brain that are activated — more or less specifically — by painful stimuli. The matrix includes the insula, prefrontal cortex, anterior cingulate cortex and amygdala (parts of the limbic system), and the thalamus.

Pain memory A hypothetical mechanism implying that a peripheral lesion induces a memory trace in the CNS (cerebrum or spinal cord) which reproduces or maintains the pain even after (surgical) removal of the pain source. An example is the phantom pain in amputees, which is often felt in those areas of the amputated limb that were painful before amputation.

Pain-facilitating system A system of neurons in the reticular formation of the upper medulla which — by their activity — enhance the discharges of spinal nociceptive neurons.

Pain threshold The earliest perception of pain following a stimulus of increasing intensity.

Pain tolerance The highest amount of pain tolerated following a noxious stimulus.

Parafunctional oral habits Prolonged low-level masticatory muscle contractions or repetitive muscle work, as probably happens during wake-time parafunctional activity such as tooth clenching or grinding.

Paralysis Loss of power of voluntary movement in a muscle through injury or through disease of its nerve supply (Sted).

Paranoid Relating to paranoia, a mental disorder characterized by the presence of delusions, often of a persecutory character, in an otherwise intact personality (Sted).

Paraplegia Paralysis of both lower extremities, and of the lower trunk in general.

Paraspinal muscles Muscles that attach to or near vertebrae.

Parenteral By some other means than through the gastrointestinal tract or lung; introduction of substances by intravenous, subcutaneous, or intramuscular injection (Sted).

Paresthesia An abnormal sensation, whether spontaneous or evoked. In contrast to dysesthesia, the term is used to describe an abnormal sensation that is not unpleasant (IASP).

Peptic ulcer A lesion caused by loss of tissue of the mucous surface of the stomach or duodenum, where the mucous membrane is exposed to acid gastric secretion (Sted).

Peptide A molecule composed of two or more amino acids connected by peptide bonds.

Periaqueductal gray matter (PAG) An aggregation of neuronal cell bodies around the cerebral aqueduct (a tube-like structure in the mesencephalon that connects the third with the fourth cerebral ventricle).

Perigenual ACC That part of the anterior cingulated cortex (ACC) that lies close to the genu (knee) of the corpus callosum.

Perimysium The loose connective tissue around a muscle fascicle (a bundle of muscle fibers).

Periosteum The thick layer of connective tissue that covers the surface of a bone except its articular cartilage.

Peritendineum The connective tissue around a tendon.

Perpetuating factors Conditions that promote the persistence of a pathological or functional disorder, e.g., myofascial pain syndrome. For the myofascial pain syndrome, the factors can be structural, such as leg-length inequality or hypermobility, ergonomic work stresses, or medical problems like hypothyroidism.

Phantom pain Pain referred to (felt in) a surgically removed limb or part thereof (IASP).

Phlebitis Inflammation of a vein.

Phosphorylation A mechanism that increases the excitability of central nociceptive neurons. Phosphorylation means that protein kinases (PKs) couple a phosphate residue to another molecule, for instance a channel protein. The phosphorylation increases the opening time or opening probability of the channels, i.e., it leads to increased ion fluxes across the membrane.

Pia mater A thin membrane of connective tissue that firmly adheres to the surface of the brain and spinal cord. The pia mater is one of the membranes of the CNS.

Piloerection (goose bumps) Piloerection occurs when tiny muscles at the base of each hair, known as *arrectores pilorum*, contract and pull the hair erect. The reflex is started by the sympathetic nervous system as part of fight-or-flight responses or in a cold environment.

Polymodal nociceptors Nociceptors that can be excited by a variety of noxious stimuli such as mechanical, chemical, and thermal.

Polymorphism DNA sequence variation that occurs due to variations in single nucleotides in the genome.

Positron emission tomography (PET) A small amount of a radio-labeled substance is injected into the patient. The substance then accumulates in the tissue to be studied. As the radioactive atoms in the substance decay, they release smaller particles called positrons. When a positron collides with an

electron they are both annihilated. In this process two photons are emitted. These photons then move in opposite directions and are picked up by the detector ring of the PET scanner. This information is used to generate three-dimensional, cross-sectional images that represent the biological activity where the radio-labeled compound has accumulated.

Post-exercise muscle soreness Pain caused by excessive or unaccustomed eccentric (lengthening) contractions (e.g., following unaccustomed descent from a mountain climb or other vigorous activity). Soreness, tenderness, and stiffness appear between 8 and 24 h after the activity.

Postganglionic fibers Fibers of the sympathetic and parasympathetic nervous system between the ganglion and the innervated tissue. In both systems, the efferent pathway consists of two cells: (1) a preganglionic neuron whose cell body is located in the central nervous system and which conducts its activity via a preganglionic fiber to the ganglion, and (2) a postganglionic neuron whose cell body is located in the ganglion, and which terminates with its postganglionic fiber in the innervated organ or tissue. In the ganglion, the neuronal activity is synaptically transmitted from the pre- to the post-ganglionic neuron.

Postsynaptic inhibition An inhibition of a postsynaptic cell effected by a hyperpolarization (an inhibitory postsynaptic potential, IPSP) of the membrane of the postsynaptic neuron.

Postural muscle A skeletal muscle that is (mainly) used for maintaining body posture.

Potentiation An influence between stimuli that leads to an enhancement of the effect of one stimulus by the other in a more than additive way.

Poupart's ligament Inguinal ligament.

Prefrontal cortex A large portion of the frontal lobe including all areas ventral to the motor cortex on the lateral and medial aspects of the hemispheres.

Pressure pain threshold (PPT) The force required to elicit pain at a specific site. This is measured by a technique called "algometry" and is measured in kilograms or pounds per square centimeter. Trigger points have a lower pressure pain threshold than surrounding nontrigger point regions, indicating that they are hypersensitive to pressure.

Presynaptic bouton A widening of the afferent axon that forms the presynaptic portion of a synapse. The bouton (French for button) contains the neurotransmitter (s).

Presynaptic inhibition An inhibition of a postsynaptic cell effected by a reduction of the amount of neurotransmitter released by the presynaptic bouton, i.e., the inhibitory transmitter does not influence the postsynaptic

neuron directly (in contrast to postsynaptic inhibition, there is no inhibitory postsynaptic potential in the postsynaptic membrane).

Prevalence The number of existing cases of a disease in a given population at a specific time (Sted).

Preventive (preemptive) analgesia Local anesthesia applied immediately before and while a painful therapy or operation is performed under general anesthesia. The concept behind preventive analgesia is that operations excite nociceptors whose activity is likely to cause sensitization of central nervous system neurons. By preventing the nociceptive impulses from reaching the spinal cord or brain stem, central sensitization and other neuroplastic changes in central nervous neurons do not occur.

Primary afferent fiber A sensory nerve fiber in a peripheral nerve. It extends from a receptive ending in the body periphery to the dorsal root ganglion or ganglion of a cranial nerve. In primary afferent fibers action potentials propagate toward the central nervous system.

Primary afferent unit The first sensory neuron in the body periphery. It includes the receptive ending, the afferent fiber, the soma in the spinal or cranial ganglion, and the central process in the dorsal root and CNS.

Primary ending of muscle spindle A receptive nerve ending that wraps around the central portion of an intrafusal muscle fiber in a spiral course. The afferent fiber of the primary ending is a Group Ia (thick myelinated) fiber that has monosynaptic connections with α-motor neurons.

Primary hyperalgesia (allodynia) Increased pain and allodynia in the region of a peripheral lesion. It can be explained by increased excitability (sensitization) of damaged nociceptors and/or dorsal horn neurons supplying that region.

Proband A person with the condition under consideration.

Projected pain Pain caused by a lesion of nerve fibers (compression or inflammation) along their course in a peripheral nerve or dorsal root. At the site of the lesion, action potentials are generated which reach central nervous neurons via the same afferent fibers that normally signal the presence of a stimulus at the receptive ending. The central neurons cannot recognize the origin of the action potentials, and interpret any activity in a nerve fiber as coming from the receptive ending. Therefore, projected pain is felt in the innervation territory of damaged nerve fibers.

Proprioceptive cells Neurons that are dominated by input from muscle spindles and tendon organs, the main proprioceptors in muscle. These cells mediate the sensation of joint angle and body posture and are involved in locomotor control. Proprioceptors and proprioceptive cells inform higher CNS centers about the inner state of the body.

Prostaglandin Prostaglandins are released in a pathologically altered muscle by the enzymatic action of cyclooxigenases. PGE_2 binds to a G protein-coupled prostanoid receptor (EP2) in the membrane of the nociceptive ending. Similar to serotonin, PGE_2 sensitizes nociceptors rather than exciting them.

Protein kinases Enzymes that phosphorylate channel proteins. Phosphorylation means that phosphate residues are coupled to the protein molecules of the channels. This makes the ion channels better permeable.

Protraction Drawing a part of the body forward.

Proximal Nearest the trunk or the point of origin (Sted).

Psychosis A mental disorder causing gross distortion or disorganization of a person's mental capacity, emotional response, and capacity to recognize reality, communicate, and relate to others (Sted).

Quadriplegia (syn.: tetraplegia) Paralysis of all four limbs.

Radiation of pain Subjective spreading of pain from a lesion to neighboring areas. The term is mainly used to describe spreading that is continuous with the site of the original pain.

Radiculopathy Pain caused by compression or another lesion of a dorsal root. The pain of radiculopathy is similar to that due to a lesion of a spinal or cranial nerve (peripheral neuropathy).

Ragged red fibers Abnormal muscle fibers found in the muscles of fibromyalgia patients. They are characterized by subsarcolemmal accumulations of pathologically altered mitochondria. Although ragged red fibers are often found in fibromyalgia patients, they cannot be considered specific for that syndrome.

Ramus (dorsal or ventral) The main divisions of a spinal nerve. A muscle system supplied by the dorsal ramus is the erector spinae muscle; the ventral rami supply the ventral body wall, and form nerve plexus for the innervation of the limbs.

Receptive ending A single sensory nerve ending with all of its branches in the body periphery.

Receptive field The body region from which a neuron can be excited or inhibited.

Receptor (1) A receptive nerve ending, i.e., all peripheral branches of a sensory nerve fiber that are located in a small volume of tissue and possess specialized membrane areas for the transduction of a stimulus into an electrical signal (the receptor potential). (2) A large molecule (often glycoprotein) built in the cell membrane. Specific agonist molecules (e.g.,

neurotransmitters, hormones) can bind to a receptor molecule and thus induce reactions in the cell.

Receptor matrix An arrangement of cell organelles (mitochondria, vesicles, and axonal reticulum, i.e., a network of fluid-filled vacuoles) embedded in a granulated axonal cytoplasm. The receptor matrix is characteristic for those parts of an axon that can perceive stimuli.

Receptor potential A local change in the membrane potential of a receptive nerve ending, caused by a stimulus. If the receptor potential is large enough, action potentials are elicited in the afferent fiber.

Reciprocal inhibition A spinal mechanism by which an antagonist (muscle) is inhibited whenever the agonist is activated.

Red muscle fibers Muscle cells that contain quantities of myoglobin and oxidative enzymes but are poor in phosphorylases. They are resistant to fatigue. Red muscle fibers are able to contract for long periods of time, because they make use of the oxydative metabolism, i.e., they consume oxygen and obtain ATP from the mitochondria. The red fibers are slow twitch fibers and are also called Type I fibers.

Referred hyperalgesia A hyperalgesia in one tissue induced by a painful lesion in another tissue or organ. An example of referred hyperalgesia in muscle is the hyperalgesia of the obliquus externus m. in patients with calculi (stones) in the upper renal tract.

Referred inhibition An inhibition of one muscle caused by a painful disorder in another muscle.

Referred pain Pain that is felt at a distance from the initiating site. Referred pain is mediated by the central nervous system, and represents peripheral and central sensitization. The area of referred pain is often discontinuous with the site of the lesion. Referred pain can occur together with local pain (at the lesion site) or in isolation. If the pain is referred from one site to several remote locations it is often described as "radiating." Referred pain is usually — but not always — segmental, occurring in myotomes innervated by the same nerve root.

Referred spasm A spasm caused in a muscle by a painful disorder in another muscle or other body structure.

Reflex An involuntary reaction to a stimulus. The reflex consists of (1) an afferent arc that conducts the information about the stimulus to the spinal cord or brain, (2) one or more central nervous synapses, and (3) an efferent arc that activates the effectors of the reflex (e.g., skeletal muscle).

Reflex sympathetic dystrophy (now called complex regional pain syndrome, CRPS) A painful disorder that is characterized by forms of pain (e.g.,

causalgia, Sudeck syndrome) that are associated with signs of sympathetic disturbances, and therefore suggest an involvement of the sympathetic system.

Refractory period That period of time directly following an action potential during which a muscle or nerve cell is not excitable (absolute refractory period) or requires a stronger than normal stimulus for excitation (relative refractory period).

Repetitive strain injury (RSI) Muscle pain induced by repetitive relatively light muscular activity at work or playing computer games that is at or beyond the muscles' tolerance. Other terms used to describe this condition are occupational myalgia and cumulative trauma.

Resonance In an oscillatory system, it is the marked increase in the amplitude of oscillations when the system is subjected to an impressed (imposed) frequency which is the same (or very close to) the natural frequency of the system. Resonance occurs at that frequency where resistance to movement is minimal.

Resting (background) discharge Impulse activity of neurons in the absence of external stimulation. Sometimes, also the term "spontaneous" discharge is used. The latter term has to be used with caution, because in most situations the presence of a stimulus cannot be excluded with certainty.

Rigidity The term generally refers to inflexibility or resistance to change, and has a number of specific meanings depending on the field of application. In medicine (neurology), rigidity describes an increase in muscle tone leading to a resistance to passive movement throughout the range of motion. Parkinson's disease is a typical example of muscle rigidity resulting from central nervous system (CNS) disorders leading to cocontraction of antagonist muscles.

Rigor mortis Irreversible contracture (in the physiological sense) of all muscle fibers after death. Normally, the binding of myosin to actin is terminated by the consumption of energy which is provided by ATP. After death, the intracellular ATP is used up after a while and not restored. Without ATP, the myosin heads cannot separate from the actin.

Rimmed vacuoles Small areas of focal destruction of muscle fibers with basophilic rims that can be seen by light microscope.

Rippling muscle syndrome A dysfunction of skeletal muscle characterized by a rolling wave of contraction that spreads laterally across the muscle in both directions following percussion of the muscle.

Rostral Relating to the snout end of an organism (Sted).

Ruffini corpuscle A flat, encapsulated mechanoreceptor supplied by several myelinated nerve fibers. The fibers form a dense arborization within a capsule of connective tissue.

Rupture (of muscle) Tearing of a muscle or its tendon.

Ryanodine receptor A calcium channel on the sarcoplasmic reticulum membrane. Ryanodine receptors mediate the release of calcium ions from the sarcoplasmic reticulum, an essential step in muscle contraction.

Sarcomere The smallest functional unit of a muscle cell. It is approximately 2.5 μm long in resting muscle. A sarcomere has three main constituents: actin and myosin filaments, and the Z band or Z disk. The actin filaments are attached to the Z disk, and interdigitate with the myosin filaments. The filaments slide against each other during shortening of a muscle. A sarcomere extends from one Z disk to the next.

Sarcoplasmic reticulum A network of branching and anastomosing tubules within the sarcoplasm (the cytoplasm of a muscle cell). The reticulum has terminal expansions (cisternae) close to the Z disk which form a reservoir for calcium ions. The reticulum fills the space between the myofibrils within a muscle cell.

Satellite trigger points (TrPs) TrPs which develop from a key TrP in another muscle. They are prone to develop in muscles that lie within the pain reference zone of key myofascial TrPs, or within the zone of pain referred from a diseased viscus, such as the pain of myocardial infarction, peptic ulcer, cholelithiasis, or renal colic.

Satellite cells (1) The cells that are present underneath the basement membrane of normal muscle cells. Satellite cells are thought to be myoblasts, i.e., cells that develop into muscle cells during development. Probably, the satellite cells can also repair small muscle lesions. (2) Cells that are found around dorsal root ganglion cells and are derived from Schwann cells.

Schwann cells Non-neuronal cells that form a sheath around axons in the peripheral nervous system.

Sciatica Pain in the lower back and hip radiating down the back of the thigh into the leg; it is usually attributed to herniated lumbar disk, but can also be due to TrPs in muscles of the lumbar or gluteal region.

Second messenger Intracellular signal molecules that activate enzymes in response to an external stimulus and change the metabolism of cells. In neurons, second messengers can change the excitability of the cells following activation of receptor molecules in the cell membrane. Examples of second messengers are Ca^{2+}, cyclic adenosine monophosphate (cAMP), and protein kinases. In this context, neurotransmitters and hormones are the first messengers.

Secondary ending of muscle spindle Receptive nerve ending that wraps around the end portions of an intrafusal muscle fiber. The afferent fiber of the secondary ending is a Group II fiber that contacts α-motor neurons via an interneuron.

Secondary hyperalgesia (allodynia) Increased pain and allodynia in body regions surrounding a lesion (where the tissue and receptors are completely intact).

Segment Applied to the spinal cord: a section where one spinal nerve with its dorsal and ventral roots originates.

Segmental (afferent) inhibition of central neurons Inhibition of local pain caused by input via thick myelinated (non-nociceptive) afferent fibers from the same region. An example of segmental inhibition is the reduction of the pain following a blow to the shin brought about by rubbing the skin of the knee region.

Sensitization (general) Process whereby a previously subthreshold stimulus can now induce neural activity.

Sensitization of a nociceptor An increase in the nociceptor's sensitivity to stimulation. The sensitization leads to a lowering of the excitation threshold; a sensitized nociceptor can be excited by nonpainful stimuli, and elicits pain in response to an innocuous stimulus.

Sensory modalities All sensations originating in a special sense organ (e.g., vision, hearing).

Sensory terminal tree The preterminal axon and its branches in the body periphery. The term is part of the concept that both group III and IV endings do not have just one sensory site, but possess several branches with many receptive loci that together enhance the sensitivity of the free nerve ending as a sense organ.

Sensory-discriminative component of pain The pain component that mediates the identification of the modality (mechanical, chemical, thermal), the site, intensity, and time course of a painful stimulus. This component is probably due to activity in the postcentral gyrus of the cortex.

Serotonin (5-hydroxytryptamine, 5-HT) One of the vasoneuroactive substances; it constricts blood vessels, sensitizes or excites nociceptors, and is released from blood platelets. Serotonin is also important as one of the main neurotransmitters in the descending pain-inhibiting tracts.

Serotonin receptors The stimulating effects of serotonin on nociceptive terminals in the body periphery are predominantly mediated by the 5-HT_3 receptor. The serotonin concentrations released in the tissue are usually not sufficient to excite nociceptors directly, but they can sensitize them, i.e., make them more sensitive to other pain-producing agents such as BKN. In the CNS, serotonin receptors mediate effects of the antinociceptive descending system (presently, more than 15 different 5-HT receptors are known in the CNS).

Shawl sign Erythema over shoulders.

Silent (sleeping) nociceptors Nociceptors that cannot be activated by mechanical stimuli under normal circumstances, but respond readily to these stimuli in inflamed tissue.

Single nucleotide polymorphisms (SNPs) Variations in gene structure due to change in a single amino acid.

Single photon emission computed tomography (SPECT) SPECT is very similar to PET. However, the substances used contain heavier and longer-lived radioactive atoms. These atoms emit high-energy photons (called gamma rays) which are then detected.

SLE Systemic lupus erythematosus.

Slowly conducting fiber A nerve fiber that has a conduction velocity of below 30 m/s. Morphologically, the fiber is either thin myelinated or unmyelinated.

Soft-tissue pain disorders A term including over 100 different painful conditions of muscle, fascia, tendon, ligament, joint capsule, bursae, periosteum, and subcutaneous tissue. The term has replaced the out-dated designation "nonarticular rheumatism." Fibromyalgia is an example of a soft-tissue pain disorder.

Somatization The term refers to preoccupation with physical symptoms, including pain, inappropriate to the actual physical disturbance. Somatization occurs mainly in response to psychic stress.

Somatomotor cortex That cortical region where motor information to skeletal muscle groups originates. The primary motor cortex comprises large portions of the precentral gyrus, the secondary motor cortex, and a small, medially adjacent, region on the medial surface of the brain.

Somatosensory Relating to sensory information from receptors of the body excluding those of the special sensory organs such as eye and ear.

Somatosensory cortex That cortical region where the information from mechanoreceptors, thermoreceptors, and possibly also nociceptors is processed. Anatomically, the primary somatosensory cortex comprises the central sulcus and the postcentral gyrus, and the secondary somatosensory cortex includes a small region at the lower end of the postcentral gyrus.

Somatostatin (SOM) One of the neuropeptides. SOM has mainly inhibitory influences on nerve cells. It is also present in other tissues (e.g., pancreatic islets).

Somatotopy The topographic association of positional relationships of receptors in the body via respective nerve fibers to their terminal distribution in specific functional areas of the cerebral cortex (Sted) and other areas of the CNS. The somatotopy reflects itself in a projection of a (distorted) image of the body on to neuron populations.

Somatotopically inappropriate neurons Neurons that have (normally ineffective) connections with body regions they do not normally supply. These connections can become effective under pathological conditions and then form the basis for spread of pain and referral.

Spasm Longer-lasting contraction of a muscle that is not under voluntary control and is not dependent upon posture. A muscle in spasm exhibits EMG activity. Spasm may or may not be painful.

Spasmodic torticollis A form of focal dystonia of the head and neck muscles which causes various abnormal movements. It is characterized by tonic (relatively continuous) or phasic (episodic) muscle spasms or tremulous shaking which can be very painful, and is accompanied by abnormal spontaneous EMG activation.

Spasticity Muscle spasm observed in conditions such as hemiplegia, brain injury, or spinal cord injury. It is associated with hyperactivity of stretch reflexes and tendon jerks, which is probably caused by a loss of supraspinal inhibitory influence on the α-motor neurons.

Spatial summation A mechanism by which subthreshold inputs to a neuron add up (and may become suprathreshold) if inputs from many body regions act on the same neuron simultaneously.

Specific muscle tone This form of muscle tone is usually defined as the viscoelastic tension, only, in the absence of muscle contractile activity confirmed by absence of EMG electrogenic activity.

Specific neuronal potassium channel openers (SNEPCOs) Drugs designed to open potassium channels in hyperexcitable central neurons. Opening the channels leads to an outward K^+ flux and a hyperpolarization of the nerve cell which render it less excitable.

Spinal nerve A large peripheral nerve whose fibers originate or terminate in one segment of the spinal cord. For instance, the human lumbar spinal cord has five segments (and vertebrae) and hence five spinal nerves.

Spinal stenosis A narrowing of the vertebral canal which contains the spinal cord and the cauda equina.

Spread of pain The term is used for describing the expansion of a region in which pain is felt. In contrast to referral of pain, the expansion is continuous with the origin of the site of pain.

Static contraction Maintained contraction without phases of relaxation.

Stiff-man syndrome (synonym: stiff-person syndrome) This is a rare neurological disorder characterized by progressive muscle stiffness of the trunk and limbs, and a heightened sensitivity the stimulation of electrogenic muscular contractions by noise, touch, and emotional distress.

Stiffness This term has two definitions that refer to either *solids* which are not easily bent, are rigid, or inflexible, or *fluids* that are firmer than liquid in consistency, e.g., thick or viscous substances (Collins English Dictionary, 3rd edn. Harper Collins, Glasgow, 1991). Stiffness of solids concerns simple displacement or deformation, and corresponds to elasticity. Stiffness of fluids concerns resistance to rate of movement, and corresponds to viscoelasticity.

Stress-induced analgesia (SIA) A mechanism of pain modulation which is, in contrast to DNIC (diffuse noxious inhibitory control), mostly due to supraspinal descending inhibitory pain pathways and is at least partially mediated by the opioid system.

Stressor A type of stress, physical or emotional.

Stretch reflex A muscle contraction in response to muscle stretch (i.e., activation of muscle spindles).

Striatal–frontal circuits Neuronal connections between the striate body (a complex formed by the caudate nucleus and the putamen, two nuclei belonging to the basal ganglia) and the cortex of the frontal lobe.

Striatum (or corpus striatum) Striate body, a complex formed by the caudate and lentiform nucleus, two nuclei in the cerebrum.

Subluxation An incomplete dislocation of a joint.

Substance P (SP) A neuropeptide. It consists of a chain of 11 peptides, has strong vasodilatory actions, and is a neuromodulator for nociceptive processes in the central nervous system.

Substantia gelatinosa The second lamina (layer) of the dorsal horn in the spinal cord.

Sudomotor fibers Sympathetic efferent fibers that activate sweat glands.

Supine The body lying face upward.

Supplementary motor area A part of the motor cortex that is located on the medial surface of the hemispheres, ventrally to the precentral gyrus.

Sympathectomy Excision of a segment of a sympathetic nerve or of one or more sympathetic ganglia (Sted).

Synapse A connection between two neurons in the CNS. It consists of a presynaptic terminal or bouton that contains the neurotransmitter, and a specialized portion of the membrane of the postsynaptic neuron. Between these two structures there is the synaptic cleft, which is several namometers wide. When an action potential arrives in the presynaptic bouton, it releases neurotransmitters into the synaptic cleft. The transmitter molecules diffuse across the synaptic cleft, and bind to molecular receptors in the postsynaptic

membrane. This leads to the opening of ion channels in the membrane or to the activation of intracellular second messenger cascades.

Synergist muscle A muscle activated in parallel with other muscles (a group of muscles are typically contracted to perform a movement).

Systemic lupus erythematosus (SLE) An inflammatory connective tissue disease with variable features, frequently including fever, weakness and fatigability, joint pain or arthritis resembling rheumatoid arthritis, diffuse erythematous skin lesion on the face, neck or upper extremities, with liquefaction degeneration of the basal layer and epidermal atrophy, lymphadenopathy, pleurisy or pericarditis, glomerular lesions, anemia, hyperglobulinemia, a positive LE test, and other evidence of an autoimmune phenomenon. Synonym: disseminated LE (Sted).

Systremma Another term for calf cramps or nocturnal leg cramps.

Tachyphylaxis Rapid appearance of progressive decrease in response following repetitive administration of a pharmacologically or physiologically active substance (Sted).

Tardive dystonia A late, tardy form of dystonia.

Taut band A palpable rope-like hardening of a muscle harboring a myofascial trigger point. Usually, a taut band contains one or more exquisitely tender spot(s), the TrP(s).

Temporal summation (1) A mechanism by which subthreshold inputs to a neuron sum up (and may become suprathreshold) if a given input from the same source acts on a neuron at a relatively high frequency (higher than 1 Hz). (2) A term used to describe the augmented response of a nociceptive dorsal horn neuron to incoming repetitive stimuli.

Tenderness Pain elicited by weak (pressure) stimuli that are not normally painful. The reason for tenderness is sensitization of nociceptors or central nervous neurons.

Tendomyopathy A painful condition of the insertion zone of a muscle. The term usually includes a distinction between generalized tendomyopathy (largely identical to fibromyalgia) and localized tendomyopathy (pain in one or a few insertion regions).

Tendon (Golgi) organ A mechanoreceptor in the tendon, which measures the tension of the muscle. It is arranged in series with the muscle. Activation of tendon organs inhibits the homonymous muscle.

Tension-type headache (TTH) TTH is the most common type of primary headache which accounts for nearly 90% of all headaches. The pain can radiate from muscle groups of the head or neck, and is associated with

symptomatically or objectively increased stiffness of affected muscles, but not typically based on electrogenic EMG contractions.

Teratogenicity The property or capability of producing fetal malformation (Sted).

Tetanic muscle contraction Repeated muscle contractions at such a high frequency that the single contractions merge. In recordings of the muscle mechanics, the muscle force is a straight line under these circumstances.

Tetrodotoxin (TTX) The toxin of the Japanese puffer fish, one of the most powerful toxins known. Nociceptive afferent fibers differ from other afferent fibers in that they are equipped with a special type of sodium channel that cannot be blocked by TTX. These channels are called TTX-resistant. Most myelinated fibers have TTX-sensitive sodium channels, and are blocked by TTX.

Thixotropy A property of many gels which become more fluid on being shaken and reform to greater viscosity on standing (e.g., ketchup). The viscoelastic tone of skeletal muscles exhibits marked thixotropy.

Threshold (1) Electrical. The minimum change in membrane potential that leads to the generation of action potentials in an excitable cell (nerve or muscle cell). Normally, the electrical threshold is approximately 30 mV more positive than the resting membrane potential. (2) Mechanical, thermal, chemical. When using these less well-defined stimuli, the lowest intensity of a stimulus that leads to a just recognizable response of a neuron or individual is taken as its threshold.

Tinel sign Pain, dysesthesia, or paresthesia upon percussion of a neuroma or nerve lesion. The peripheral basis of the Tinel sign is the mechanosensitivity of sprouting nerve fibers in the neuroma or in the nerve lesion.

Tinnitus The sensation of noises in one or both ears (Sted).

Titin A long, coiled molecule that connects the myosin filaments of a sarcomere to the Z disk. It is assumed to act like a spring and brings the sarcomere back to its original length after stretch. Titin contributes to the elastic stiffness of a muscle.

Topography The description of any part of the body, especially in relation to a definite and limited area of the surface (Sted).

Tract A bundle of nerve fibers that connect two centers (nuclei) within the CNS. An exemption from this rule is primary afferent fibers in the dorsal columns that run from mechanoreceptors in the body periphery to the dorsal column nuclei (gracile and cuneate nuclei).

Transcription factor An intermediate gene product (e.g., of immediate-early genes) that is involved in the transcription of a DNA (deoxyribonucleic acid) sequence into an mRNA (messenger ribonucleic acid) sequence.

Transcutaneous electrical nerve stimulation (TENS) A method that is used to inhibit nociceptive neurons in the CNS by stimulating myelinated non-nociceptive afferents in a peripheral nerve through the intact skin. TENS uses the segmental (afferent) inhibition mechanism for its effect.

Transient receptor potential receptor subtype 1 (TRPV1) This receptor is one of the most important molecules for the induction of pain; it was formerly called vanilloid receptor subtype 1 (VR1). The natural stimulant for the TRPV1 receptor is capsaicin, the active ingredient of chilli peppers.

Transverse tubules Invaginations of the muscle cell membrane; they have close contact with the sarcoplasmic reticulum (SR). Action potentials propagating along the muscle cell membrane invade the transverse tubulus to release Ca^{++} from the SR.

Tremor An involuntary trembling movement (Sted).

Triad Electronmicroscopic structure of a muscle cell formed by two cisternae (terminal expansions of the sarcoplasmic reticulum) and a tubular invagination (transverse tubule) of the cell membrane. The triad is an essential structure for electrogenic activation of muscle contraction.

Trigger point (TrP) Central TrP: a tender localized hardening in a skeletal muscle. *Clinical characteristics* include circumscribed spot tenderness in a nodule which is part of a palpably tense band of muscle fibers, patient recognition of the pain evoked by pressure on the tender spot as being familiar, pain referred in the pattern characteristic of TrPs in that muscle, a local twitch response, painful limitation of stretch range of motion, and some weakness of that muscle.

Trismus Trismus is defined as a firm clenching of the jaw due to tonic spasm of the muscles of mastication which inhibits ability to normally open the mouth, due to one of many causes. Lockjaw is an example of trismus caused by tetanus infection. In practice, the term is commonly applied not only to restricted opening of the mouth because of muscle spasm, but also because of fibrotic contractures and/or adhesions.

Tropomyosin A protein molecule associated with the actin filament that (together with troponin) masks the binding site for myosin in a resting muscle.

Troponin A protein molecule associated with the actin filament that (together with tropomyosin) masks the binding site for myosin in a resting muscle.

Tumor necrosis factor (TNF) A multifunctional proinflammatory cytokine, secreted predominantly by monocytes/macrophages in the body periphery and by microglial cells in the CNS.

Twitch A momentary contraction of a muscle fiber (Sted) or a group of muscle fibers.

Type 1 interferon system The system includes proinflammatory cytokines, interferon-alpha and interferon-beta, that have several functions one being activation of the immune system. The interferons are major inducers of MHC class I and II expression on cells to facilitate presentation of antigens, for example to T cells.

Tyrosine kinase A (TrkA) receptor The ligand of this receptor molecule is nerve growth factor (NGF). NGF is well-known for its sensitizing action on nociceptors in the body periphery and neurons in the CNS; it is synthesized in muscle, and its synthesis is increased during pathophysiological changes of the muscle (e.g., inflammation).

Unidirectionality of pain referral The term describes the usual situation that stimulation of a lesion (e.g., a TrP) causes referred pain, but that stimulation of the area of referral does not elicit pain at the site of the original lesion.

Unmyelinated fiber A nerve fiber that lacks a myelin sheath. Note that these fibers still have a thin sheath formed by Schwann cells in the body periphery or glial cells in the CNS.

Varicosity Neuroanatomy: expanded portions of the peripheral preterminal axon or ending of a slowly conducting sensory fiber group III or IV fiber in muscle). The varicosities contain mitochondria, vesicles and other cell organelles. In the vesicles, neuropeptides and other substances are stored, and are released from the fiber when the receptive ending is excited.

Vasomotor fibers Sympathetic efferent fibers that innervate smooth muscle of blood vessels.

Vasoneuroactive substances Substances that dilate or constrict blood vessels and increase the sensitivity of nociceptors or excite them. Examples are bradykinin (BK), serotonin (5-HT), and prostaglandins (PGs, particularly PGE_2). The substances are ubiquitously present in the organism and are released by tissue lesions.

Ventral root Fiber bundles leaving the spinal cord at the ventrolateral circumference of the spinal cord. They contain efferent somatomotor and preganglionic autonomic fibers.

Ventricle In neuroanatomy, the term is used for cerebral ventricles. The ventricles are interconnected cavities in the brain filled with cerebrospinal fluid.

Ventrobasal complex (VB) The term includes two nuclei of the thalamus: nucleus ventralis posterolateralis (which receives somatosensory input from the body except the face) and nucleus ventralis posteromedialis (which receives somatosensory input from the face region).

Vesicle In neurons: a microscopic sac inside the presynaptic portion of a nerve cell and also within receptive nerve endings. Vesicles are formed by membrane material and contain neurotransmitters and other substances.

Viscerosomatic pain Referred pain syndromes in which pain in a visceral organ (visceral pain) is referred to the body wall (somatic pain). Visceral referred pain can mimic myofascial pain, and myofascial pain can mimic visceral pain. This is the familiar pain of heart attack, but is commonly seen in the pelvic organs as a cause of abdominal and pelvic region pain.

Viscoelastic tone The combined viscous and elastic tension of a resting muscle caused by the physical properties of the soft tissues. One causal factor seems to be that in a resting muscle a certain proportion of the actin filaments stick to the myosin filaments. Viscoelastic tone occurs without EMG activity.

Viscosity The resistance to fluid flow, set up by shear stresses within the flowing liquid.

Visual analog scale (VAS) A tool for measuring the severity of a patient's pain. The patient is asked to make a mark on a line, usually 10 cm long, that has 0 designated at one end and 10 at the other. Zero represents no pain and 10 represents the most severe pain that the patient can imagine.

von Frey hairs Synthetic or natural hairs used for quantitative mechanical stimulation of skin receptors. They are mounted on a short handle so that they can be placed vertically (with their long axis perpendicular to the surface) on the skin.

Voxel-based morphometry (VBM) VBM identifies minute differences in the composition of brain tissues, while discounting large-scale differences (like anatomy and position). All structural images are spatially normalized to the same stereotactic space, and then segmented into different images (white matter, gray matter, cerebrospinal fluid). The resulting statistical maps can be compared between groups.

Wheal A circumscribed evanescent area of edema of the skin, appearing as an urticarial lesion, slightly reddened, and accompanied by itching (Sted). The wheal around a lesion is probably due to an increase in the permeability of blood vessels caused by the release of substance P.

Whiplash injury Hyperextension–hyperflexion injury of the neck (Sted). Often, this injury occurs in a car accident when a moving car hits a stopped one from the rear.

White matter A tissue component of the CNS which contains mainly fiber tracts and only a few neuronal cell bodies. In the white matter, the conduction of impulse activity between CNS centers occurs, but no information processing takes place.

White muscle fibers Muscle cells that have a pale appearance because they contain less myoglobin than red fibers. The white fibers are also called Type II fibers; they have predominantly glycolytic metabolism, and contract in a fast twitch. They fatigue quickly.

Wind-up The increase in the magnitude of response in dorsal horn neurons to repeated C-fiber input. The increase occurs if the identical input is repeated at short intervals (less than 2 s). The underlying mechanism is temporal summation; apparently, the NMDA receptor is involved.

Winging (of the scapula) An abnormal scapular posture characterized by lifting of the medial margin of the scapula from the thorax wall due to muscle weakness.

Work-related (occupational) musculoskeletal disorders Chronic muscle pain mainly due to poor ergonomics of the workplace. The pain occurs often in persons who perform monotonic contractions at low force level with the same muscle or muscle compartment (e.g., musicians, assembly-belt workers). Psychic stress and time pressure play an additional important role.

Z band The borderline region between two sarcomeres. Actin filaments are fixed to the Z bands.

Zygapophyseal joints The small joints connecting the vertebrae.