Pain, 54 (1993) 241–289

PAIN 02331

Review Article

Nociception from skeletal muscle in relation to clinical muscle pain

S. Mense

Institut für Anatomie und Zellbiologie, Universität Heidelberg, W-6900 Heidelberg (Germany)

(Received 5 August 1992, revision received 15 December 1992, accepted 24 February 1993)

Key words: Muscle pain; Visceral pain; Cutaneous pain; Receptive field; Afferent fiber; Dorsal root ganglion; Dorsal horn neuron; Nociception; Antinociception; Neuropeptide; Receptor specificity; Noxious stimulus; Receptor sensitization; Convergence; Neuroplasticity; Modulation; Motor reflex; Sympathetic reflex; Central nervous pathway; Trigeminal pathway; Referred pain

Contents

Correspondence to: Prof. S. Mense, Institut für Anatomie und Zellbiologie, Universität Heidelberg, Im Neuenheimer Feld 307, W-6900 Heidelberg, Germany. Tel.: (6221) 564193; FAX: (6221) 563071.

I. Introduction

The practical relevance of muscle pain is usually underestimated in the public, although its prevalence and severity compare with those of other painful conditions. A recent survey has shown that 14.4% of the United States population suffers from chronic pain related to the joints and musculoskeletal system (Magni et al. 1990). The prevalence of myofascial pain in pain patients ranges from 30% to more than 80% (Fishbain et al. 1986; for a short review on the epidemiology of myofascial pain, see Fricton 1990). Interestingly, the bulk of the data on neurophysiology of pain has been obtained in studies of cutaneous nociception, although skin pain is clinically much less relevant than muscle and visceral pain.

Muscle pain differs in many ways from other types of pain. Subjective differences are that pain associated with muscle lesions is described as aching and cramping, while cutaneous pain is characterized by its sharp, pricking, stabbing or burning nature. First and second pain elicited by electrical activation of thin myelinated and non-myelinated afferent fibers in a muscle nerve have the same dull and aching quality (Torebjörk et al.

1984a). In contrast to cutaneous pain, which is localized with great accuracy, muscle pain is difficult to localize, with the exception of pain from fascia and periosteum that is often perceived as originating in a single spot (Kellgren 1938; Lewis 1942; Staff 1988). Visceral pain, like muscle pain, is difficult to localize and is hard to distinguish from muscle pain. Both show referral, i.e., pain is not (only) felt at the site of the tissue lesion but (also) remote from this site (see below). The main difference between these two forms of pain is that visceral pain is mainly referred to the skin, whereas muscle pain is generally referred to other deep somatic (non-visceral) structures such as muscle, fascia, tendon, joint, and ligament (Kellgren 1938), if it is referred at all.

Tissue-threatening (noxious) stimulation of any muscle and of skin always elicits pain. However, noxious stimulation of viscera does not always produce pain and not all viscera are sensitive to noxious stimuli (Gebhart and Ness 1991). Viscera generally refer pain to the skin; the skin very rarely, if ever, refers pain to other regions (Lewis 1942). Both muscle and visceral pains are associated with autonomic symptoms such as drop in blood pressure, sweating, and nausea (Feinstein et al. 1954). Cutaneous pain does not show this association.

Considering objective differences between nociception from muscle and other tissues, it is generally assumed that innervation density decreases in the order skin, muscle, and viscera, although exact figures are neither available nor easily obtained in view of the fact that skin is approximately 2-dimensional and muscle 3-dimensional. In the nerve to the cat gastrocnemius-soleus (GS) muscle, approximately one-half of all fibers are afferent (Langford 1983; Mitchell and Schmidt 1983).

Most of the dorsal horn cells processing information from muscle nociceptors receive additional (convergent) input from cutaneous receptors (Craig and Kniffki 1985; Hoheisel and Mense 1990). In many studies on dorsal horn cells with input from cutaneous nociceptors, neurons have been described that appeared to be specifically driven by noxious stimulation of the skin. The actual degree of input convergence onto these neurons is difficult to assess, however, since deep tissues have often not been searched for receptive fields (RFs) (for general reviews on nociception, see Dubner and Bennett 1983; Perl 1984; Willis 1985a; Besson and Chaouch 1987). Dorsal horn neurons driven by visceral receptors likewise exhibit convergent input from the skin and/or deep somatic structures (Cervero 1983; Foreman et al. 1984). Recent data indicate that information from muscle and cutaneous nociceptors is processed differently in the spinal cord. One example is that the input to dorsal horn neurons from muscle nociceptors is subject to a stronger descending inhibition than is the input from cutaneous nociceptors (Yu and Mense 1990a).

In the present review, data are presented from the standpoint of a basic scientist; therefore, the clinical aspects may be considered rather theoretical by some. The aim of the article is to build a few bridges across the gap between clinical and basic research in the field of muscle pain. This includes the risk of misunderstandings and misinterpretations.

The term 'muscle pain' is used for pain originating in striated muscle including its fascia and tendinous insertions. Nociception is defined as the sum of all those neuronal events that are involved in the identification of and reaction to a noxious (tissue-threatening) stimulus. In contrast to pain, which requires consciousness for its occurrence, nociception can be studied in anesthetized animals. Of course, in interpreting experimental results, possible effects of the anesthesia have to be taken into consideration.

II. Anatomy and physiology

II-A. The peripheral apparatus

Available clinical and experimental evidence indicates that small-diameter afferent fibers from muscle have to be activated in order to elicit pain. These fibers conduct action potentials at a relatively slow velocity (below 30 m/sec in the cat) (Gasser and Grundfest 1939; Brock et al. 1951). Histologically they are either thin myelinated (A-δ or group-III fibers) or non-myelinated (C or group-IV fibers). In this article the afferent fiber types are named groups I-IV according to the nomenclature of Lloyd (1943) which was developed specifically for muscle afferent fibers. An afferent fiber together with its receptive ending is called an afferent unit. A receptive ending typically consists of several branches or terminals which together form the receptor in the physiological sense. An afferent neuron is called 'primary' if its cell body is located outside the central nervous system (CNS).

II-A.1. Fiber composition of muscle nerves

The nerve to a locomotor muscle in the cat (the lateral GS) is composed of approximately one-third myelinated and two-thirds non-myelinated fibers (Table I) (Stacey 1969; Mitchell and Schmidt 1983). Of the latter, 50% are sensory and, of these, 43% have been found to be nociceptive (Mense and Meyer 1985). In the sternomastoid nerve of the rat, the (afferent) group-IV fibers likewise constitute approximately one-half of all the non-myelinated fibers and thus the great majority of afferent units in that nerve (Gottschall et al. 1980; Sandoz and Zenker 1986). Data obtained from one muscle nerve cannot be transferred to other

TABLE I

FIBER COMPOSITION OF THE NERVE TO THE LATERAL GASTROCNEMIUS-SOLEUS MUSCLE IN THE CAT (from Mitchell and Schmidt 1983).

Myelinated 1200			
Motor		720	60%
Aα	Skeletomotor	382	53%
Aβ	Skeleto- and fusimotor	14	2%
Aγ	Fusimotor	324	45%
Sensory		480	40%
I	Spindle primary sens. endings (Ia)	144	30%
	Tendon organs (Ib)	72	15%
II	Spindle second. sens. endings	144	30%
	Spray (Ruffini) endings	5	< 1%
	Lamellated (paciniform) endings	5	< 1%
III	'Free' nerve endings	110	23%
Unmyelinated 2000			
Motor			
C	Vasomotor	1000	50%
Sensory			
IV	Sensory	1000	50%

muscle nerves, as considerable differences have been reported to exist between different muscles. For instance, neck muscle nerves of the cat are known to contain unusually high numbers of sensory and gamma motor fibers (Richmond et al. 1976), and the receptive properties of group-III receptors in hindlimb muscles differ from those in neck muscles. One possible explanation for these differences is that the muscles have different functions and environmental conditions; in contrast to neck muscles, locomotor hindlimb muscles often have to contract with maximal strength and under ischemic conditions (Abrahams 1986).

II-A.2. Structure and peptide content of muscle nociceptors

Electron microscopic investigations have shown that the main type of receptive ending connected to small-diameter afferent fibers is the free nerve ending. In the light microscope, this type of ending lacks a corpuscu-

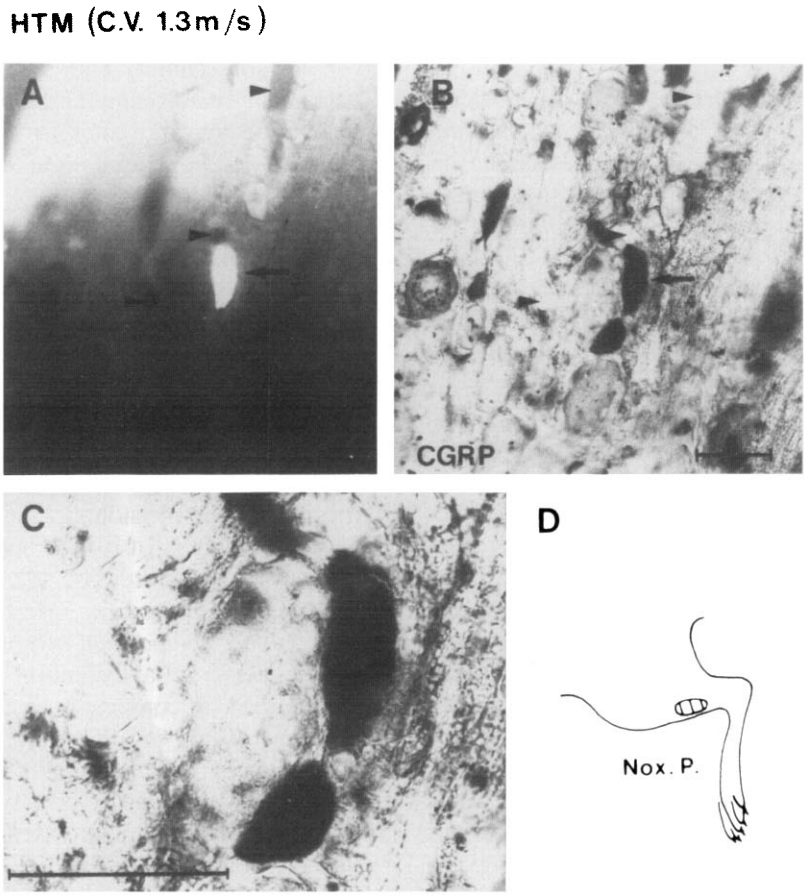

Fig. 1. Immunocytochemical data from a rat DRG cell that terminated in a HTM (presumably nociceptive) ending in skeletal muscle. A: fluorescent soma of the DRG cell (arrow) marked with intracellular iontophoresis of Lucifer Yellow. The arrowheads indicate histological landmarks (e.g., blood vessels). B: same section as in (A) following incubation with antibodies to CGRP. Scale: 50 μm. C: enlargement of (B). Scale: 50 μm. D: location of RF in the anterior tibial muscle. The receptor required noxious pressure stimulation (Nox. P.) for activation. Conduction velocity (C.V.) of afferent fiber, 1.3 m/sec (from Mense 1991).

lar receptive structure. Group-IV fibers are assumed to terminate exclusively in free nerve endings while group-III fibers supply both free nerve endings and other types of muscle receptors (e.g., paciniform corpuscles). The typical location of free nerve endings in skeletal muscle is the wall of arterioles and the surrounding connective tissue; the capillaries proper are not supplied with these endings (Stacey 1969). The marked sensitivity of free nerve endings to chemical stimuli, particularly to those associated with disturbances of the microcirculation, may be related to their location in or close to the wall of blood vessels.

More recent data demonstrate that 'free' nerve endings are not free in the strict sense, as they are almost completely ensheathed by Schwann cells. Only small areas of the axonal membrane remain uncovered by Schwann cell processes and are directly exposed to interstitial fluid (Andres et al. 1985; Heppelmann and al. 1990). The exposed membrane areas are supplied with mitochondria and vesicles and show other structural specializations characteristic of receptive areas; they are assumed to be the site where external stimuli act. The electron microscopic reconstruction of free endings in the calcaneal tendon of the cat revealed the existence of different morphological types of ending connected to group-III and -IV afferent fibers (Andres et al. 1985). At present, it is not possible to correlate morphological with functional types observed in electrophysiological experiments (see below). Therefore, it can be stated that muscle nociceptors are most probably free nerve endings, but their exact ultrastructure is unknown. Whether all nociceptors look alike is likewise an open question. The existence of different morphological types supports the notion that the free nerve endings of skeletal muscle do not form a homogeneous population but comprise functionally different (e.g., nociceptive and non-nociceptive) receptors.

Neuropeptides are assumed to modulate the transmission of sensory information in the CNS (Hökfelt et al. 1980; Buck et al. 1982; Cuello 1987; Kow and Pfaff 1988). They are present in primary afferent units of small diameter and can be released from their terminals in the spinal cord together with transmitter substances (e.g., glutamate). No neuropeptide has been found that can be considered specific for afferent fibers from muscle. Dorsal root ganglion (DRG) cells projecting in a muscle nerve have been shown to contain substance P (SP), calcitonin gene-related peptide (CGRP) and somatostatin (SOM) and thus present a peptide pattern similar to that of cutaneous nerves, whereas visceral afferent units lack immunoreactivity to SOM (Molander et al. 1987; O'Brien et al. 1989). Whether a particular neuropeptide or combination of neuropeptides is associated with a particular type of muscle receptor is unknown. Preliminary data from experiments in which single DRG cells with receptive endings in muscle were first functionally identified and then injected with a dye indicate that at least some cell bodies the peripheral processes of which terminate in muscle high-threshold mechanosensitive (HTM, presumably nociceptive) receptors exhibit CGRP-like immunoreactivity (CGRP-like IR) (Fig. 1).

It has to be emphasized, however, that CGRP-like IR is not only present in nociceptive units but also in other types of muscle receptors (e.g., muscle spindles and other low-threshold mechanosensitve (LTM) units). SP-like IR likewise has been found in LTM receptors, e.g., in nerve fibers of Krause corpuscles in the dog's tongue (Ichikawa et al. 1988). Most of the cutaneous and deep receptor types studied so far showed CGRP-like IR in some of their cell bodies in the DRG (Hoheisel and Mense 1989a). The only condition for the presence of CGRP-like IR seemed to be that the afferent unit had a small soma size and/or a slow conduction velocity. This finding suggests that CGRP may be present in many thin myelinated or non-myelinated muscle afferent units irrespective of their function. Of the two types of CGRP (alpha- and beta-CGRP, which differ in one amino acid in the rat) (Ishida-Yamamoto and Tohyama 1990) the former is present in large DRG cells, whereas small and medium-sized neurons contain both types (Noguchi et al. 1990).

In skeletal muscle, CGRP also exerts important influences via motor fibers. The peptide coexists with acetylcholine (ACh) in a subpopulation of alpha-motoneurons; it enhances the contractions of striated muscle (Takami et al. 1985) and increases intracellular cyclic adenosine monophosphate (cAMP) levels and the spontaneous release of ACh (Takami et al. 1986; Jinnai et al. 1989). The synthesis of ACh receptors at the neuromuscular junction is likewise increased by CGRP (Fontaine et al. 1986; New and Mudge 1986).

It has to be kept in mind that neuropeptides also influence immune cells (for a review, see Morley et al. 1987) and synoviocytes (Lotz et al. 1987). These actions may be of particular importance for the development and maintenance of chronic arthritis and other inflammatory disorders of deep somatic tissues.

Of the above-mentioned neuropeptides, SP is of particular interest since it has been and still is discussed as a transmitter or modulator of pain sensations (Nicoll et al. 1980; Dubner and Bennett 1983; Duggan et al. 1988). On the other hand, there is also evidence speaking against such a function (Buck et al. 1982; Frenk et al. 1988; Kellstein et al. 1990). An important finding in this regard is that the great majority (10 of 12) of individually identified nociceptive DRG cells of the cat did not show SP-like IR (Leah et al. 1985). Virtually all primary afferent units exhibiting SP-like IR also show CGRP-like IR (Lee et al. 1985; Ju et al. 1987; Cameron et al. 1988; Garry et al. 1989); both

peptides are presumably released together when the fiber is active. In the spinal cord, CGRP has been reported to prolong the action of SP by inhibiting its degradation (Le Greves et al. 1985) and to facilitate synaptic transmission in general by enhancing the calcium influx into afferent fibers (Ryu et al. 1988). Not all noxious stimuli appear to release SP in the dorsal horn; formalin injected into the rat hindpaw has been reported to lead to an inhibition of SP release (McCarson and Goldstein 1991).

Neuropeptides are released not only from the spinal terminals of afferent fibers but also from the receptive endings in the periphery (Kruger 1987). By their strong vascular and other biological actions, SP and CGRP are likely to influence the biochemical environment of the receptors from which they are released (Holzer 1988). Actually, it has been shown that the bulk of SP, after being synthesized in DRG cells, is transported to the peripheral nerve endings (Brimijoin et al. 1980). The release of this neuropeptide from nociceptive peripheral nerve endings is the central factor in a cascade of events that leads to neurogenic inflammation (Lembeck and Holzer 1979). In this regard the permeability increasing action of SP and of the neurokinins A and B is of importance (Gamse and Saria 1985; Couture and Kerouac 1987), whereas CGRP acts as a vasodilator (Brain et al. 1985; Öhlén et al. 1987). There is evidence showing that CGRP enhances the plasma extravasation induced by SP and the neurokinins A and B (Gamse and Saria 1985) but reduces the vasodilatory action of SP by desensitizing muscle arterioles to the peptide (Öhlén et al. 1988).

The role of SP and CGRP in the mediation of muscle pain is a matter of discussion. In comparison to skin nerves, muscle nerves have been reported to contain less SP (McMahon et al. 1984). This finding has been teleologically explained by assuming that the vasodilation and plasma extravasation caused by release of SP from afferent fibers in skeletal muscle would be deleterious for muscle tissue, since it is surrounded by a fascia. Because of the fascia, a SP-induced muscle edema would result in an extremely high increase in interstitial pressure and could cause muscle necrosis. Red muscles are possibly more endangered, as they contain more SP than white ones (Zenker et al. 1988).

On the other hand, SP-like IR and CGRP-like IR have been shown to be more common in the cell bodies of afferent fibers from muscle than in those from skin (O'Brien et al. 1989). Therefore, SP and CGRP are likely to be involved in painful alterations of muscle tissue. The mechanisms by which these neuropeptides contribute to muscle pain may be complex; intramuscular injections of CGRP or SP alone have been reported not to elicit pain in humans, whereas a combination of both, or of CGRP with neurokinin A, was painful (Pedersen-Bjergaard et al. 1991a,b).

A comparative study on the distribution of various peptides in the nervous system of the horse and pig (Merighi et al. 1990) has yielded data similar to those obtained in the cat and rat; therefore, neuropeptides can be expected to have a comparable distribution and function in man.

II-A.3. Spinal terminations of fine afferent fibers from muscle

II-A.3.a. Whole nerve staining. The method of transganglionic transport of the enzyme horseradish peroxidase (HRP, in some studies conjugated to wheat-germ agglutinin (WGA)) has been extensively used to visualize the spinal terminations of peripheral nerves. In these experiments HRP is injected into peripheral tissues or applied to the proximal end of a cut nerve; it is picked up by the nerve fibers and transported across the DRG to the spinal terminations of the fibers. The enzyme can be detected by its reaction with a chromagen (usually tetramethylbenzidine) which stains the HRP-containing fibers dark blue.

From the various muscle nerves studied so far similar results were obtained with regard to the termination of afferent fibers in the ventral horn and central spinal gray, but they disagree with regard to the dorsal horn. Bakker et al. (1984) observed no projection to the superficial dorsal horn from the suboccipital muscle nerve, and Abrahmas et al. (1984) reported only sparse labeling in the substantia gelatinosa (lamina II) from neck muscle nerves in the cat. In contrast, Nyberg and Blomqvist (1984) and Abrahams and Swett (1986) described labeling in the spinal laminae I and V from cat neck and forelimb muscles. Other groups found projections to the superfical dorsal horn from some, but not all, neck muscles (Amman et al. 1983).

Differing results have likewise been obtained in studies of the projections of the GS muscle. Molander and Grant (1987) did not find any projections from the rat GS to the superficial dorsal horn; Brushart and Mesulam (1980) and Brushart et al. (1981) reported a dense projection to the substantia gelatinosa in the rat, and Kalia et al. (1981) described a diffuse projection of GS afferent fibers to laminae I-V. Other groups found clear terminations from the cat GS muscle in laminae I and V, but not in lamina II (Mense and Craig 1988).

These conflicting results are difficult to interpret. Methodological differences (WGA-HRP and free HRP may be picked up differently by myelinated and nonmyelinated fibers) and differences between the species and muscles studied may contribute to heterogeneity of the data. If positive findings (presence of labeling) are rated higher than the lack of labeling in certain laminae, the bulk of the data indicates that the fine muscle afferent fibers terminate mainly in laminae I and V in the cat and thus have a termination pattern similar to that of visceral afferents (Kuo et al. 1983; Nadelhaft et

al. 1983; Cervero and Connell 1984). In contrast, afferent fibers from the skin show dense terminations in laminae II-IV and only few projections to lamina I (Koerber and Brown 1980; Marfurt 1981). Another interesting difference between muscle and skin nerves has been reported by Ygge (1989) who found that spinal projections of the cutaneous branch of the radial nerve are somatotopically organized, whereas those of the muscle branch lack a somatotopy. This arrangement may contribute to the diffuse nature of muscle pain. It has to be kept in mind, however, that the somatotopy of primary afferent fibers is not necessarily also present at the level of dorsal horn neurons. Some of the latter cells possess extended dendritic trees and sample their input from large portions of the dorsal horn.

II-A.3.b. Intra-axonal staining of single fibers. With this method the spinal terminations of a physiologically identified fiber can be visualized. First, the functional properties of the receptive ending are determined by recording the impulse activity intra-axonally with a micropipette containing a dye, and then the dye (e.g., HRP) is injected into the axon (Brown et al. 1977; Light and Perl 1979). The results obtained from HTM afferent units supplying skeletal muscle and other deep somatic tissues indicate that these units project either to lamina I only or to lamina I and deeper laminae (IV and V; Fig. 2) (Mense et al. 1981; Hoheisel et al. 1989). By contrast, afferent fibers from non-proprioceptive LTM receptors in deep tissues terminated mainly in laminae II and IV-VI. The differential termination of presumably nociceptive and non-nociceptive afferent units supports the assumption that these neurons really form different functional groups and are not part of one single polymodal receptor population (see below).

The above single-fiber data were obtained from myelinated afferent units conducting in the group II and III range (2.5–40 m/sec in the cat). The method of intra-axonal injection of dyes is not (yet) applicable to non-myelinated fibers because of their small diameter (< 1 μm in the cat) (Stacey 1969). The spinal terminations of group-IV afferent units have been studied by Sugiura et al. (1986, 1989) by injecting a dye into the soma of identified neurons in the DRG. In these experiments, group-IV afferent units from the skin and viscera of guinea pigs were studied; the main

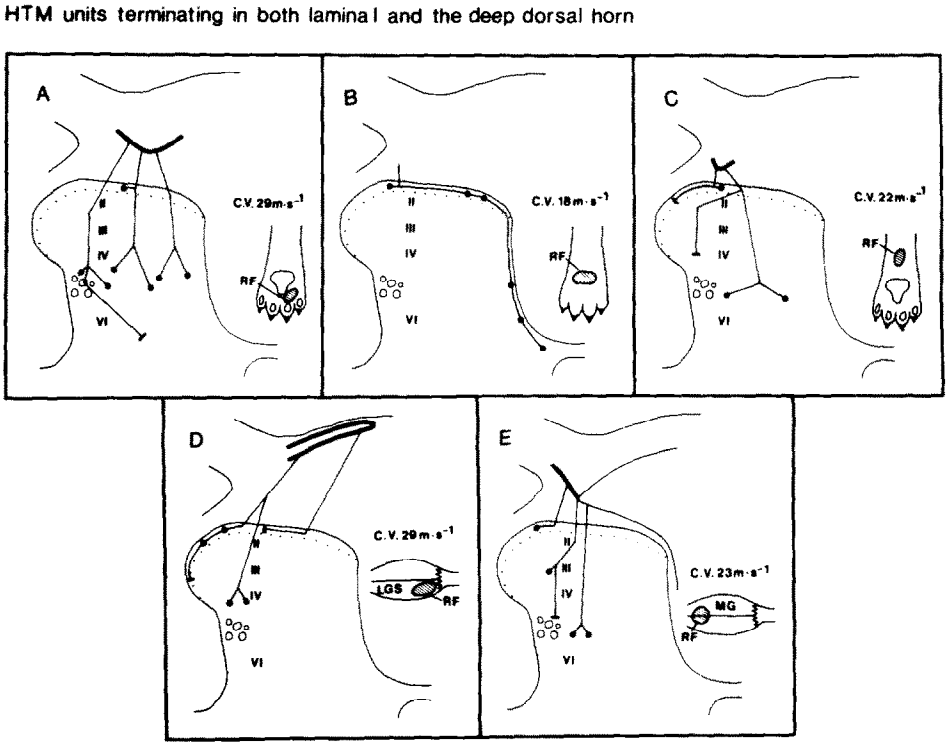

Fig. 2. Schematic trajectories of the spinal terminals of five HTM units with endings in deep tissues of the cat. The units were reconstructed from serial sections and projected onto a standardized cross-section of the lumbar spinal cord. The approximate border between laminae I and II is indicated by the dotted line. The thick bar outside the dorsal horn represents the stem axon; filled circles indicate areas containing synaptic boutons. Collaterals ending without visible boutons are marked by a short bar at their end. In cases where two or more collaterals ran closely together, only one is drawn for reasons of clarity. The approximate size of the RF in the deep tissues is indicated by the hatched area. D and E: the skin overlying the RFs in the triceps surae muscle was opened. LGS, lateral gastrocnemius-soleus muscle; MG, medial head of gastrocnemius muscle; C.V., conduction velocity of afferent fiber (from Hoheisel et al. 1989).

terminations of cutaneous receptors were in laminae I and II if they were nociceptive and in inner and outer lamina II if they had a low mechanical threshold.

Whether lamina II is a major projection area for muscle group-IV afferent fibers is an open question. In many studies using transganglionic transport of dyes, this lamina was free from labeling (cf., Nyberg and Blomqvist 1984; Mense and Craig 1988). On the other hand, terminations of a limited number of muscle group-IV afferents in lamina II have been described by McMahon and Wall (1985) in a neurophysiological study.

It has to be kept in mind that information from muscle nociceptors may reach the spinal cord not only via dorsal but also via ventral roots. Coggeshall and Ito (1977) described afferent fibers running in the ventral root of the cat. These units had a small diameter and some of them terminated in deep nociceptors. The non-myelinated sensory fibers in the ventral root have been shown to arise from DRGs (Coggeshall et al. 1980).

II-A.4. Properties of muscle nociceptors under physiological conditions

A nociceptor has been defined as a receptive ending that is activated by noxious (tissue-threatening, subjectively painful) stimuli and that is capable by its response behavior to distinguish between innocuous and noxious events. As an additional feature the nociceptor may have a high stimulation threshold; this characteristic is useful for the recognition of nociceptors in animal experiments when mechanical or thermal stimuli are applied (Dubner and Bennett 1983; Perl 1984; Besson and Chaouch 1987).

Recordings of the electrical activity of single muscle afferent units in anesthetized cats and rats have shown that, in skeletal muscle, nociceptors as defined above are present. If tested with a variety of different natural stimuli (mechanical and chemical), these receptors do not respond to everyday stimuli such as weak local pressure, contractions and stretches within the physiological range but require noxious intensities of stimulation for being activated (Bessou and Laporte 1960; Paintal 1960; Mense and Meyer 1985). As can be seen in Fig. 3, a liminal activation of a muscle nociceptor may occur if the intensity of stimulation approaches noxious levels without being frankly tissue damaging, e.g., during unphysiological stretch (Fig. 3A) or during maximal contractions (Fig. 3B). Teleologically, this property is presumably highly important, since a nociceptor is supposed not (only) to signal tissue damage but to prevent its occurrence.

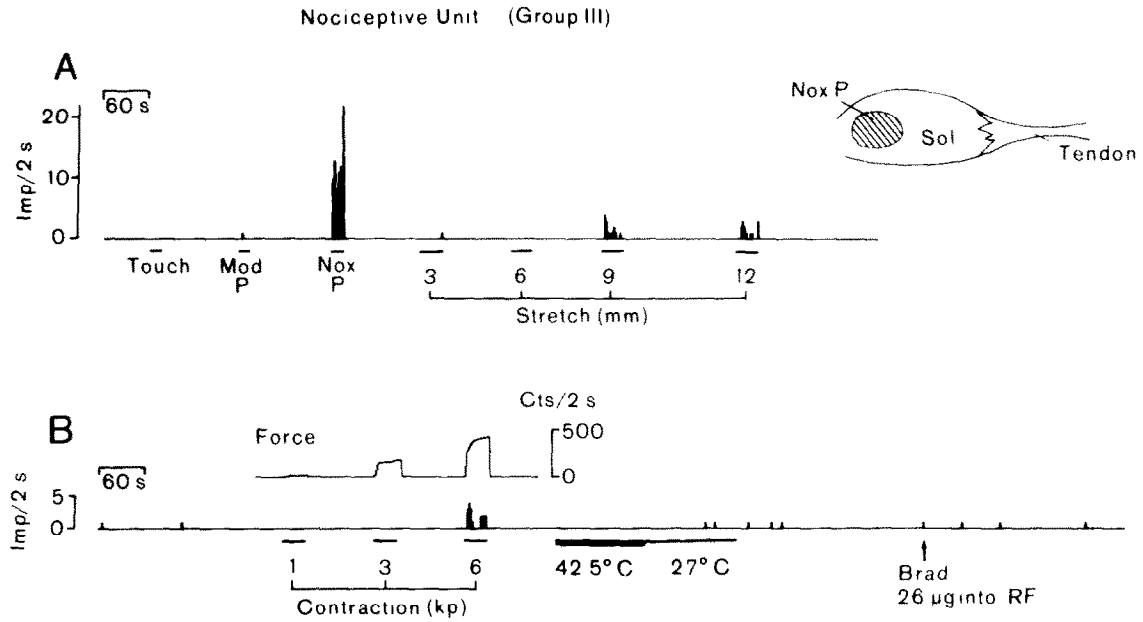

Fig. 3. Response behavior of a nociceptive group-III afferent unit from the soleus muscle in the cat. The discharge activity (impulses/2 sec) is plotted on the ordinate against time on the abscissa. Periods of stimulation are marked by short bars underneath the abscissa. A: Touch, touching the RF with a painter's brush; Mod. P., moderate (innocuous) local pressure; Nox. P., noxious local pressure (the pressure stimuli were applied by hand using a forceps with broadened tips); Stretch, stretching the muscle by pulling at the calcaneal tendon. A stretch of approximately 6 mm was the upper limit that could be produced by bending the paw. B: contraction, rhythmic isometric contractions of the triceps surae muscle induced by electrical stimulation of the GS muscle nerves (every second a train of 500 msec duration at a frequency of 50 Hz was applied). The force of contraction is shown by the strain gauge recording above the histogram (arbitrary units); the force was set to the kP figures by adjusting the stimulus intensity. The figures of warm and cold stimulation indicate temperatures of water circulating through thermodes in contact with the RF. Please note that the receptor behaved like a mechanonociceptor in that it responded to Nox. P. but not to an injection of the algesic agent bradykinin (Brad.) into the RF. Unphysiological stretch (exceeding 6 mm) and maximal contractions (6 kP) elicited liminal activity in this receptor (modified from Mense and Meyer 1988).

II-A.4.a. Conduction velocity and resting activity. In the GS muscle of the cat, the conduction velocity of nociceptive afferent units spans the entire spectrum of groups III and IV units (0.3–30 m/sec) (Paintal 1960; Iggo 1961; Mense and Meyer 1985; Mense 1986). Nociceptors have been found to be more numerous among group-IV than group-III units (43% vs. 33%) (Mense and Meyer 1985). Recent microneurographic data have shown that muscle nociceptors in humans likewise possess afferent fibers conducting in the group III and IV range (0.6–13.5 m/sec) (Simone et al. 1991; Marchettini 1992).

In contrast to the skin where nociceptors usually have no resting activity (defined as discharges in the absence of intentional stimulation) a small proportion of cat muscle nociceptors (approximately 25%) have been found to exhibit such an activity (Berberich et al. 1988). The discharges consist of single or grouped impulses at irregular intervals; the mean frequency is very low and does not exceed a few impulses per minute in intact muscle. The functional significance of the resting discharge is unknown. It will probably not elicit subjective sensations because single impulses in (cutaneous) nociceptive fibers have been reported not to reach consciousness (Torebjörk and Hallin 1974; Torebjörk 1985).

II-A.4.b. Mechanical sensitivity. In the original studies by Paintal (1960) and Bessou and Laporte (1960) on group-III and by Iggo (1961) on group-IV muscle receptors many units were found that could be activated by local pressure stimulation. Some of these had a high mechanical threshold and also responded to noxious chemical stimuli. Paintal denoted these receptors 'pressure-pain receptors' and assumed that one of their functions was to elicit pain sensations from muscle. Most of the group-IV and many of the group-III units lack a sensitivity to small degrees of muscle stretch (Iggo 1961; Franz and Mense 1975; Kumazawa and Mizumura 1977; Kaufman et al. 1982). Stretching a cat gastrocnemius muscle with forces exceeding 4 N resulted in activation of a small proportion of group-IV receptors all of which did not respond to local pressure stimulation (Kniffki et al. 1978). This finding indicates that mechanosensitive group-IV units possess a direction sensitivity.

The most effective stimulus for activating muscle nociceptors in animal experiments is squeezing the muscle with a forceps with broadened tips. The force required for receptor activation is close to that needed to elicit pain from a muscle of similar size in humans; repeated application of a stimulus of this intensity leads to visible tissue damage (Paintal 1960; Iggo 1961; Franz and Mense 1975).

The size of the RF of a muscle nociceptor can only be determined 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 spotlike to several square centimeters in the gastrocnemius muscle of the cat and dog (Kumazawa and Mizumura 1977; Mense and Meyer 1985). In microneurographic recordings from fascicles of the common peroneal nerve in humans the mean RF sizes of muscle receptors with moderate to high mechanical thresholds were found to be 3.2 cm^2 for group-III and 4.7 cm^2 for group-IV units (Simone et al. 1991). The RFs of cutaneous polymodal nociceptors appear to be smaller: cat, < 2 mm^2 (Bessou and Perl 1969); rabbit, 6–32 mm^2 (Kenins 1988).

An unexpected finding was that many afferent units had two RFs, i.e., they could be activated from two separate areas in the muscle. In the deep tissues of the cat tail, afferent units were found that had one RF in deep tissues (muscle, joint, periosteum) and another one in the skin distal to the deep RF (Mense et al. 1981). The anatomical basis of this feature may be branching of the afferent fiber close to its area of termination. Anatomical and neurophysiological studies (Devor et al. 1984; Pierau et al. 1984) have shown that afferent units with long branched axons are relatively rare (a few percent of all afferent fibers), but they may be functionally relevant since they are likely to reduce the spatial resolution of the nociceptive system and thus could contribute to the diffuse nature of deep pain.

A relatively high proportion (approximately one-third) of all group-IV units recorded from dorsal rootlets were found not to respond to mechanical probing of the muscle (Franz and Mense 1975). Many of these (44%) could be excited by close intra-arterial injection of the endogenous algesic agent bradykinin (BKN) and therefore may be nociceptors. Under the conditions of an in vivo experiment it is difficult to tell whether an afferent unit really lacks a mechanosensitivity or whether the mechanosensitive RF has not been found because of its small size and/or unfavorable location. The recently detected 'silent' or 'sleeping' nociceptors offer a new interpretation of this set of data (see below).

II-A.4.c. Chemical excitability. Particularly effective stimulants for free nerve endings in skeletal muscle of laboratory animals are endogenous pain-producing substances such as BKN, 5-hydroxytryptamine (5-HT), and potassium ions in concentrations of 60 mM or higher (Fock and Mense 1976; Kumazawa and Mizumura 1977; Kaufman et al. 1982). Hypertonic NaCl solutions (4.5–6.0%) are likewise effective excitants of group-III and -IV muscle receptors but, similar to potassium, its stimulating effects are considered to be unspecific (i.e., not mediated by pharmacological re-

ceptors), since all muscle receptors including primary endings of muscle spindles are excited by this stimulus (Iggo 1961).

On a molar basis, the nonapeptide BKN has been found to be the most effective stimulant for muscle nociceptors (Fock and Mense 1976). It is cleaved from its precursor molecule kallidin (which is present in plasma proteins), if pathological deviations from the normal environmental conditions occur (e.g., lowering in pH, ischemia, blood clotting). 5-HT is released from platelets following vascular damage, and large amounts of potassium are present in the sarcoplasm of each muscle cell from which it leaks into the interstitial fluid if the cell membrane is injured. BKN and 5-HT also have strong actions on blood vessels and appear to influence the vasculature at lower concentrations than nerve endings; these substances belong to the so-called 'vasoneuroactive substances' (Sicuteri 1967).

It has to be pointed out that the above substances, particularly BKN, excite not only nociceptors but also non-nociceptive endings in muscle (Mense 1977). There may be a quantitative difference, however, as nociceptors in the skin have been shown to be activated at lower concentrations of BKN than are other receptor types (Szolcsányi 1987). Some of the mechanisms by which BKN activates neurons have been elucidated. By acting on molecular BKN receptors (B_1 and B_2) (Barabé et al. 1984) it increases neuronal excitability by inhibiting after-hyperpolarization (Weinreich and Wonderlin 1987), influences neuronal activity by activating phospholipase C and increasing chloride conductance (Wood et al. 1990) and has a general activating effect on second messengers (Burgess et al. 1989). These mechanisms are probably also involved in sensitization processes (see Section II-B).

The typical muscle nociceptor responds to both noxious local pressure and injections of BKN (close arterial or intramuscular), but there are also receptors that can be activated by only one type of noxious stimulation (mechanical or chemical). This finding may indicate that different types of nociceptors are present in skeletal muscle, similar to the skin where mechano-, mechano-heat, and polymodal nociceptors have been found (Perl 1984; Willis 1985; Besson and Chaouch 1987).

The doses of pain-producing substances required to excite muscle nociceptors in animal experiments are similar to those eliciting muscle pain in humans (Lindahl 1961; Coffman 1966). The same applies to the time course of receptor activation (latency and duration) which, in the case of BKN injections, closely resembles that of painful sensations elicited by BKN in humans. These findings increase the probability that chemically induced muscle pain is really due to activation of that subset of free nerve endings that are classified as nociceptors in animal experiments.

BKN activates almost exclusively the slowly conducting afferent units (groups III and IV) and not the encapsulated stretch receptors (Mense 1977), but an excitability by BKN cannot be taken as an indication of the nociceptive nature of a receptor. It is well known that slowly adapting mechanoreceptors of the skin also respond to BKN (Fjällbrant and Iggo 1961; Beck and Handwerker 1974). Identification of a receptive ending ideally includes administration of all possible stimuli that may act on the ending under physiological circumstances. If only mechanical stimuli are used, the majority of the units classified as HTM will be nociceptive, but some receptors will be included which actually are thermosensitive (see below).

II-A.4.d. Thermal sensitivity. All the studies conducted so far on muscle group-IV receptors agree that some of these units (19%, in the study of Mense and Meyer 1985) respond to small temperature changes in the innocuous range (20–40°C) (Iggo 1961; Kumazawa and Mizumura 1977). Many thermosensitive endings exhibit a discharge behavior similar to that of cutaneous thermoreceptors and may fulfill thermoreceptive functions. They differ from nociceptors in that most of them do not respond to BKN (Hertel et al. 1976; Mense 1986). Upon mechanical stimulation they have a very high threshold and do not encode the stimulus intensity very well in their discharges. The response to noxious local pressure is probably not an indication of HTM properties but reflects an activation of thermoreceptors by a tissue-threatening mechanical (i.e., inadequate) stimulus. Such responses are known to occur in warm and cold receptors if the intensity of the mechanical stimulus exceeds physiological limits. Taken together, these properties speak against a nociceptive, and for a thermoreceptive, function of these afferent units from muscle. Possibly, they form an input channel for thermoregulation (cf., Jessen et al. 1983).

Other group-IV muscle receptors have been reported to have a thermal threshold in the noxious range (> 43°C or < 20°C) (Iggo 1961; Kumazawa and Mizumura 1977). Most of these units also respond to endogenous algesic agents and noxious local pressure (Mense, unpublished) and thus behave like polymodal nociceptors in the skin.

It has to be kept in mind that many cutaneous mechanoreceptors exhibit a certain dependence of their discharges on temperature; these receptors may behave like 'spurious thermoreceptors' (Iggo 1969). Therefore, a susceptibility of a receptive ending to temperature changes does not necessarily reflect a thermoreceptive or thermonociceptive function.

II-A.4.e. Effects of hypoxia and adrenaline in vitro. Many painful conditions are associated with ischemia and/or altered function of the sympathetic nervous system. In experiments in vivo, the effects of catecholamines and of ischemia (hypoxia) are difficult to be

studied separately, since administration of catecholamines also influences the blood supply to the receptors. The in vitro preparation offers the opportunity to apply catecholamines without interfering with the oxygen supply.

Data obtained from a rat hemidiaphragm-phrenic nerve preparation have shown that in the diaphragm LTM and HTM receptors can also be distinguished. The latter require high intensities of mechanical stimulation which are unlikely to occur under physiological conditions and probably fulfill nociceptive functions (Kieschke et al. 1988).

In this preparation, hypoxia of approximately 20 mmHg in the organ bath had an excitatory action on both LTM and HTM units. In some receptors, the mechanical threshold determined with von Frey hairs was lowered during hypoxia. These data indicate that hypoxia may be an important factor in the control of the excitability of nociceptors in deep tissues.

Adrenaline concentrations of 0.5–5 μM in the organ bath had a differential effect on LTM and HTM receptors. About one-half of the latter responded with an increase in discharge frequency, whereas the sensitive mechanoreceptors showed little activation. A finding of probable clinical significance was that nociceptors which initially were not responsive to adrenaline often developed a sensitivity to the catecholamine when their RFs were irritated by a constant mechanical stimulus of noxious intensity (Kieschke et al. 1988). This finding suggests that damaged nociceptors, e.g., in pathologically altered tissue, are more sensitive to adrenaline than receptors in intact tissue.

II-A.4.f. Recordings of muscle nociceptors in man. The technique of recording the activity of single fibers in human nerves with percutaneously introduced needle electrodes has been extensively used in studies of cutaneous nociceptors (for a review, see Torebjörk et al. 1984a), but data on muscle nociceptors are largely missing. Only recently was it possible to record from single group-III and -IV muscle afferent units in man (Simone et al. 1991; Marchettini 1992). The preliminary results show that the response behavior of human muscle nociceptors is indistinguishable from that of nociceptors in the cat and rat. The receptors respond to strong local pressure and algesic substances with a discharge frequency and time course similar to that observed in animal experiments.

A particularly useful feature of the microneurographic set up is that the recording electrode can also be used for stimulating the afferent fiber under study (Torebjörk et al. 1984b). Repetitive electrical stimulation of muscle afferent units classified as nociceptive led to the cramp-like sensations that are characteristic of muscle pain (Simone et al. 1991). These data support the assumption that the muscle receptors characterized as nociceptive in animal experiments are the ones that mediate muscle pain in humans.

II-A.5. Receptor polymodality versus receptor specificity

Interpretation of the data presented above is based on the concept of specificity of sensory afferent units. This means that the endings are specialized for the reception of a particular adequate stimulus and that the activation of such an ending always elicits the same subjective sensation. Thus, nociceptors elicit pain irrespective of the stimulus that activates them. Because of the broad responsiveness of some muscle afferent units when tested with mechanical and chemical stimuli, some authors consider these units to be polymodal receptors fulfilling nociceptive as well as ergoreceptive functions (Kumazawa and Mizumura 1977). Ergoreceptors are muscle receptors with slowly conducting fibers which are activated during muscular contractions (Kaufman et al. 1983, 1984a; Mense and Stahnke 1983) and are assumed to be involved in the circulatory and respiratory adjustments during physical activity (Kao 1963).

In the present paper the specificity concept has been favored for the following reasons. (1) In each species and type of preparation used, LTM and HTM could be clearly distinguished. The difference in response behavior between these receptors was so great that the alternative interpretation, namely that they form two subgroups of one receptor population, appears unlikely. Group-III and -IV receptors classified as LTM in animal experiments respond to weak mechanical stimuli with a discharge frequency that reaches a considerable percentage of their maximal discharge. Therefore, these responses cannot be considered as liminal activations of nociceptors by weak stimuli. (2) The broad sensitivity of many units to mechanical and chemical stimuli does not mean that every receptor responds to every stimulant. In contrast, most receptors have a preferential sensitivity to a certain stimulus or a combination of stimuli. When ischemic contractions are used as a stimulus, only a small proportion of receptors are activated, although all endings in the contracting muscle are under the influence of the same biochemical changes. (3) The experiments employing intra-axonal injections of HRP into single group-III units showed that the spinal terminations of units classified as nociceptive differed from those of LTM receptors (Hoheisel et al. 1989). These morphological data support the view that slowly conducting afferent units from deep somatic tissues do not form a functionally homogeneous population of receptors. The critical experiment for testing the validity of this interpretation is to stimulate single LTM and HTM units in a human muscle nerve and record the subjective sensations of an awake subject (cf., Macefield et al. 1990).

The actual degree of specificity of muscle nociceptors is difficult to assess. It is unknown, for instance,

whether the various subjective forms of muscle pain (e.g., aching and cramping) are mediated by different types of muscle nociceptors. It also has to be kept in mind that the relationship between receptor type and subjective sensation is lost when the central processing of the afferent information is disturbed. An example is neuropathic pain which can be elicited by activation of non-nociceptive myelinated fibers.

A serious problem for the interpretation of the data obtained in animal experiments is the possible sensitization of nociceptors by the unsterile surgical exposure of deep tissues or by repetitive testing of the receptors with noxious stimulus intensities (see below). As sensitized nociceptors often lower their mechanical threshold into the innocuous range, they could be mistaken as LTM receptors. In fact, for a particular LTM unit under study, sensitization cannot be ruled out (unless it has an intermittent discharge of high frequency which is usually an indication of sensitization). It is unlikely, however, that all or a large proportion of the LTM muscle receptors described in the literature are sensitized nociceptors, since LTM group-III receptors have also been found in intact muscles that were not surgically exposed (Hoheisel and Mense 1990).

II-A.6. Section summary

Small-diameter (0.5–6 μm), slowly conducting (0.5–30 m/sec) afferent fibers from muscle have to be activated in order to elicit pain. Histologically, these fibers are either thin myelinated (A-δ or group-III fibers) or non-myelinated (C or group-IV fibers). Of the latter, more than 40% terminate in free nerve endings with nociceptive properties. A nociceptor is a receptive ending that is activated by noxious (tissue-threatening, subjectively painful) stimuli and is capable by its response behavior to distinguish between innocuous and noxious events. DRG cells projecting in a muscle nerve exhibit immunoreactivity to the neuropeptides SP, CGRP and SOM. CGRP-like immunoreactivity appears to be present in many nociceptive and non-nociceptive muscle receptors. Muscle afferent fibers, including nociceptive ones, terminate in lamina I and in and around lamina V of the dorsal horn. Particularly effective stimuli for free nerve endings in skeletal muscle are strong mechanical forces and endogenous pain-producing substances such as BKN, 5-HT, and potassium ions. Hypoxia and increased levels of adrenaline likewise activate nociceptors in deep tissues. In awake subjects, cramp-like

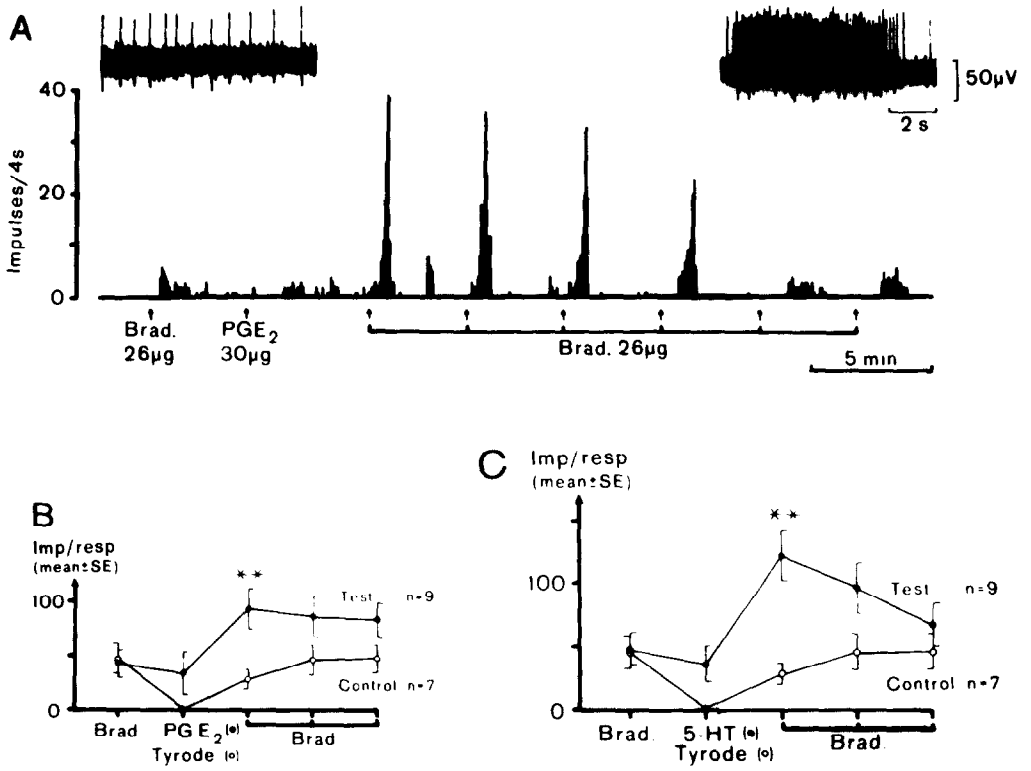

Fig. 4. Sensitization of cat group-IV muscle receptors to bradykinin (Brad.) by PGE_2 and 5-HT. Injections of Brad., PGE_2, and 5-HT were given into the muscle artery. A: unit conducting at 2.09 m/sec. Insets show peak fiber activity during the Brad. response before (left) and 5 min after (right) injection of PGE_2. Bin width of histogram: 4 sec. B: statistical evaluation of experiments in which a sequence of intra-arterial injections of Brad., PGE_2, and 3 times Brad. at intervals of 3 min was given (●). In the control series, the vehicle Tyrode solution was injected instead of PGE_2 (○). ** $P < 0.01$ (U test). C: same evaluation as in (B) for 5-HT (modified from Mense 1981).

sensations that are characteristic of muscle pain can be elicited by electrical stimulation of nociceptive afferent units from muscle. These and other data support the assumption that specific nociceptors are present in skeletal muscle.

II-B. Modulatory influences at the receptor site

II-B.1. Endogenous substances

II-B.1.a. Bradykinin. Experiments employing chemical stimulation have shown that the sensitivity of muscle nociceptors is not constant but can be easily increased by endogenous vasoneuroactive and other substances. This process of receptor sensitization accompanies all types of tissue lesions (e.g., trauma, inflammation) and is the main peripheral mechanism underlying the clinical symptoms of tenderness and hyperalgesia.

Besides an excitatory action, BKN has also a sensitizing effect on muscle nociceptors. A nociceptor sensitized by BKN has a lowered mechanical threshold and, therefore, can be activated by innocuous stimuli. BKN-induced sensitization differs from that observed in inflamed tissue in that most receptors do not exhibit an increase in resting activity following BKN administration. A possible explanation for this difference is that during inflammation many sensitizing substances are released together in a particular combination which induces resting activity. The BKN dose required for sensitizing muscle nociceptors was found to be lower than that required for activating the units, i.e., excitation of nociceptors is not a prerequisite for their sensitization (Mense and Meyer 1988).

The BKN-induced sensitization appears to be a quite specific process because (1) slowly conducting muscle afferent units with LTM properties (presumably nonnociceptive receptors) were not sensitized, and (2) sensitization affected not all aspects of the nociceptor function. Some units were sensitized to stretch and contractions but not to local pressure stimuli, whereas other receptors exhibited increased sensitivity predominantly to local pressure (Mense and Meyer 1988). A differential sensitization has also been observed in cutaneous nociceptors, which can be sensitized by carrageenan to heat but not to mechanical stimuli (Handwerker and Reeh 1991). These findings underline the fact that sensitization of a (cutaneous) nociceptor is not necessarily associated with enhanced mechanical excitability (Kocher et al. 1987). Similar results have been obtained from articular group IV receptors sensitized by prostaglandin E_2 (PGE_2) (Schaible and Schmidt 1988). Such a differential sensitization of nociceptors appears to be a general phenomenon.

II-B.1.b. Combined actions of substances. Prostaglandins (PGs) of the E type and 5-HT have been shown to sensitize slowly conducting muscle afferent units to

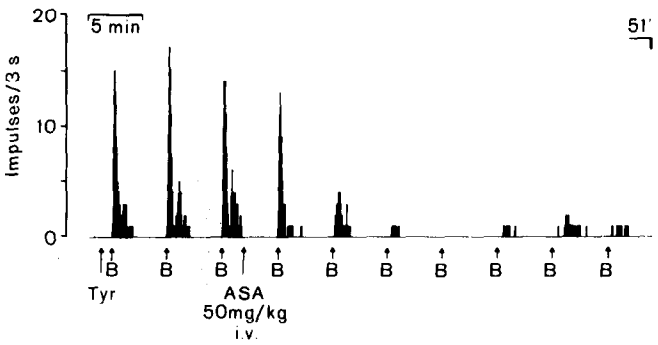

Fig. 5. Reduction of the bradykinin-induced activations of a muscle group-IV receptor by ASA. The receptor did not respond to mechanical stimuli; C.V., 2.05 m/sec. Arrows mark injections of the following solutions: Tyrode (Tyr) i.a. as a control, bradykinin (B) 130 μg i.a., and ASA i.v. Bin width of histogram: 3 sec (from Mense 1982).

BKN, i.e., following administration of PGE_2 and 5-HT, respectively, BKN has a stronger excitatory action on the receptors (Fig. 4) (Mense 1981). BKN on the other hand is known to release PGE_2 from tissue cells (Jose et al. 1981) and also from sympathetic efferent fibers (Levine et al. 1986). By this mechanism, BKN is capable of potentiating its own action. Other examples of such a cascade-like liberation of endogenous substances is the release of PGE_2 from synoviocytes by SP (Lotz et al. 1987) and the release of PGs from sympathetic fibers by noradrenaline (Levine et al. 1986). There is evidence indicating that PG-induced sensitization of nociceptors is mediated by the cAMP second-messenger system (Taiwo et al. 1990). Presumably, such interactions between endogenous substances are quite common, since the agents are released together from pathologically altered tissue.

The findings that BKN releases PGs from tissue cells and that PGs potentiate the stimulating action of the kinin on muscle afferent units led to the assumption that acetylsalicylic acid (ASA), by its blocking effect on the PG synthesis, should be capable of reducing or abolishing the excitatory action of BKN. In fact, BKN-induced activations of slowly conducting muscle afferent units were found to be strongly reduced by ASA (Fig. 5). The complete lack of a BKN effect 15 min after injection of ASA in Fig. 5 indicates that BKN itself (without the sensitizing effect of PGs) had only a subthreshold action on the unit. These results demonstrate that in the BKN-induced excitation of muscle group-IV receptors there is a PG component which can be abolished by ASA. Moreover, these data prove the peripheral site of action of ASA, since they were obtained from primary afferent fibers whose connections with the CNS had been cut.

II-B.1.c. Leukotrienes. Leukotrienes (LTs) are likewise released from tissue cells under pathological conditions, and some (e.g., LTB_4) have been shown to promote inflammatory processes and induce hyperalge-

sia in behavioral experiments (Samuelsson 1983; Piper 1984; Samuelsson et al. 1987). LTD_4 appears to be the only LT whose influence on single muscle receptors has been tested so far (Mense and Hoheisel 1990). This type of LT did not have a sensitizing but rather a desensitizing effect on rat muscle nociceptors. The desensitization after infiltration of the RFs with 100 ng/μg LTD_4 expressed itself in a reduction of the response magnitude to mechanical stimulation. Whether this effect is associated with subjective hypoalgesia is unknown. The increased synthesis of LTs by lipoxygenase following a drug-induced block of cyclo-oxygenase has been discussed as a mechanism that may contribute to the analgesic action of cyclo-oxygenase blockers (Schweizer et al. 1984).

II-B.1.d. Other chemical influences. The following factors have been shown to possess a modulatory action on cutaneous nociceptors, but they have not yet been tested systematically on muscle receptors.

Protons are very effective stimulants and modulators of mechano-heat nociceptors with non-myelinated afferent fibers. A lowering of the pH to 6.1 has been shown to excite approximately 40% of the receptors without signs of adaptation and tachyphylaxis. (Handwerker and Reeh 1991; Steen et al. 1992). In contrast to BKN and inflammatory lesions (Kocher et al. 1987), a low pH also sensitizes cutaneous nociceptors to mechanical stimuli.

As to the peripheral function of the neuropeptides that are present in muscle afferent units, CGRP and SP have been studied in more detail. CGRP-like IR can be found in fibers associated with the vasculature of striated muscle and in motor end plates where it binds to specific pharmacological receptors and increases the synthesis of a ACh-receptor subunit (Popper and Micevych 1989). In receptive nerve endings and primary afferent neurons in general, trophic functions of the neuropeptide (maintenance of tissue integrity and renewal following lesions) may dominate over nociceptive ones (Kruger et al. 1989). Under pathological conditions (experimental arthritis in rats) the CGRP content of DRGs has been found to be increased (Kuraishi et al. 1989).

SP may exert its main functions not in the dorsal horn but in the periphery, as the bulk of the neuropeptide is transported from the DRG into the peripheral branches of the neuron (Brimijoin et al. 1980). Injected locally into the hind paw of rats, SP induces hyperalgesia which has been ascribed to a sensitization of nociceptors to inflammatory mediators (Nakamura-Craig and Smith 1989).

Preliminary results obtained from a rat hemidiaphragm-phrenic nerve preparation in vitro (Reinert et al. 1992) have shown that diaphragmatic HTM units increase their resting discharge in the presence of SP (10–100 μM). The responses of the receptors to local

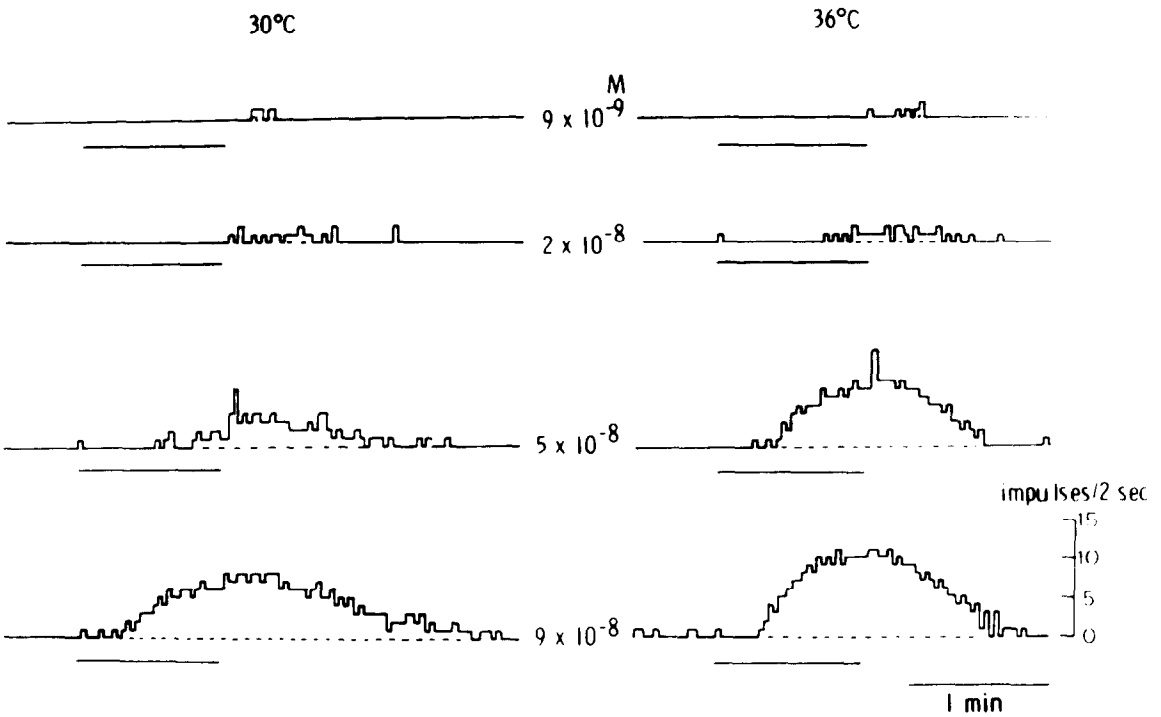

Fig. 6. Thermal effects on the BKN-induced responses of a polymodal visceral receptor of the dog in vitro. The left column of data shows responses at 30°C, the right column at 36°C. BKN concentrations are given in the middle. The periods of BKN administration are marked by the bars underneath the abscissa. Note that at the higher temperature the latency to onset of the response was shorter and the maximal discharge rate higher (from Kumazawa et al. 1987).

pressure stimulation were not significantly altered by SP, however. The data suggest that SP may have a modulatory function in muscle pain, but does not sensitize muscle nociceptors to mechanical stimuli. The neuropeptide may be of clinical importance in situations where its concentration in nervous tissue is increased, e.g., during chronic inflammation (Lembeck et al. 1981).

In recent years, data have accumulated indicating that opioids, in addition to triggering antinociceptive mechanisms at the spinal and supraspinal level, have an analgesic action at the peripheral receptor site. The responses of dorsal horn cells to a peripheral inflammatory stimulus have been shown to be reduced by local injection of a kappa-agonist into the inflamed tissue (Haley et al. 1990). Likewise, the μ-receptor agonist fentanyl has been reported to increase the pressure pain threshold in inflamed paws by a peripheral action (Stein et al. 1988). A possible mechanism for the peripheral effects of opioids is that they bind to opioid receptors on axons of small-diameter nerve fibers (Young et al. 1980) and influence the release of SP from nerve endings (Yaksh 1988). These events are thought to lead to an inhibition of the cAMP second-messenger system in nociceptive endings, which is followed by a decreased neuronal excitability (Levine and Taiwo 1989). At present, the significance of the peripheral action of opioids for muscle pain is still obscure.

II-B.2. Temperature

The effects of temperature on the chemically induced discharges of nociceptive afferent units have been studied in a spermatic nerve preparation in vitro (Kumazawa et al. 1987). Subthreshold increases in temperature enhanced the responses of the receptors to algesic stimulants such as BKN (Fig. 6). This mechanism may contribute to the hyperalgesia of inflamed tissue and could explain the beneficial effects of cooling on inflammatory pain.

II-B.3. Section summary

The sensitivity of muscle nociceptors is not constant but can be increased by a variety of endogenous substances (e.g., BKN, PGE_2, 5-HT) which are released from pathologically altered tissue. The PG-induced sensitization of nociceptors is probably mediated by the cAMP second-messenger system. The depressing action of ASA on muscle nociceptor activity can be explained by assuming that the drug abolishes the PG-induced receptor sensitization by blocking cyclooxygenase. In contrast, LTD_4 appears to have a desensitizing effect on muscle nociceptors. Other factors with a probable sensitizing action on nociceptors are increase in temperature and lowering of pH. Nociceptor sensitization accompanies all types of tissue lesions (e.g., trauma, inflammation) and is the main peripheral mechanism underlying the clinical symptoms of tenderness and hyperalgesia.

II-C. Behavior of muscle nociceptors under pathophysiological conditions

II-C.1. Ischemic contractions

Interruption of the blood supply to a resting extremity for prolonged periods of time (20 min) is not painful (Lewis et al. 1931) and does not evoke cardiovascular reflexes (Staunton et al. 1964). However, if the muscle is forced to contract under ischemic conditions, pain develops within about 1 min (Lewis et al. 1931). The mechanisms underlying this type of ischemic pain are still a matter of controversy. Accumulation of acidic metabolites including lactate (Moore et al. 1934), potassium ions (Harpuder and Stein 1943) or the lack of oxidation of metabolic products (Pickering and Wayne 1933–1934) have been proposed as causal factors.

A substance probably involved in nociception from an ischemic muscle is BKN. The kinin is released from plasma proteins during ischemia (Sicuteri et al. 1964; Nakahara 1971; Gomazkow 1975) and, because of its strong action on nociceptors, is likely to contribute to the pain of intermittent claudication. In contrast to lactate, phosphate, and potassium ions, BKN is an effective stimulant for muscle group-III and -IV afferent units (Kniffki et al. 1978).

Ischemia alone is not an effective stimulus for slowly conducting muscle afferent units unless it lasts for long periods of time. Ligation of an artery to a resting muscle for 5 min in an anesthetized cat does not activate muscle group-III and -IV units (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 developed a bursting background activity 15–60 min after the onset of ischemia. The increase in activity lasted for periods of several minutes up to half an hour, before the units fell silent and could no longer be activated by electrical stimulation of the muscle nerve (Mense 1991). The latter finding indicates that the ischemia affected not only the receptive ending but also the afferent fiber. Possibly, the lack of energy associated with the ischemia caused a depolarization of the axonal membrane which, after transient activation, led to a block of the action potential generating system.

Bessou and Laporte (1958) were the first to show that during ischemic contractions muscle group-IV afferent units are activated. They used the technique of antidromic collision to record the activity of group-IV fibers from intact GS muscle nerves in cats and found that a large proportion of these units became active during tetanic contractions under ischemia. Single-fiber

recordings from group-III and -IV muscle receptors yielded a relatively small population of units (approximately 10%) which reacted in a way that suggested an involvement in the mediation of ischemic pain (Mense and Stahnke 1983). Most of the receptors tested did not react at all, although the ischemic stimulus was extremely strong (the contractions were continued until the muscle was no longer capable of maintaining its contractile force).

The receptors responding to ischemic contractions were not or only weakly activated during contractions without arterial occlusion but showed strong excitations when the same amount of muscle work was repeated under ischemic conditions (Fig. 7). The time course of the activation was similar to that of the pain induced in human volunteers performing ischemic contractions (Lewis et al. 1931): there was a delay of almost 1 min after onset of the contractions before the receptor activity rose, and the discharge frequency remained at an elevated level after the contractions had been discontinued but ischemia maintained. All the receptors exhibiting strong reactions to ischemic contractions were group-IV units; group-III receptors were not or only liminally affected (Paintal 1960; Kaufman et al. 1984b).

The mechanisms of receptor activation during ischemic contractions are unknown. The analysis of the time course of temperature and force during the contractions showed that thermal and mechanical changes can be largely excluded as stimulating factors. A speculative interpretation is that the ischemia-induced decrease in pO_2 or pH releases BKN, PGE_2 and potassium ions (Harpuder and Stein 1943; Uchida and Ueda 1969; Jennische et al. 1982) which sensitize muscle nociceptors so that they respond to the force of contraction. When the contractions are discontinued under maintained ischemia, a basal level of receptor activation and pain persists because of the high intramuscular concentration of chemical stimulants. Recent data indicate that CGRP may also be involved in nociception during ischemia; the peptide has been shown to be released from ischemic heart muscle with BKN enhancing the release (Franco-Cereceda et al. 1989). In view of the fact that during exhausting work

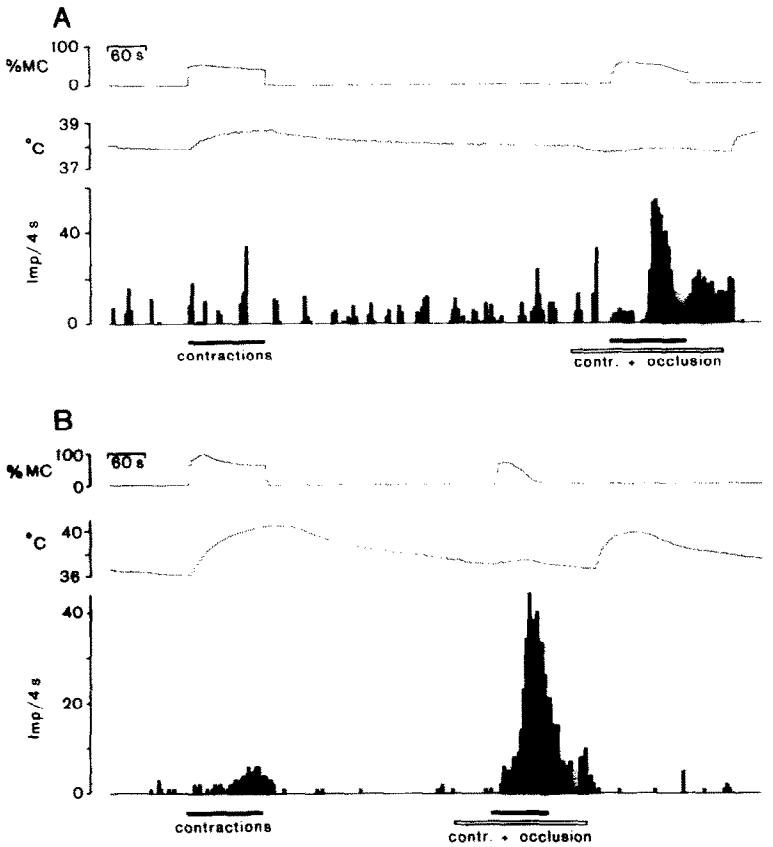

Fig. 7. Activation of group-IV muscle receptors by ischemic contractions. The upper trace in (A) and (B) shows the force developed by the muscle in percent of maximal contraction (MC), the middle trace the intramuscular temperature measured with a needle thermistor, and the lower trace the histogram of the fiber activity (bin width 4 sec). A: unit not responding to contractions (Contr.) of 50% MC without ischemia, but showing clear excitation during contractions after occlusion of the muscle artery (occlusion). C.V. of afferent fiber: 1.10 m/sec. B: receptor with a delayed, small response to contractions without ischemia, and a strong excitation by ischemic contractions. C.V. of afferent fiber: 0.70 m/sec. In this case, the force of contraction was set to 100% M.c. Neither unit could be activated by muscle stretch (from Mense and Stahnke 1983).

the pH inside the muscle may drop to 6.0–6.6 (Caldwell 1956; Sahlin et al. 1976) and that a low pH is a powerful sensitizing factor for cutaneous nociceptors (Steen et al. 1992) an ischemia-induced increase in proton concentration may contribute to ischemic pain.

II-C.2. Inflammation

Data on the behavior of group-III and -IV receptors in inflamed muscle are available from the cat and rat. In these animals, an experimental myositis can be induced by infiltrating the triceps surae muscle with carrageenan, a sulfated polysaccharide. The carrageenan-induced myositis is thought to be a neurogenic inflammation mediated by the release of SP and other agents from nociceptive afferent units. In the knee joint of the rat, SP has been shown to have strong inflammatory actions (Lam and Ferrell 1990). In the case of myositis the role of SP is questionable because of the reported low concentration of this peptide in skeletal muscle (see above). A few hours after carrageenan injection the muscle exhibits all the signs of myositis (hyperemia, edema, infiltration by polymorphonuclear leucocytes) (Berberich et al. 1988). These changes are known to be associated with the release of vasoneuroactive substances which appear in an inflamed rat paw in a temporal order, namely 5-HT and histamine first (up to 1.5 h after the carrageenan injection), then BKN, and finally PGs (> 2.5 h after carrageenan) (DiRosa et al. 1971).

In cat and rat the inflammation-induced changes in the response behavior of slowly conducting muscle afferent units are qualitatively the same although quantitative differences exist. As the main effect of an inflammation, an increase in the resting activity of the receptors has been described. Both the proportion of units exhibiting resting discharge and the mean discharge frequency were higher in inflamed muscle (Berberich et al. 1988; Diehl et al. 1988).

The resting discharge was irregular, often of intermittent nature, with phases of bursting activity alternating with long periods of silence. Such discharges are likely to cause (spontaneous) pain if they occur in nociceptive afferent units. An increased resting discharge was not only present in HTM (presumably nociceptive) units but also in receptors responding to innocuous pressure. In inflamed tissue, the latter ones probably comprise true LTM receptors and sensitized (originally high-threshold) units.

Another inflammation-induced change in the response behavior of muscle receptors was an increase in the proportion of receptors responding to weak mechanical stimuli. In normal muscle of the cat, approximately 80% of the group-IV units required noxious pressure for being activated; this proportion dropped significantly in inflamed muscle. A possible reason for this change is a sensitization of nociceptive (originally HTM) units which have a lowered mechanical threshold in inflamed muscle and respond to weak stimuli such as innocuous local pressure. This mechanism offers an explanation for the tenderness of inflamed muscle and the pain during movement. Apparently, tenderness is mainly due to a sensitization of group-IV receptors as the mechanical threshold of group-III units did not change significantly. In contrast, spontaneous pain and dysesthesias are probably caused by activity in group-III units, as these were the only ones that showed a significant increase in background activity in inflamed muscle (Berberich et al. 1988).

The inflammation-induced sensitization of muscle receptors is probably caused by a release of vasoneuroactive substances and neuropeptides from the inflamed tissue. It appears that in the course of neurogenic inflammation SP can be released from nerve endings independent of their electrical activity (Holzer 1988). The neuropeptide induces the release of histamine from tissue mast cells whose direct vasodilating action in inflamed tissue is still a matter of debate (Barnes et al. 1986; Holzer 1988; Coderre et al. 1989).

Other substances probably involved in the induction and/or maintenance of inflammatory processes are CGRP and neurokinin A (Wallengren and Hakanson 1987). The results of a recent study suggest that the local release of nitric oxide may be involved in the vasodilation of a carrageenan-induced inflammation (Ialenti et al. 1992). The action of these latter substances on nerve endings remains to be established.

II-C.3. Section summary

The mechanisms underlying the pain of ischemic contractions are still a matter of controversy. Accumulation of lactate and potassium ions or the lack of oxidation of metabolic products have been proposed as causal factors. Single-fiber recordings from group-IV muscle receptors in cats yielded a small population of units which were not or only weakly activated during contractions without arterial occlusion but showed strong excitations when the same amount of muscle work was repeated under ischemic conditions. Possibly, the ischemia-induced decrease in pO_2 or pH releases BKN and PGE_2 which sensitize muscle nociceptors so that they respond to the force of contraction. In inflamed muscle, group-III and -IV receptors had a higher level of resting discharge and the proportion of units responding to weak mechanical stimuli was higher. A possible reason for the latter change is a sensitization of nociceptive units by inflammatory substances (e.g., BKN and PGE_2; possibly also CGRP and neurokinin A). This mechanism offers an explanation for the tenderness of inflamed muscle and the pain during movements.

II-D.4. Silent nociceptors

In tissues other than muscle (joint, skin, viscera) so-called silent or sleeping nociceptors have been described (Grigg et al. 1986; Häbler et al. 1988; Meyer and Campbell 1988; Handwerker et al. 1991). In normal, intact tissue, these receptors cannot be activated by mechanical stimuli, but in inflamed tissue the endings respond readily to local pressure stimulation or joint movement. The afferent input from these receptors may have an enhancing effect on pain sensations, since the recruitment of formerly silent receptors is likely to lead to spatial summation in dorsal horn neurons. In skeletal muscle such receptors have not yet been found.

II-E. Non-nociceptive muscle receptors with slowly conducting afferent fibers

Under experimental conditions many group-III and -IV muscle afferent units can be activated by innocuous deformations of the muscle, by forceful stretch and muscle contractions. It appears that a relatively high proportion of the slowly conducting muscle afferent units, particularly those conducting in the group-III range, are LTM receptors. Their thresholds are above those of muscle spindles and tendon organs but still clearly within the physiological range. In contrast to LTM receptors in the skin which show saturation in their discharges upon high-intensity stimulation, LTM receptors in muscle continue to increase their discharge frequency when the stimulus reaches noxious intensities (Mense and Meyer 1985).

One subtype of the non-nociceptive group-III and -IV muscle receptors is strongly activated during muscle contractions (Fig. 8) (Kaufman et al. 1983, 1984a) and shows an almost linear relationship between muscle force and discharge rate (Mense and Stahnke 1983). As stated above, these units may function as ergoreceptors; recently, evidence has been presented that they release neurokinins from their spinal terminals during muscle contractions (Duggan et al. 1991).

Whether the non-nociceptive group-III and -IV muscle receptors elicit subjective sensations is unknown. Judging from their response behavior, the LTM units could mediate pressure and force sensations from skeletal muscle and also from the tendon, where these endings are likewise present (Mense and Meyer 1981). Intrafascicular microstimulation of single joint afferents has been reported to elicit innocuous deep sensations in subjects (Macefield et al. 1990).

There is some evidence in the literature indicating that muscle receptors with slowly conducting fibers may form the afferent limb for acupuncture effects. The analgesia produced by needling of the point Ho-ku on the hand has been shown to be abolished after

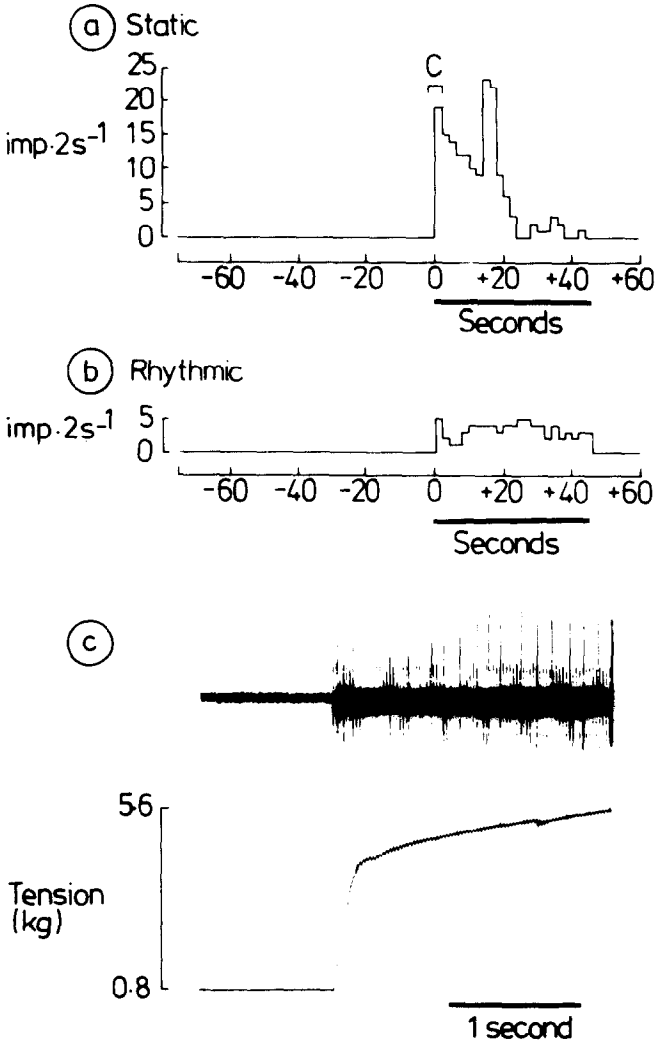

Fig. 8. Stimulation of a group-III afferent unit from the triceps surae of the cat by static (a) and rhythmic twitch contractions (b). The period of muscular contraction is depicted by the bar. c: discharge of the group-III unit during the period of time depicted by the bracket with the (C) over it in (a). Note that the impulse generated by the group-III afferent rises above the stimulus artifact (from Kaufman et al. 1984a).

infiltration of the deep tissues with a local anesthetic, whereas local anesthesia of the skin overlying the acupuncture point was without effect (Chiang et al. 1973). An input via fast-conducting deep afferents is apparently not required; such an input could easily be evoked by stretching muscles and moving joints, but these maneuvres are not part of the acupuncture treatment.

Muscle afferent units that are activated during muscle contractions are being discussed as the afferent limb for exercise-induced analgesia or hypalgesia. Rats running in a wheel have been shown to exhibit an increased threshold for vocalization upon electrical stimulation of the tail (Shyu et al. 1984). The increase in pain threshold during exercise was associated with the release of endorphins (Shyu et al. 1982). A specula-

tive interpretation of these data would be that the excitation of non-nociceptive group-III and -IV muscle receptors (in isolation during physical exercise, together with nociceptors during acupuncture) activates brain-stem neurons which inhibit spinal nociceptive neurons via the descending antinociceptive system (Chang 1980; He 1987). It has to be emphasized, however, that at present the connection between muscle receptors and acupuncture effects is very indirect and far from being proven. Recent evidence indicates that even the established concept of exercise-induced analgesia may be the product of a misinterpretation of experimental data (Padawer and Levine 1992).

II-E.1. Section summary

A relatively high proportion of the muscle receptors with slowly conducting afferent fibers, particularly of the group-III units, have LTM (non-nociceptive) properties. They respond strongly to weak mechanical stimuli or muscle contractions. Judging from their discharge behavior, these units could mediate pressure and force sensations from skeletal muscle or may function as ergoreceptors. The assumption that muscle receptors with slowly conducting fibers form the afferent limb for acupuncture effects or for exercise-induced analgesia is not proven.

II-F. Properties of dorsal horn cells driven by nociceptive input from muscle

II-F.1. Location and morphology

The first studies dealing with slowly conducting input from muscle to dorsal horn neurons were performed in the cat; cells receiving input from muscle group-III fibers were found mainly in the neck of the dorsal horn (lamina V) (Pomeranz et al. 1968). Later studies showed that the superficial dorsal horn (laminae I and II) likewise is an important region for nociception from deep somatic tissues (Cervero et al. 1976). A considerable proportion of cat lamina-I neurons that could be driven by noxious stimulation of muscle were found to project to the thalamus, i.e., they were part of the spinothalamic tract (STT) (Craig and Kniffki 1985). In the cat, input from slowly conducting muscle afferents is relayed to higher centers also by the spinocervical tract (SCT) (Hong et al. 1979) whose neurons of origin are located in laminae III-V (for a review of the SCT, see Brown 1973). Further ascending tracts that probably convey information from deep nociceptors to higher centers are the spinoreticular tract (SRT) (Fields et al. 1977; Maunz et al. 1978), the dorsal column postsynaptic system (DCPS) (Angaut-Petit 1975) and possibly also the spinomesencephalic tract (Wiberg and Blomqvist 1984; Hylden et al. 1986).

Similar data have also been obtained from the rat and monkey. In the monkey, nociceptive input from muscle and tendon has been shown to influence cells of the STT (Yoss 1953; Foreman et al. 1979a,b). Interestingly, some of the STT cells with deep RFs are located not in the dorsal but in the ventral horn (lamina VIII) and many show convergent input from deep tissues and skin (Willis 1985b). In the rat, nociceptive cells are mainly located in laminae I and IV-VI, including those responding to noxious stimulation of deep tissues (Menétrey et al. 1977; Yu and Mense 1990a). The rat SRT has been reported to contain a portion which carries information predominantly from high-threshold receptors in deep tissues. The cells of origin of this part of the SRT are situated in the dorsolateral funiculus rather than in the dorsal horn (Menétrey et al. 1980). Recently, evidence for the existence of a spinohypothalamic tract which may mediate autonomic and emotional reponses to pain has been found in the rat (Burstein et al. 1990).

The location of dorsal horn cells that are probably involved in muscle pain fits well with that 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 units have been found to form synaptic boutons 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 be indicative of a monosynaptic connection between primary

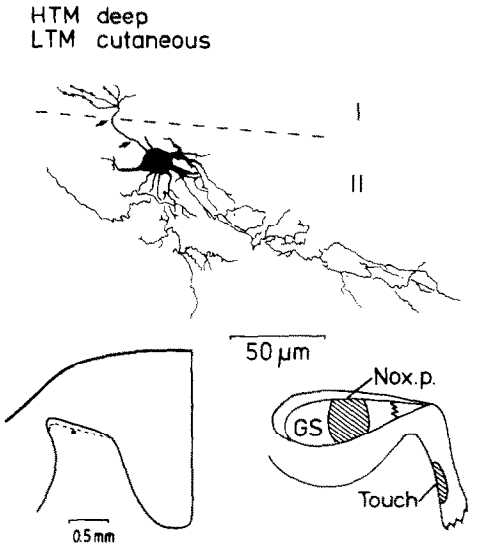

Fig. 9. Intracellularly stained dorsal horn neuron with convergent input from the skin and muscle in the cat. The cutaneous RF on the dorsum of the paw had a low mechanical threshold and could be activated by touch (LTM cutaneous); the deep RF in the triceps surae muscle required noxious pressure (Nox. p.) for activation (HTM deep). The neuron had the shape of a stalked cell; its soma was located within lamina II at the border to lamina I. The arrows point to the presumable axon which terminated with several boutons en passant et terminaux in lamina I (Hoheisel and Mense unpublished).

and secondary afferent neurons that mediate muscle pain.

The morphology of dorsal horn neurons processing input from muscle nociceptors seems to be heterogeneous. They include marginal cells in lamina I, stalked cells (presumably non-projecting interneurons) in lamina II (Fig. 9), and large multipolar cells in lamina V and VI. From the work of several groups (e.g., Light et al. 1979; Bennett et al. 1984; for reviews see Brown 1981; Mense 1990) no evidence has been obtained indicating that the functional properties of a dorsal horn cell are reflected in its morphology. Therefore, dorsal horn cells mediating muscle pain cannot be recognized by their morphology.

II-F.2. Response types

II-F.2.a. Neurons driven exclusively by input from deep tissues. When recording from dorsal horn neurons with deep input (particularly in the ventral layers of the dorsal horn), many units are encountered that have properties of proprioceptive cells in that they are dominated by input from muscle spindles and tendon organs; such cells are usually disregarded in studies on deep nociception.

Dorsal horn neurons responding exclusively to activation of muscle nociceptors are extremely rare in the cat (Craig and Kniffki 1985). In a sample of several hundred cells with deep input studied in the author's laboratory during the last years, less than 10 neurons belonged to this type. However, approximately 20% of the dorsal horn cells with deep input were found to be exclusively driven by nociceptors in other deep tissues such as joint, ligament, and tendon (Hoheisel and Mense 1990). The neurons did not respond to innocuous mechanical stimuli but required noxious intensities of stimulation for activation. These units apparently represent a HTM or nociceptive-specific (NS) cell population for nociception from deep tissues similar to the NS cells described in studies on cutaneous nociception. In the above study on cat dorsal horn neurons, the activity from muscle nociceptors was found to be processed by convergent cells which received additional input from the skin.

In a recent study on rat dorsal horn neurons (Yu and Mense 1990a), the great majority (approximately 80%) of the cells with exclusively deep input belonged to the HTM type ('HTM deep neurons'). In contrast to data obtained from the cat, many HTM deep neurons in the rat had RFs in skeletal muscle. The remaining cells with exclusively deep input had a mechanical threshold in the innocuous range and responded strongly to weak deformation of muscle and other deep tissues ('LTM deep neurons'). The discharge frequency of these neurons increased with the stimulus strength from innocuous to noxious intensities, i.e., they behaved like multireceptive or wide-dynamic-range (WDR) cells which, in studies of cutaneous nociception, are characterized by a combined input from non-nociceptive and nociceptive receptors. In neurons with deep input, however, the occurrence of maximal discharge frequency during noxious stimulation may be due either to addition of nociceptive input or to exclusive input from LTM muscle receptors, since the latter likewise respond maximally to noxious stimuli (see above).

In the above study (Yu and Mense 1990a) LTM neurons, in the sense of cells that have a low threshold and show saturation in their discharge frequency upon strong stimulation, were missing among the dorsal horn cells with deep input. Nevertheless, the neurons with

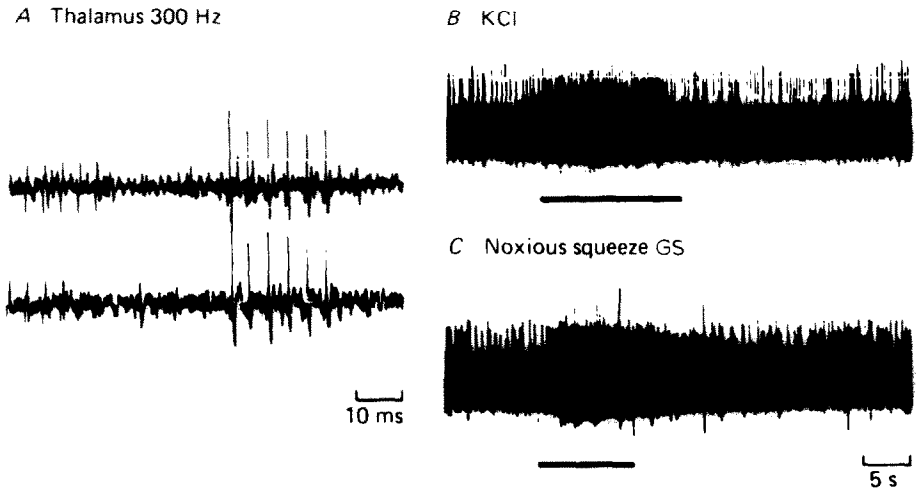

Fig. 10. Responses of a lamina-I STT neuron in the cat dorsal horn to noxious stimulation of the GS muscle. A: constant latency activation by electrical stimulation of the thalamus at a frequency of 300 Hz. B: increase in discharge frequency following injection of a painful dose of KCl (0.3 ml of a 0.32 M solution) into the muscle artery. C: response to noxious local pressure applied to the distal end of the GS muscle (from Craig and Kniffki 1985).

deep input and low mechanical threshold were denoted 'LTM deep', since their strong responses to weak mechanical stimuli was their characteristic property.

The LTM and HTM deep neurons differed not only in the mechanical threshold of their RFs but also in their stimulus response functions. The HTM deep cells, many of which had RFs in skeletal muscle, had a positively accelerating stimulus response function, whereas the response curve of the LTM deep cells decelerated. The steeper response characteristic of HTM deep neurons may explain why muscle pain of increasing intensity, e.g., during ischemic contractions, becomes intolerable very fast.

II-F.2.b. Neurons with convergent input. It has long-been known that many of the non-proprioceptive dorsal horn neurons with muscle input have additional input from other sources such as cutaneous and other deep receptors (Pomeranz et al. 1968). Cutaneous nociceptors and cold receptors are particularly effective in driving these cells (Craig and Kniffki 1985). Upon mechanical stimulation, the convergent cells exhibit multiple (mostly two or three) separate RFs in the skin and deep tissues (Hoheisel and Mense 1990). The responses of a convergent STT neuron to noxious stimulation of the GS muscle are shown in Fig. 10. Investigations of neurons with input from the knee joint (Schaible et al. 1987a) or from craniofacial receptors (Sessle and Hu 1991) yielded the same result, namely that the afferent input from a large proportion of the deep nociceptors converges on dorsal horn neurons that can be also driven by other input sources.

In a systematic study on mechanosensitive non-proprioceptive dorsal horn neurons in the rat, 17.7% of the cells were found to have convergent input from deep and cutaneous receptors, 35.5% had exclusive input from deep somatic tissues, and 46.8% could be driven from the skin only. The actual degree of convergence is probably greater than is apparent from these figures, since in the standard experimental set-up not all possible input sources can be tested. In fact, some of the neurons with 'exclusively' deep or mixed cutaneous-deep input also responded to inflation of a small balloon in the rectum or to squeezing the testes (Yu and Mense 1990a). These data indicate that a considerable proportion of dorsal horn cells have convergent input from deep, cutaneous, and visceral receptors.

In a study directed specifically at dorsal horn neurons processing input from muscle nociceptors in the cat, no cell was found that was exclusively driven by this receptor type (Hoheisel and Mense 1990). All the units with nociceptive input from muscle also responded to innocuous or noxious mechanical stimulation of the skin. In contrast to cutaneous nociception which is partly mediated by NS neurons, nociception from muscle seems to operate without dorsal horn cells that are exclusively driven by muscle nociceptors. The situation is similar to visceral nociception, where a marked viscerosomatic convergence and an almost complete lack of NS neurons with exclusive input from visceral nociceptors has been described (Cervero 1983; Foreman et al. 1984).

Whether the HTM deep neurons alone or together with the convergent neurons are responsible for the induction of deep pain is unknown. Input convergence from different sources does not rule out the possibility that a neuron fulfills a specific function. In studies on dorsal horn cells with cutaneous input in monkeys, WDR cells have been reported to participate in the encoding process by which noxious stimuli to the face are perceived (Dubner et al. 1989). In contrast, NS cells were assumed to mediate the affective component of pain sensations. Other authors, however, have discussed the NS neurons as mediating the quantitative (discriminative) aspects of pain sensations (Perl 1980).

Extensive convergence at the level of the second order neurons is one possible explanation for the ill-localized nature of muscle and other forms of deep pain; it makes it difficult, however, to understand how third- and higher-order neurons extract the information on muscle pain from the activity of second order neurons.

II-F.3. Arrangement of receptive fields

In more than 70% of the neurons with convergent input from cutaneous and deep receptors, the arrangement of RFs was such that the deep RF was located proximal to the cutaneous one. Among the cells with input from muscle nociceptors this arrangement was the only one existing (Hoheisel and Mense 1990). As convergence in the spinal cord is considered to be the neuroanatomical basis for pain referral (see below), this finding may be of importance for referred pain or referred tenderness from muscle. It has to be emphasized, however, that the sensations possibly evoked by the convergent cells are unknown.

A statistical analysis in which the proximo-distal location of the RF on the hindlimb was correlated with the medio-lateral location of the recording site in the dorsal horn, showed that cells with deep RFs on the distal hindlimb were located medially in the dorsal horn and those with proximal RFs were located laterally (Yu and Mense 1990b). Interestingly, in convergent neurons with RFs in both skin and deep tissues the correlation was significant for deep but not for cutaneous RFs. Assuming that the cells with nociceptive input from deep tissues mediate deep pain, this somatotopy combined with relatively small RF sizes could form the neuroanatomical 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.

The well-known diffuse character and poor localization of muscle and other forms of deep pain is probably due to other, as yet unknown, factors. Among these possible factors are the large rostro-caudal extent of the spinal projection of muscle nerves (see Mense and Craig 1988) and the descending influences that inhibit the spinal processing of nociceptive information from deep tissues (see below).

II-F.4. Behavior under pathological conditions

Systematic studies of the discharge behavior of dorsal horn neurons during pathological alterations of skeletal muscle are missing. Preliminary results obtained in the author's laboratory indicate that an acute carrageenan-induced myositis leads to a raised background discharge in rat dorsal horn neurons and to an expansion of the spinal region in which cells can be driven by input from that muscle (U. Hoheisel, K. Koch and S. Mense, unpublished). In the literature, information is available on the behavior of dorsal horn neurons driven by joint receptors in chronic polyarthritic rats (Calvino et al. 1986), in cats with an acute arthritis (Schaible et al. 1987b), and in rats with a subacute adjuvant-induced inflammation of the subcutaneous tissues of the hindpaw (Hylden et al. 1989). Although the results were obtained from different species under different experimental conditions, they led to the same conclusion, namely that an inflammation of deep tissues induces an enhanced excitability in dorsal horn neurons which is expressed in increased background discharge, enlarged and/or multiple RFs, enhanced responsiveness to mechanical stimuli, and increased convergence from peripheral sources (e.g., skin and deep tissues). There is evidence indicating that the inflammation-induced increase in excitability is associated with an increased expression of c-*fos* mRNA in the nuclei of the neurons followed by an elevation in preprodynorphin mRNA (Draisci and Jadorola 1989). The c-FOS protein acts as a transcription factor; it influences the synthesis of cellular proteins and thus is capable of changing the functional properties of the cell (Dragunow et al. 1989).

The increased background activity in nociceptive and other cells may cause the spontaneous pain and dysesthesia that are present in many arthritis and myositis patients. The tenderness of the inflamed tissue is probably due not only to a sensitization of peripheral nociceptors but also to a sensitization of dorsal horn cells (see below). This central sensitization may cause tenderness and/or hyperalgesia not only by a general enhancement of excitibility 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 (Dubner 1992).

II-F.5. Section summary

Neurons probably involved in nociception from muscle and other deep somatic tissues are situated in lamina I and in and around the neck of the dorsal horn (laminae IV-VI). In the cat, input from slowly conducting muscle afferents is relayed to higher centers mainly by the spinothalamic and spinocervical tracts; other possible pathways are the spinomesencephalic and spinoreticular tracts and the DCPS. No evidence has been obtained indicating that nociceptive cells possess particular morphological features. Neurons with input from deep nociceptors exhibit a somatotopical arrangement in that cells with RFs in the distal hindlimb are located medially in the dorsal horn and those with proximal RFs are located laterally. Dorsal horn neurons responding exclusively to activation of muscle nociceptors are extremely rare in the cat and rat; the activity from muscle nociceptors is processed to a large extent by convergent cells which receive additional input from the skin. Whether neurons with exclusive input from muscle nociceptors and/or convergent neurons are responsible for the induction of muscle pain is unknown. A longer lasting painful lesion (e.g., an acute experimental myositis) leads to raised background discharge in dorsal horn neurons and to an expansion of the spinal region in which cells can be driven by input from the inflamed muscle. The inflammation-induced increase in excitability of dorsal horn neurons (central sensitization) is associated with an increased expression of the c-*fos* mRNA in the nuclei of the neurons. The central sensitization may cause tenderness and hyperalgesia in patients by a general enhancement of neuronal excitibility.

II-G. Signs of neuroplasticity in neurons processing input from muscle nociceptors

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.

After their induction by a nociceptive input, neuroplastic changes may become independent of the input as has been shown in a study of the hyperexcitability of rat dorsal horn neurons following inflammation of the paw (Hylden et al. 1989). On a long time scale the neurons do not only change their discharge behavior but also their morphological appearance; particularly

remarkable changes have been described for axodendritic synapses (Calverley and Jones 1990).

In dorsal horn neurons, neuroplastic changes require input via non-myelinated or thin myelinated afferent fibers, i.e., afferent activity in thick myelinated A 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). In experiments on anesthetized animals, plastic changes in dorsal horn neurons can be easily demonstrated following noxious chemical stimulation of skeletal muscle.

An example is given in Fig. 11. The first injection of BKN into the RF in the semitendinosus muscle led to a lowering in the mechanical threshold of the injected RF and to a large expansion of its size. Simultaneously, the threshold of the non-injected RF in the GS muscle dropped to innocuous levels. The lowering in mechanical threshold of the injected RF can be attributed to a BKN-induced sensitization of the nociceptors in the semitendinosus muscle, but the expansion of the injected RF and the lowering in threshold of the RF in the GS muscle suggest that the excitability of the recorded dorsal horn neuron has increased, i.e., a central sensitization has occurred. Following the second injection of BKN, the lowering in threshold of the non-injected RF in the GS muscle persisted for more than 30 min (at that time the recording of the neuron's activity was discontinued). This means that the BKN-induced CNS effect lasted much longer than the afferent activity elicited by intramuscular injection of the kinin (Mense and Meyer 1988).

The sensitization of the dorsal horn neuron in Fig. 11 was probably induced by a strong activation of the slowly conducting afferent fibers connecting the neuron with its RFs, since fast-conducting afferent units from muscle are not excited by BKN (cf., Mense 1977). Injections of BKN into muscles outside the RF of the recorded neuron showed that by such a procedure similar changes in response behavior can be induced; approximately one-half of the neurons tested developed new RFs. The neurons were not excited by the BKN injection, i.e., the activation of a cell was not a prerequisite for its sensitization.

One possible explanation for these findings is that slowly conducting muscle afferents are activated by BKN and release neuropeptides from their spinal terminals which alter the responsiveness of dorsal horn neurons. A similar hypothesis was derived from experiments in which the flexor reflex of rats was increased for prolonged periods of time following activation of muscle C fibers as a conditioning stimulus (Woolf and Wall 1986). Since the afferent limb of the reflex was not activated by the conditioning stimulus, the underlying mechanism was called 'heterosynaptic facilitation'.

Results from experiments in which SP was applied

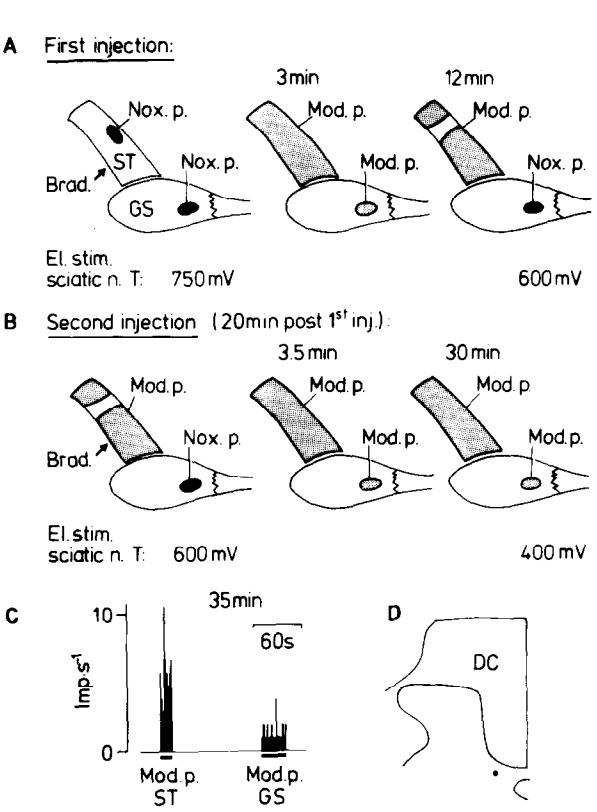

Fig. 11. Changes in RF properties induced in a cat dorsal horn neuron by intramuscular injection of a painful dose of bradykinin (Brad., 100 µg in 1 ml of Tyrode). A (left panel): situation before injection of Brad. The neuron had two RFs, one in the semitendinosus (ST) and the other in the GS muscle; both had a high mechanical threshold and required noxious local pressure (Nox. p.) for activation. (middle panel): 3 min after infiltration of the RF in the ST muscle with Brad. The injected RF is enlarged and now responds to moderate (innocuous) pressure (Mod. p.). The RF in the GS muscle likewise shows a decrease in threshold. (right panel): 12 min after injection of Brad. The RF in the GS muscle has regained its high mechanical threshold. B (left panel): situation 20 min after injection of Brad., time of second injection. The Brad. effects were reproducible and lasted for more than 30 min. The electrical threshold of the neuron dropped from 750 mV at the beginning of (A) to 400 mV at the end of (B). C: histogram of the neuron's responses to Mod. p. 35 min after the second injection of Brad. to show that this weak stimulus evoked strong activations in the formerly high-threshold cell. D: location of recording site in lamina VII of the dorsal horn. RFs marked in black had a high, shaded ones a low mechanical threshold (from Hoheisel and Mense 1989b).

iontophoretically to dorsal horn neurons have demonstrated that the neuropeptide may be involved in the induction of neuroplastic changes by causing long-lasting depolarization in many of these cells, predominantly in nociceptive ones (Henry 1976; Randic and Miletic 1977; Zieglgänsberger and Tulloch 1979). The SP-induced depolarization could be an important step in triggering neuroplastic processes in that it abolishes the Mg^{2+} block of the *N*-methyl-D-aspartate (NMDA)-

-sensitive Ca^{2+} channel. Normally, the block prevents Ca^{2+} ions from entering the cell and acting as an intracellular second messenger which, among other effects, induces the expression of immediate early genes (IEGs) such as c-*fos* (Hunt et al. 1987; Marx 1987; Morgan and Curran 1989; Dickenson and Sullivan 1991; Spitzer 1991; Dubner and Ruda 1992). In fact, the combined action of SP and NMDA channel activation has been proposed as a possible mechanism for the sensitization of STT cells which may underly the development of hyperalgesia in patients (Dougherty and Willis 1991). The importance of NMDA receptor activation for the developement of hyperalgesia has also been stressed in behavioral experiments in rats (Sher et al. 1992). There is evidence indicating that the release of nitric oxide may be an important link in the pathway from NMDA receptor activation to neuroplastic changes (Garthwaite 1991; Moncada et al. 1991).

Systematic studies of the neuroplasticity-inducing properties of SP in neurons mediating nociception from muscle are still lacking. In the author's laboratory, the action of SP on the responsiveness of dorsal horn neurons with input from deep tissues was examined in anesthetized rats. The lumbosacral spinal cords of the animals were superfused with defined concentrations of SP and the excitability of the neurons tested by electrically stimulating the major spinal nerves of the hindlimb. The effects of the neuropeptide were heterogeneous; some neurons acquired a new A- or C-fiber input, other cells lost an existing input, and again others showed a decrease in spike amplitude so that the neuron could no longer be used for recording. At a concentration of 100 μM in the superfusate, SP affected 75% of the neurons studied, the main effect being the unmasking of a formerly ineffective input. The unmasking of fiber connections to dorsal horn neurons may be of clinical relevance, particularly if A-fiber input from LTM receptors gains access to nociceptive dorsal horn cells. This situation may lead to allodynia in patients (Woolf and Thompson 1991).

At a concentration of 100 μM, SP not only influenced the electrical excitability of the neurons but also induced marked RF changes in a large proportion of the cells tested. The SP-induced changes were comparable to those observed after intramuscular BKN injections and consisted of expansion of existing RFs and formation of new RFs.

The data show that at least part of the dorsal horn neurons possess synaptic connections which are ineffective under normal circumstances. Activation of muscle nociceptors by a strong noxious stimulus can unmask these connections (similar processes can occur following input interruption) (cf., Wall 1977). The unmasking leads to a change in RF size and/or response properties of the cells. Comparable effects have been observed in neurons of the subnucleus caudalis and oralis of the trigeminal spinal tract nucleus (Hu et al. 1992). SP is surely one of the factors that is capable of unmasking neuronal connections in the dorsal horn. The finding that the time course of the induction of c-*fos* expression and that of SP effects are similar (Bravo 1990) supports the assumption that SP is involved in neuroplastic changes including hyperalgesia following carrageenan-induced inflammation of deep tissues (Satoh et al. 1992).

II-G.1. Section summary

The term neuroplasticity describes longer-lasting alterations of neuronal behavior and morphology in response to a triggering stimulus. Input via muscle C fibers is particularly effective in inducing such changes; activity in thick A fibers is not sufficient. One possible mechanism for the induction of neuroplastic changes is that slowly conducting muscle afferents release SP from their spinal terminals which alters the responsiveness of dorsal horn neurons. A SP-induced depolarization could allow Ca^{2+} ions to enter the cell through an NMDA-sensitive channel. The Ca^{2+} ions could act as an intracellular second messenger which induces the expression of immediate early genes such as c-*fos*. A considerable proportion of dorsal horn neurons appears to possess synaptic connections which are ineffective under normal circumstances. Activation of muscle nociceptors by a strong noxious stimulus can unmask these connections, possibly via SP release. If A-fiber input from LTM receptors gains access to nociceptive dorsal horn cells, allodynia may result.

II-H. Spinal reflexes and muscle nociception

II-H.1. The flexor reflex

In 1951, Brock and coworkers studied the effects of afferent volleys in muscle nerves on motoneurons and found that the actions of group-II and -III muscle afferents were similar in that both elicited a flexor reflex pattern by activating flexor motoneurons and inhibiting extensor motoneurons. From these findings the concept of the 'flexion reflex afferents' comprising group-II, -III, and -IV fibers emerged. It has to be emphasized that the concept is based on data from experiments dealing with locomotion rather than nociception. Therefore, the term 'flexion reflex afferents' does not imply that the afferent units are nociceptive and the reflex is nocifensive (Eccles and Lundberg 1959; Holmqvist and Lundberg 1961).

Whereas the occurrence of a flexor reflex upon activation of cutaneous nociceptors is a common experience, elicitation of the reflex by nociceptors in deep tissues has been less well studied. O'Leary et al. (1935) were among the first to demonstrate that electrical stimulation of small-diameter afferent fibers in a muscle nerve leads to a reflex contraction of flexor (and

extensor) muscles. As electrical stimulation excites all nerve fibers irrespective of their function, and as not all of the slowly conducting muscle afferent units can be considered nociceptive (Mense and Meyer 1985), experiments employing natural stimuli had to be performed in order to show that the nociceptors or 'pressure-pain receptors' (Paintal 1961) of skeletal muscle are capable of facilitating the flexor reflex. Electrical stimulation of articular nerves at group-III and -IV fiber strength (Gardner 1950) and inflammation of the knee joint (Ferrell et al. 1988) likewise has been reported to elicit or facilitate the flexor reflex.

Intracellular recordings from alpha-motoneurons in cats have shown that input via muscle group-III and -IV afferent units induced by noxious chemical stimulation of the GS muscle (an extensor) inhibits most of the GS motoneurons, whereas flexor motoneurons are facilitated (Kniffki et al. 1981). These effects are associated with the appearance of excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs), respectively.

Most of the above studies were performed in spinalized animals; therefore, the data cannot be directly transferred to human beings with intact neuraxis.

More recent data indicate that a short-lasting input via non-myelinated afferent fibers from muscle facilitates the flexor reflex for a long period of time, the duration of facilitation lasting much longer than that induced by a comparable input from the skin (Wall and Woolf 1984). Reflex facilitations for prolonged periods of time have also been observed following intrathecal application of SP and CGRP (Woolf and Wiesenfeld-Hallin 1986). NMDA receptor activation appears to be involved in the reflex facilitation, as it can be abolished by NMDA antagonists (Woolf and Thompson 1991).

Induction or facilitation of the flexor reflex by nociceptive afferent units from muscle is of clinical interest, since these mechanisms could offer an explanation for long-lasting muscle spasms. According to a widely held concept, the spasms are due to a vicious cycle which is triggered by nociceptive input from joint or muscle. The nociceptive input elicits the flexor reflex, and the contracting muscle compresses its own vasculature and/or consumes large amounts of oxygen if the contraction is of sufficient strength and duration. Thus the muscle is forced to perform contractions under ischemic conditions. Ischemic contractions activate muscle nociceptors which maintain the flexor reflex (Dorpat and Holmes 1962; Emre and Mathies 1988).

Direct experimental evidence supporting this concept of a vicious cycle is missing. In fact, results from animal experiments indicate that a prolonged patholog-

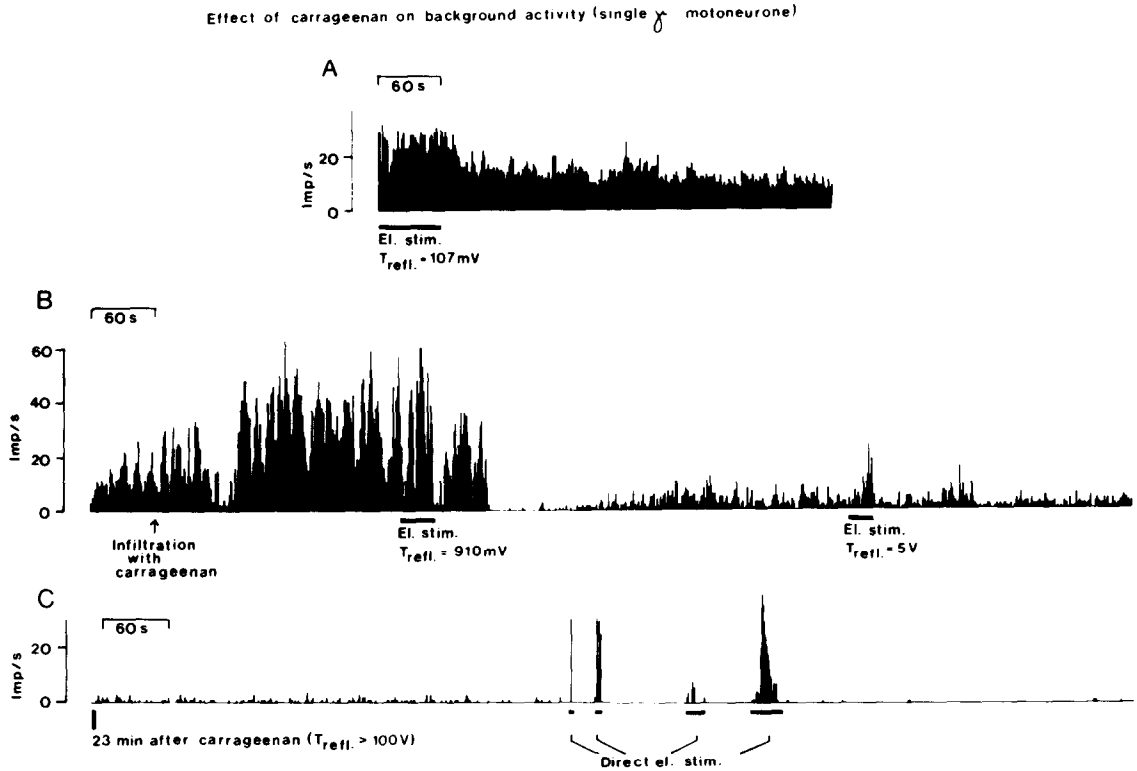

Fig. 12. Impulse activity of a single gamma-motoneuron supplying the medial gastrocnemius muscle during induction of an inflammation in the lateral gastrocnemius-soleus (LGS) muscle. A: background activity before induction of the inflammation. B: at the time indicated by the arrow, the LGS muscle was infiltrated with the inflammation-inducing agent carrageenan. C: at the beginning of the panel, the reflex threshold (T_{refl}) was higher than the 100 V available. Electrical stimulation of the sciatic nerve (Direct el. stim.) was performed after the unit had become silent in order to show that the neuron's action potentials could still be recorded. Please note that the carrageenan injection itself caused an activation which was followed by a complete inhibition of the background activity and reflex excitability (from Mense and Skeppar 1991).

ical input from deep tissues abolishes the capability of C fibers from muscle to facilitate the flexor reflex for prolonged periods of time (Wall et al. 1988). A further problem for the understanding of muscle spasms is the fact that according to the above-mentioned flexor reflex concept, spasms should be present predominantly in flexor muscles, which is not the case.

II-H.2. Gamma reflexes as a possible cause of muscle spasms

In older clinical literature, there are reports postulating that an increased activity or excitability of the gamma-motoneuron system is the reason for the rigidity of parkinsonian patients and for the painful spasms that sometimes develop in cases of rheumatism and stiff-man syndrome (Brochocki 1962; Dietrichson 1971; Mertens and Ricker 1968). The increased activity in gamma-motoneurons is assumed to lead to a higher discharge frequency in muscle spindle afferent fibers which in turn activate alpha-motoneurons. By this mechanism the same vicious cycle as described above can be triggered, if the activation of alpha-motoneurons is so strong that it leads to ischemic contractions.

It has to be emphasized that the concept of an involvement of gamma-motoneuron reflexes in disorders of muscle tone has been strongly objected to by other authors (for a review, see Burke 1983). Experimental support for the assumption that activation of muscle nociceptors leads to increased activity in homonymous gamma-motoneurons is weak. There is general agreement that group-I afferent units from muscle have only negligible effects on homonymous fusimotor neurons, and that group-II units mainly elicit activations (Noth and Thilman 1980; Appelberg et al. 1983a,b). The actions of the slowly conducting afferent units are less clear. In the literature, both excitatory and inhibitory influences of these units on gamma-motoneurons have been reported (Tanji and Kato 1972; Ellaway et al. 1982; Appelberg et al. 1983c). Apparently, the flexor reflex concept cannot be applied to the gamma system (Appelberg et al. 1983c).

In a study in which muscle group-III and -IV receptors were activated by intra-arterial injections of algesic chemicals, both extensor and flexor gamma-motoneurons were excited (Hong et al. 1978). As the input elicited by this type of stimulation is probably not purely nociceptive (Mense 1977), the results obtained with administration of algesic agents do not mean that muscle nociceptors generally have an excitatory action on homonymous fusimotor neurons.

Recently, the effects of an experimental myositis of the lateral GS muscle (LGS) on the activity of gamma-motoneurons supplying the synergistic medial head were studied (Mense and Skeppar 1991). The main findings were that the resting activity of the gamma-motoneurons was significantly reduced by inflammation (Fig. 12) and that the reflex excitability of the neurons by electrical and mechanical stimulation of afferent units from the inflamed muscle was likewise inhibited. In contrast, the electrical excitability of gamma-motoneurons supplying the antagonistic anterior tibial muscle was (slightly) enhanced in animals with a myositis of the LGS muscle.

The results were interpreted as indicating that input via nociceptive muscle afferent units (some of the group III and most of the group IV) inhibits the homonymous gamma-motoneurons whereas input via non-nociceptive fibers (most of group II and some of group III) has an excitatory influence. In order to explain the net activation by noxious chemical and mechanical stimuli (which produce a mixed input via non-nociceptive and nociceptive fibers) the additional assumption has to be made that the excitatory influences are stronger than the inhibitory ones.

Teleologically, the inhibition of homonymous fusimotor neurons induced by myositis may be an advantage, since it could reduce the forces acting on the damaged muscle. The postulated activation of the gamma system by a muscle lesion was not present; it apparently requires an input different from that elicited by a myositis. There is evidence in the literature indicating that an increase in gamma activity may occur (at least in part of the neurons) if the site of the lesion is outside the muscle, e.g., in a neighboring joint (Freeman and Wyke 1967; He et al. 1988).

II-H.3. Sympathetic activity as a possible enhancing factor in muscle nociception

Available data concerning the contribution of sympathetic efferent activity to pain in general is controversial. As to muscle pain, an additional problem is that most of the studies have been performed on cutaneous pain. At the level of the primary afferent neuron, the bulk of the data indicate that a normal nociceptor is neither activated nor sensitized by sympathetic efferent activity (Barasi and Lynn 1986). There is evidence, however, that nociceptive endings that have been sensitized by noxious stimuli may be activated by sympathetic efferent activity (Roberts and Elardo 1985). Whether these findings can be generalized is unclear at present, since other groups arrived at a different conclusion (Shea and Perl 1985).

Data obtained from receptors in a rat hemidiaphragm-phrenic nerve preparation in vitro (see Section II-A.4.e) have shown that adrenaline increases the resting discharge in HTM receptors and sensitizes them to mechanical stimulation. Particularly susceptible to adrenaline were endings that were under the continuous influence of a noxious mechanical stimulus (Kieschke et al. 1988). Hypoxia likewise sensitized some of the diaphragmatic receptors. These results support the assumption that nociceptors in a damaged muscle

may be directly activated and/or sensitized by sympathetic efferent activity. A new aspect is that sympathetic postganglionic fibers in pathologically altered tissue are able to release PGE_2 (Basbaum and Levine 1991) which in turn may sensitize nociceptors.

Data obtained from patients point in the same direction, namely that sympathetic efferent activity may enhance pain only under special circumstances. Sympathetic ganglionectomy has been reported by Lewis (1942) not to influence pain sensations from the upper extremity, but a stellate blockade in fibromyalgia patients has been shown to relieve the pain, possibly by improving the microcirculation in painful muscles (Bengtsson and Bengtsson 1988).

There is evidence in the literature indicating that sympathetic activity may be involved indirectly in muscle pain by increasing the neuromuscular muscle tone. The increase in tone may be brought about by a sympathetically induced activation of the intrafusal muscle fibers of the muscle spindle. This mechanism may contribute directly to the mechanical tension of a muscle or may induce muscle contractions via the monosynaptic stretch reflex (for a review of this aspect, see Grassi and Passatore 1988).

An interesting new concept states that in cases of sympathetically maintained pain, the pain is not caused by an increased sympathetic outflow but by a supersensitivity of vessels and/or nerves to sympathetic transmitter substances (Drummond et al. 1991). Results from animal experiments support this assumption by showing that following a partial nerve lesion nociceptors of the skin become sensitive to sympathetic efferent activity and noradrenaline (Sato and Perl 1991). When considering possible effects of sympathetic efferent activity on nociception from muscle it has to be kept in mind that the functional organization of postganglionic sympathetic fibers to muscle is different from that of fibers supplying the skin. Therefore, both subsystems can react differently under the influence of an adverse stimulus. For instance, the sympathetic activity in a muscle nerve can rise and that in a skin nerve remain unchanged during immersion of a hand in ice water (Fagius et al. 1989).

II-H.4. Section summary

Electrical stimulation of small-diameter muscle afferent fibers or activation of muscle nociceptors leads to a reflex contraction of flexor muscles and facilitates the flexor reflex for a long period of time. The latter effect can also be elicited by intrathecal application of SP and CGRP. NMDA receptor activation appears to be involved in the reflex facilitation. A widely held concept states that chronic spasms are due to a vicious cycle which is maintained by a pain–spasm–pain feedback. The feedback loop to alpha-motoneurons has not been proven to exist, however, and the activity of gamma-motoneurons has been shown to be reduced during a longer-lasting experimental muscle lesion. Increase in alpha or gamma activity is more likely to occur if the site of the lesion is not inside but outside the muscle, e.g., in a neighboring joint. Sympathetic efferent discharges are probably not capable of activating or sensitizing normal muscle nociceptors, therefore, the existence of a vicious cycle between muscle nociceptors and sympathetic efferent fibers is doubtful. Sympathetically maintained pain may be caused by a supersensitivity of vessels and/or nerves to sympathetic transmitter substances rather than by an increased sympathetic outflow.

II-I. Descending influences on spinal neurons processing information from deep nociceptors

Cooling the spinal cord rostral to the recording site is a widely used technique to block neuronal activity traveling in tracts of the dorsal half of the spinal cord. The technique is particularly useful for abolishing the influence of descending antinociceptive tracts some of which are known to course in the dorsolateral funiculus (Basbaum and Fields 1984). Systematic studies employing this method have been performed in the cat and rat. In dorsal horn neurons driven by input from deep somatic tissues, cooling of the spinal cord induced an increase in resting activity, in response magnitude to noxious stimulation of muscle, in convergence from different receptor types, and in the number of RFs per neuron (Hong et al. 1979; Hoheisel and Mense 1990). These data indicate that dorsal horn neurons which presumably mediate deep pain are subjected to a strong descending inhibition which is tonically active. The inhibition controls not only the excitability of the neurons by external stimuli but also the degree of convergence from different input sources.

Parts of the descending antinociceptive system appear to act quite specifically on the input from nociceptors in deep tissues. This interpretation is based on the finding that in dorsal horn neurons with convergent input from cutaneous and deep nociceptors, the responses to stimulation of deep tissues were strongly enhanced by the spinal cold block, whereas the effects of cutaneous stimulation on the same neuron were more or less unaffected (Yu and Mense 1990a). A similar tonic descending inhibition has been observed in neurons with input from joint (Cervero et al. 1991).

The tonic nature of the descending inhibition suggests that a transmitter substance is continuously released at the supraspinal origin of the antinociceptive tract(s). Injections of transmitter antagonists into the third cerebral ventricle in rats have demonstrated that the tonic inhibitory influence on dorsal horn neurons with input from deep nociceptors can be abolished by naloxone, but neither by the alpha-adrenergic receptor

blocker phentolamine nor by the serotoninergic blocker methysergide (Yu et al. 1991).

In neurons with convergent HTM input from deep tissues and skin, the intracerebroventricular injection of naloxone enhanced the responses to deep stimulation with little effect on the responses to activation of cutaneous nociceptors (Fig. 13). The data suggest that at the supraspinal level the inhibitory pathways that act tonically on deep nociception use endogenous opioids as a transmitter substance.

II-I.1. Section summary

Dorsal horn neurons with input from deep nociceptors are subjected to a strong descending inhibition which is tonically active. In convergent neurons the input from deep nociceptors is more strongly inhibited than is the input from cutaneous nociceptors. The inhibitory pathways appear to include opioidergic synapses at the supraspinal level.

II-J. Supraspinal mechanisms of nociception from muscle

II-J.1. Trigeminal level

In comparison to limb muscles, much less information is available on the afferent fibers from masticatory and other head muscles. The data indicate that many of the slowly conducting muscle afferent units, including nociceptive ones, project to the subnucleus caudalis (laminae I and IV-V) and interpolaris of the trigeminal spinal tract nucleus (Nishimori et al. 1986; Shigenaga et al. 1988; Arvidsson and Raappana 1989; Nazruddin et al. 1989). In this area, second-order neurons can be found that behave similarly to those in the spinal dorsal horn (Dubner and Bennett 1983). Only a few cells receive an exclusively nociceptive input from deep tissues, and many nociceptive neurons (WDR and NS cells) have convergent input from several sources including masticatory muscles, the temporomandibular joint (TMJ), facial or intra-oral skin, and viscera (e.g., larynx). Neurons of this type are located predominantly

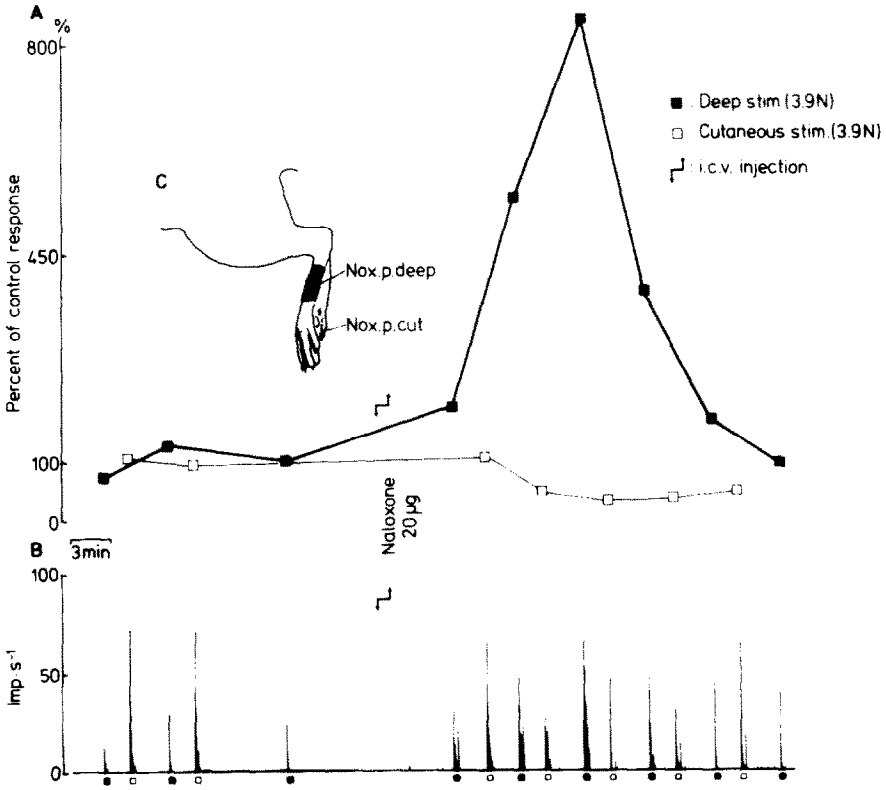

Fig. 13. Effect of 20 μg naloxone i.c.v. on the mechanically induced responses of a HTM neuron with convergent input from the skin and deep tissues. A: response curve to repeated stimulation of the deep RF (■) and cutaneous RF (□). The curve was normalized relative to the control response (= 100%) which was defined as the mean of the pre-injection responses to deep or cutaneous stimulation. B: histogram of the neuron's activity from which the data of (A) were obtained. Bin width: 1 sec. C: location of RFs. Both the cutanous RF in the plantar skin of toes 2 and 3 (shaded) and the deep RF (black) required noxious pressure stimulation for activation (Nox. p. cut. and deep, respectively). The stimuli were applied using a forceps with broadened tips (area 2 cm^2) which was closed with a force of 3.9 N (from Yu et al. 1991).

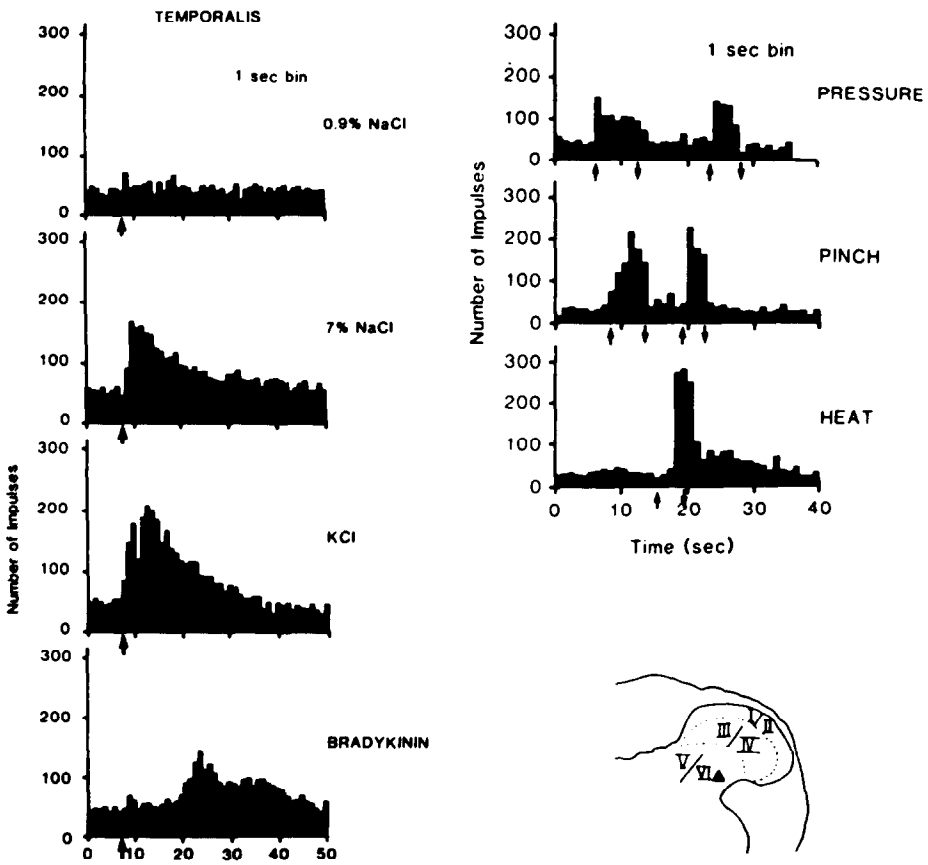

Fig. 14. Responses of a neuron in the feline trigeminal subnucleus caudalis to noxious stimulation of the facial skin and temporalis muscle. (left column): histograms of the neuron's activity in response to injections of algesic agents into one of the arteries of the temporalis muscle. Injection of 0.9% NaCl served as a control. Arrows indicate time of onset of injection that lasted 8–10 sec. (right column): responses to stimulation of the cutaneous RF with innocuous pressure, noxious pinch, and noxious heat. Arrows indicate time of stimulus onset and offset. The inset shows the histologically verified recording locus in the trigeminal subnucleus caudalis (modified from Amano et al. 1986).

in the superficial layers (laminae I and II) and in laminae V and VI of the subnucleus caudalis (Fig. 14) (Amano et al. 1986; Sessle and Hu 1991).

The extensive convergence and large RF size of the WDR and NS cells in the subnucleus caudalis have been considered as the neurophysiological basis of the diffuse nature and referral which are typical features of craniofacial and TMJ pain. Signs of neuroplastic changes in convergent trigeminal neurons following noxious stimulation of hypoglossal muscle afferents have likewise been described (Sessle and Hu 1991). An interesting finding that may be of relevance for the understanding of temporomandibular disorders in patients is that noxious chemical stimulation of the TMJ in cats leads to reflex activation of masticatory muscles (Broton and Sessle 1988). Such reflexes may induce long-lasting increases in tension of craniofacial muscles. When considering motor reflexes at the trigeminal level, differences in organization between spinal and trigeminal reflex pathways have to be kept in mind. Whereas input via muscle afferent fibers at the spinal level induces reciprocal effects ipsi- and contralaterally (e.g., inhibition of ipsi- and activation of contralateral extensors), muscle input at the trigeminal level has the same action on the ipsi- and contralateral motoneurons of a given muscle (Nakamira et al. 1973).

II-J.2. Thalamic level

Little information is available concerning the processsing of information from muscle nociceptors in the thalamus. In experiments employing electrical stimulation of muscle nerves and recording of thalamic-evoked potentials, Mallart (1968) found a sole input from high-threshold (group III) muscle afferents from the cat hindlimb to the ventrobasal (VB) complex and the medial thalamus. More recent data show that a small number of nociceptive neurons with musculotendinous input are present in the ventral and dorsolateral periphery of the ventroposterolateral (VPL) nucleus and in the transitional zone between VPL and ventrolateral nucleus of the cat (Kniffki and Mizumura 1983), i.e., in one of the regions STT cells are known to project to in this species (Carstens and Trevino 1978). The location of nociceptive neurons in the periphery of the VPL appears to be typical for the cat; in the rat, nociceptive cells with cutaneous and articular input have been

found intermingled with tactile neurons within the VB proper (Hellon and Mitchell 1975; Guilbaud et al. 1980; Guilbaud 1991).

In polyarthritic rats, cells of the VB have unusual response characteristics with long afterdischarges and lowered mechanical thresholds (Gautron and Guilbaud 1982). Interestingly, cells of the nucleus centralis lateralis in 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 (Guilbaud 1991). Such changes are probably associated with a (central) sensitization of thalamic neurons (Guilbaud et al. 1989).

In humans, an area ventral to the VB, the ventrocaudal parvocellular nucleus of Hassler, is considered to be specific for the mediation of pain (Hassler 1976). It is possible, however, that other nuclei of the thalamus (e.g., the posterior and medial nuclei) also process information from fine deep afferents, at least from nociceptive ones. 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 were reported to respond to noxious stimulation of deep tissues in this species (Dong et al. 1978). It is questionable, however, whether WDR and NS cells in the medial and posterior thalamic nuclei are capable of mediating the sensory-discriminative component of pain, since recordings in awake monkeys have shown that these neurons have large, often bilateral RFs. In contrast, the ventral posterior nuclei (VPL + VPM) of the monkey contain neurons that respond differentially to innocuous and noxious stimuli and have small, contralateral RFs (Casey and Morrow 1983). Whether 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).

II-J.3. Cortical level

The significance of the somatosensory cortex for the processing of nociceptive information is still difficult to assess, and this is particularly true for nociception from muscle. In areas 3b and 1 of the monkey, neurons have been shown to exist which receive input from cutaneous nociceptors (Kenshalo and Isensee 1983). Many cells in the primate primary somatosensory cortex (SI) fulfill an important requirement of nociceptive neurons in that they not only respond differentially to innocuous and noxious stimuli but also encode the intensity of a stimulus in the noxious range (Kenshalo et al. 1988). The somatosensory cortex of the rat likewise receives a remarkable nociceptive input as has been shown in a study performed by Lamour et al. (1983a). Out of 292

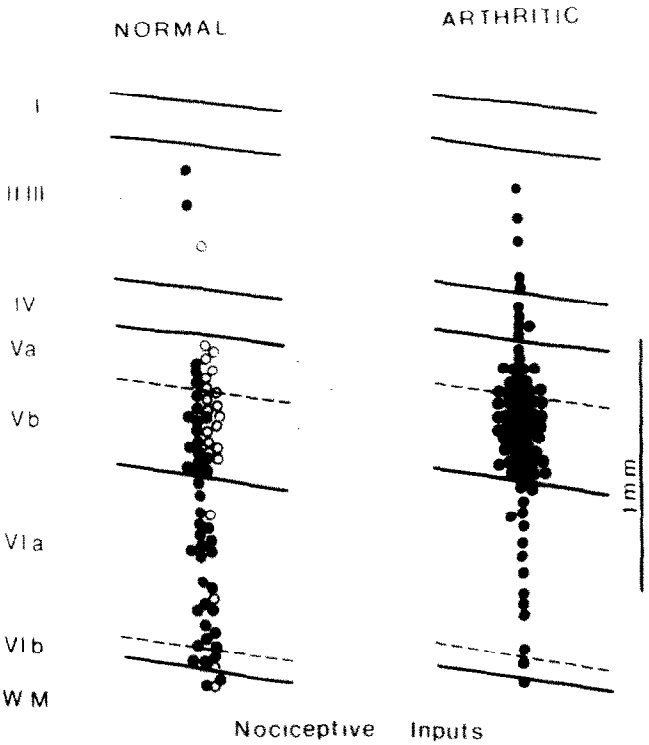

Fig. 15. Localization of neurons receiving nociceptive input in the rat somatosensory cortex. Please note that in the normal rat (left half) the neurons were approximately evenly distributed in laminae V and VI, whereas in arthritic animals (right half) the great majority was located in lamina V (from Guilbaud 1988).

cells with peripheral RFs, 91 responded to noxious stimulation. Among these 13 units were driven from deep tissues. The proportion of cortical neurons driven by deep input has been reported to change if pathological alterations occur in the periphery. In arthritic rats, the nociceptive input from joints shifts from cortical layers V-VI to layer V, and the pathological input invades cortical areas that normally do not respond to joint input (Fig. 15) (Lamour et al. 1983b,c; Guilbaud 1991).

As to the input from skeletal muscle, data from the cat and monkey show that activity in group-I muscle afferent units mainly influences neurons in Brodmann areas 3a and 3b (Sirisko and Sessle 1983; Iwata et al. 1985), whereas group-II and -III muscle input projects to area 4 and the secondary somatosensory cortex (SII) (Wiesendanger 1973; Hore et al. 1976; Hanson 1985). The segregation between these two input sources is not very distinct, however, and in the face region of SI of the awake monkey (areas 3b, 1 and 2) very few neurons were encountered that responded to deep input at all (Huang et al. 1989). Up to now, there are only a few reports that deal specifically with the input from muscle nociceptors to cortical neurons. In one of theses studies (Iwamura et al. 1981), noxious stimuli (strong

local pressure and injections of algesic substances) have been applied to the GS muscle in cats during a systematic search for neurons in area 3a responding to these stimuli. The authors found a small fraction (< 10%) of the cells with deep input from the contralateral hindlimb to be responsive to nociceptive input from muscle. In the anterior ectosylvian area of the cat, neurons have been described which responded in a specific way to high-intensity electrical and mechanical input from the hypoglossal nerve and muscle (Hanson 1985).

Recent data obtained in awake humans with the use of positron emission tomography (PET) and magnetic resonance imaging (MRI) demonstrate that noxious stimulation of the skin leads to an increase in blood flow (indicative of neuronal activation) in the contralateral SI and SII and in the anterior cingulate cortex, although such a pain-specific activation of the somatosensory cortices has not been found in all of the studies (Jones et al. 1991; Talbot et al. 1991; Roland 1992). The nociceptive region in the anterior cingulate cortex (Brodmann area 24) is assumed to mediate the aversive component of pain. Comparable studies employing noxious stimulation of muscles in humans have not been performed. Since patients with thalamic lesions may have cutaneous analgesia, but still feel deep pain elicited by intramuscular injections of hypertonic saline (Marshall 1951), it is possible that at the thalamic and cortical level deep pain is processed differently from cutaneous pain.

II-J.4. Section summary

In experimental animals, nociceptive afferent fibers from masticatory and other head muscles project to the subnucleus caudalis and interpolaris of the trigeminal spinal tract nucleus. Many nociceptive neurons in this region have convergent input from several sources including masticatory muscles, the TMJ, and facial or intra-oral skin. In the cat thalamus, nociceptive neurons with musculotendinous input are present in the periphery of the VPL nucleus; in the rat and monkey, nociceptive cells have been found intermingled with tactile neurons in the nucleus proper. There is experimental evidence indicating that under pathological conditions nociceptive pathways to the thalamus may be opened which are silent or ineffective in the intact organism. The significance of the somatosensory cortex for the processing of nociceptive information from muscle is unclear. Slowly conducting muscle afferent fibers, including nociceptive ones, project to areas 3a and 4 of SI and to SII. The anterior ectosylvian area of the cat is another area of interest for muscle nociception. In arthritic rats, the nociceptive input from joints invades cortical areas that normally do not respond to this input.

III. Possible mechanisms of various types of clinical muscle pain

III-A. Nociceptor pain

III-A.1. Trauma

III-A.1.a. Tear and blow. Strong mechanical forces acting on muscle tissue excite nociceptors mechanically and disrupt blood vessels and muscle fibers. Tissue damage triggers several mechanisms which result in an increase in the tissue concentration of endogenous biologically active substances. (1) From the broken muscle fibers potassium leaks into the interstitial fluid and depolarizes nerve endings and fibers. (2) The extravasation of blood from damaged blood vessels leads to liberation of 5-HT from platelets and of BKN from plasma proteins. BKN in turn releases PGs from various tissue cells; all these substances sensitize muscle receptors. (3) The activation of muscle nociceptors is associated with a release of neuropeptides from the nerve endings (e.g., CGRP and SP, see above). This in turn triggers the liberation of further substances such as histamine from tissue mast cells.

The muscle pain accompanying an acute trauma can be explained by assuming that the immediate pain is caused by the direct mechanical activation of muscle nociceptors whereas the ensuing tenderness is due to a sensitization of the receptors by vasoneuroactive and other substances released from the damaged tissue and/or blood constituents.

III-A.1.b. Overload. A muscle that is forced to perform physical work of unaccustomed intensity or duration is likely to be physically damaged. An impressive example is the pectoralis muscle in migrating birds which exhibits massive histological alterations including swelling and necrosis of muscle fibers following a one night's flight without rest (Schumann and Berger 1974). Similar changes have been observed in biopsy material from human muscle 48 h after heavy eccentric exercise (Stauber et al. 1990). The histological picture resembles that of a necrotic inflammation with disruption and swelling of muscle fibers and cellular infiltration of the extracellular space (Round et al. 1987). Other groups have stressed the relevance of muscle fiber swelling as the main feature following eccentric exercise but have questioned the interpretation of the histological changes as inflammatory (Fridén et al. 1988).

The characteristics of eccentric contractions (or negative work) are that the external forces acting on the muscle are greater than those produced by the muscle itself (Cavanagh 1988). The muscle performs lengthening contractions; walking downhill or downstairs is the typical situation in which extensor muscles of the leg contract in this way. The damage to the muscle fiber has been explained by assuming that during negative

work a smaller number of motor units is active than during positive work of the same intensity. Therefore, mechanical stress to the Z bands and connective tissue, particularly to the in series elastic elements, is higher (Hough 1902; Asmussen 1956; Jones et al. 1989). This view has been supported by histological data showing that the histological muscle damage is greater after eccentric than after concentric (shortening) contractions (Armstrong et al. 1983). Isometric contractions are likewise capable of producing fatigue and soreness, particularly if they are performed at long muscle length (Jones et al. 1989).

A common symptom following unaccustomed exercise is muscle soreness (tenderness and stiffness) (cf., Jones et al. 1987) which usually occurs with a delay of more than 12 h after the end of the exercise. Owing to this long delay, it is unlikely that an increased lactate concentration is a causal factor for the soreness. Muscle lactate has been reported to decrease with a half-time of 9.5 min after exhausting work (Sahlin et al. 1976). This means that within about 1 h the lactate concentration will have returned to normal values. Muscle enzymes such as glucose-6-phosphate dehydrogenase and creatine kinase (Jones et al. 1987) exhibit a more delayed increase, but whether these enzymes contribute to soreness is unknown.

Another hypothesis attempting to explain the pain of a sore muscle is the 'spasm theory' by DeVries (1966). It is based on the finding that increased electrical activity is present in sore muscle. The spasms are assumed to be the source of pain and tenderness; static stretching of the muscle was found to reduce the EMG activity and to relieve the pain. Other groups, however, were unable to reproduce the postulated close relationship between EMG activity and pain of a sore muscle (McGlynn et al. 1979). More recent data question the presence of increased EMG activity in relaxed sore muscles (Lund et al. 1991). The shortening of the affected muscle appears to be due to swelling of the connective tissue and not to neuromuscular activity (Howell et al. 1985; Jones et al. 1987).

The above-cited histological data rather support the original 'torn-fiber theory' of Hough (1902), which states that during unaccustomed exercise fibers of the connective tissue are ruptured by contracting muscle fibers. The reason for the ruptures is that in an untrained muscle the fibers lack coordination and exert a higher mechanical stress on the connective tissue. The damage leads to repair processes which are accompanied by local swelling and sensitization of nociceptors and thus exhibit some aspects of an inflammation (Staton 1951; Jones et al. 1987). PGs do not appear to play an important role in these events, since PG synthesis-inhibiting drugs have been reported not to influence the subjective soreness after eccentric exercise (Kuipers et al. 1985).

III-A.2. Myositis

The different forms of myositis (e.g., polymyositis, dermatomyositis, myositis due to infections) are associated with the subjective symptoms of weakness, spontaneous pain, tenderness, and paresthesias (DeVere and Bradley 1975; Ansell 1984). The raised background discharge in nociceptive nerve endings in inflamed muscle (Berberich et al. 1988) may account for spontaneous inflammatory pain. With regard to central nervous transmission the bursting type of discharge that is typical of afferent units from inflamed muscle is probably very effective because of temporal summation at spinal and higher-order synapses.

Tenderness of inflamed muscle is probably due to the sensitization of nociceptors by inflammatory substances. A sensitized nociceptor has a lowered mechanical threshold and is likely to be activated by weak physiological stimuli. It is unknown at present whether all muscle nociceptors have the capability of being sensitized to mechanical stimuli or whether tenderness is caused by the sensitization of a special subset of receptors. Since in animal experiments muscle nociceptors have been found that were sensitized to local pressure but not to stretch (and vice versa) (Mense and Meyer 1988), tenderness upon palpation and pain during movement may be elicited by different populations of muscle nociceptors.

The paresthesias (sensations of pressure and tension) of some myositis patients may be due to the fact that not only nociceptive but also non-nociceptive (LTM) receptors with slowly conducting afferent fibers exhibit sensitization and increased resting activity in inflamed muscle (Berberich et al. 1988). It is unknown, however, if LTM muscle receptors elicit subjective sensations at all. Indirect evidence from animal experiments suggests that this may be the case. In area 2 of the monkey cortex, neurons are present which respond to slight mechanical distortion of deep tissues without being sensitive to muscle stretch (Mountcastle and Powell 1959; Dreyer et al. 1974). These findings suggest that activity from deep LTM receptors, which are different from muscle spindles, has access to cells in the postcentral gyrus and therefore may be capable of eliciting conscious sensations.

The reason for the weakness of an inflamed muscle is unknown, although many deviations from normal laboratory figures can be found in myositis patients (Robinson 1991). A mechanism that might contribute to the sensation of weakness is that inhibition of homonymous gamma-motoneurons (see above) and the accompanying decrease in muscle spindle input lead to a disfacilitation of alpha-motoneurons which under these conditions require more central effort for their activation.

III-A.3. Intermittent claudication

The various substances possibly involved in the production of ischemic pain have been addressed in Section II-C.1. Lactate does not appear to be of importance for the pain of intermittent claudication, since it activates muscle nociceptors only at high concentrations that are unlikely to occur in a contracting muscle (Kniffki et al. 1978). A combined action of lactate with other substances cannot be excluded, however. Ischemic pain arising in cardiac muscle does not seem to be dependent on lactate, since patients with McArdle's disease, who cannot produce lactate due to an enzyme deficiency, tend to have strong anginal pain (Rodbard 1975).

The situation is complicated by the fact that 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.

BKN (presumably together with PGs) is one of substances that are considered to promote ischemic pain. One reason for this assumption is that BKN has the necessary sensitizing and stimulating properties for muscle nociceptors, another one is the clinical finding that treatment with a proteinase inhibitor, which prevents the release of BKN from its precursor molecule kallidin, prolongs the distance patients with intermittent claudication are able to walk without pain (Digiesi et al. 1975). Another pain-enhancing or -promoting factor are potassium ions which leave the contracting muscle fiber and accumulate in the extracellular fluid during ischemia (Hnik et al. 1976).

In animal experiments, only group-IV muscle receptors have been found to be strongly excited by ischemic contractions (Mense and Stahnke 1983; Kaufman et al. 1984b); therefore, the pain of intermittent claudication may be an example of muscle pain that is exclusively or predominantly due to activity in non-myelinated (as opposed to thin myelinated) nociceptive fibers.

III-A.4. Changes in muscle tension

III-A.4.a. Cramp. A cramp has been defined as a sudden, involuntary, painful contraction of voluntary muscles (Joekes 1982; Layzer 1985). EMG activity during cramp has been reported to be higher than during maximal voluntary contractions (MVC) (Lanari et al. 1973). As possible reasons for the increased electrical activity, excessive activation of alpha- and gamma-motoneurons by descending impulses, decreased inhibition of spinal neurons, and impulse generation in the motoaxon itself, have been proposed (Layzer and Rowland 1971). Cramps are most easily provoked if the muscle is contracted unstretched, i.e., with a minimal distance between its insertion points, so that only little tension builds up within the tendons. This suggests that lack of activation of tendon organs, which are known to inhibit homonymous motoneurons (Granit 1950; Eccles et al. 1957), may promote the development of cramps (Lanari et al. 1973; Weiner and Weiner 1980).

The mechanisms of the pain during cramps are largely unknown. There is evidence indicating that the characteristic feature of a cramp is a contraction of only part of the muscle at an extremely high frequency (Layzer 1985). The resulting shearing forces between contracting and inactive portions of the muscle may activate muscle nociceptors directly and thus elicit pain. An interesting hypothesis is that the mechanical forces may also activate intramuscular motor nerve terminals, a mechanism which could maintain the cramp (Layzer 1985).

III-A.4.b. Long-lasting increase in muscle tone. For a long time, increased muscle tone has been regarded as a possible source of pain. This assumption has never been proven by scientific studies, however. An additional problem is that the term 'muscle tone' is not unequivocally defined. For the purpose of this article, a visco-elastic tone which is determined by the physical properties of the tissue (osmotic pressure of fluids, elastic tension of connective tissue, pressure exerted by fascia), is distinguished from a neuromuscular tone which is caused by a weak and constant activation of a small number of motor units (cf., Clemmesen 1951).

It is generally agreed that a completely relaxed muscle is silent in the EMG (Taverner 1954; Douglas et al. 1989), i.e., under these conditions there is only a visco-elastic tone. In the sense of the above definition, a muscular hypertonus can be due either to a change in passive tissue factors (e.g., inflammatory swelling) or to an increase in neuromuscular activity. The clinical definition of muscle tone often implies resistance to passive movements, i.e., besides properties of the muscle itself spinal reflex phenomena may come into play which contribute to the muscle 'stiffness' (Helliwell et al. 1988; Douglas et al. 1989).

Moderate increases in neuromuscular tone such as occur during mental or psychic stress are usually not perceived as painful and can be abolished by voluntary relaxation. Examples of painful changes of neuromuscular muscle tone are spasms which have been defined as sustained involuntary contractions which can be painful or not (Taverner 1954). Both cramps and spasms cannot be terminated by voluntary relaxation.

Painful spasms are often accompanying symptoms of other diseases such as skeletomotor disturbances in general, rheumatism, or multiple sclerosis (Brochocki 1962; Ashworth 1964). It is unlikely that the pain of muscle spasms is due to a direct mechanical activation of muscle nociceptors by the increased muscle tension, since the increase in intramuscular pressure is probably

not sufficiently high. Another possible mechanism for the activation of nociceptors is that in spastic muscle the blood vessels are compressed so that the muscle contracts under ischemic conditions. As described in Section III-D.2 this situation is assumed by some to lead to a vicious cycle that maintains the spasm.

III-A.5. Section summary

Nociceptor pain is characterized by a peripheral tissue lesion which activates nociceptors. The immediate pain accompanying an acute muscle trauma is probably caused by direct mechanical activation of muscle nociceptors, and the ensuing tenderness by sensitization of the receptors by endogenous substances. The muscle soreness that follows heavy eccentric exercise is accompanied by massive histological alterations such as necrosis of muscle fibers and cellular infiltration. The tenderness of a sore muscle is most likely due to a chemical sensitization of nociceptors. Inflammatory muscle pain is probably caused by a raised background discharge in muscle nociceptors which are excited by inflammatory substances. These substances are also responsible for the sensitization of nociceptors and the associated tenderness. The pain of intermittent claudication does not seem to be dependent on the accumulation of lactate. BKN, PGs and potassium ions are candidate substances that may promote ischemic pain. The pain of a muscle cramp may be due to a contraction of only part of the muscle at a high frequency. The resulting shearing forces could activate muscle nociceptors directly. Muscle tone can be considered as consisting of two components, a visco-elastic and a neuromuscular tone. A muscular hypertonus can be due to a change in either component. Examples of a painful increase of neuromuscular muscle tone are spasms. A possible factor for the activation of nociceptors in spastic muscle is compression of blood vessels which results in ischemic conditions for the contracting muscle.

III-B. Referred muscle pain

It is well known that muscle pain and tenderness, similar to visceral pain, is not (only) perceived at the site of a lesion but usually is referred. If only the referred muscle pain or tenderness is present, localization of the pain source may be difficult (Staff 1988). As muscle lesions often show a typical and constant pattern of pain referral, the patterns can be used for locating the muscle that contains the source of pain. This is particularly true for the pain caused by trigger points which consist of palpable and tender hardenings within a taut band of muscle fibers. Forced palpation of the trigger point elicits a twitch of the taut band and reproduces the referred pain (Travell and Rinzler 1952; Travell and Simons 1983). A remarkable feature of the referral of muscle pain is that it is not confined to the borders of one dermatome or myotome, although its constancy suggests that it follows fixed anatomical pathways (Travell and Rinzler 1952). The elegant experiments of Bogduk (1980) have shown, however, that referral of deep pain from the dorsal to the ventral ramus of a lumbar spinal nerve, i.e., within the same segment, can be particularly effective.

A discussion of the mechanisms of pain referral is not within the scope of this article. As the connectivity of dorsal horn neurons with input from muscle nociceptors is similar to those involved in visceral nociception, the referral concepts developed for visceral pain (convergence-projection theory by Ruch (1949) and convergence-facilitation theory by MacKenzie (1909)) may also apply to muscle pain. A central assumption of 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. The reason for the mislocalization of the pain source is seen in the fact that nociceptive neurons in lower centers receive convergent inputs from various tissues 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, 1989a; Yu and Mense, 1990a), joint (Schaible and Schmidt 1987a) and viscera (Cervero 1983; Foreman et al. 1984) exhibit an extensive convergence from these sources, often in addition to input from the skin.

It is tempting to speculate that the dorsal horn neurons receiving convergent input from, e.g., muscle and joint are responsible for the referral of muscle pain to neighboring joints (Kellgren 1938), but this explanation is probably too simple. Many of the neurons with muscle input have additional RFs in the skin, but referral of muscle pain (experimental and pathological) to the skin does not seem to occur (Kellgren 1938; Lewis 1942). The asssumption that convergent cells mediate cutaneous pain does not solve the problem, because then there is no function for the deep RF; referral of skin pain to deep tissues has not been described. The statement that neurons with RFs in both skin and muscle may be involved in the cutaneous hyper- and hypoalgesia that often accompanies muscle pain (Sinclair et al. 1948; Hockaday and Whitty 1967) is so general that it does not explain anything.

Another relatively new problem for the understanding of referred muscle pain is the finding that dorsal horn neurons can change the size, number and nature (high-threshold or low-threshold) of their RFs rapidly in the presence of noxious stimuli to muscle (Hoheisel and Mense 1989b; Hu et al. 1992). Thus the input convergence onto a given neuron is not a constant

feature; it may develop acutely under the influence of a peripheral lesion. A finding supporting this view is that the stimulus-induced formation of new RFs or changes in existing RFs in animal experiments often take several minutes during which new synaptic connections may become effective (see above). Evidence obtained in clinical studies likewise suggests that referral of deep pain may not be brought about by the use of fixed connections; referral occurs only (or predominantly) if the pain reaches a high intensity (Sinclair et al. 1948; Torebjörk et al. 1984b), and it needs time to develop (Inman and Saunders 1944). A possible interpretation of these data is that referral of muscle pain reflects the formation of new central nervous connections and thus may be another aspect of neuroplasticity.

Whether the mechanisms causing spread or radiation of muscle pain are different from those underlying referral is unknown. Parallels are that radiation is marked only if the pain is intense, that it has a slow time course and that radiation to the skin does not occur (Inman and Saunders 1944). Possibly, referral of muscle pain to closely neighboring regions is perceived as spread or radiation.

An interesting aspect of muscle pain and referral is that visceral pain can be referred not only to the skin but also to skeletal muscle (Sinclair et al. 1948). Thus pain in the pectoralis muscle can accompany coronary infarction (Travell and Rinzler 1952). The muscle to which visceral pain is referred often shows signs of hyperalgesia (Vecchiet et al. 1990).

III-B.1. Section summary

Referred muscle pain is perceived remote from the site of a muscle lesion. The pain is usually referred to other deep tissues and often to sites outside the dermatome or myotome that contains the lesion. One possible reason for the mislocalization of the pain source is that nociceptive dorsal horn neurons receive convergent inputs from various tissues so that higher centers cannot identify the actual input source. A new finding is that the input convergence onto a given neuron may develop acutely under the influence of a peripheral lesion. Thus, referral of muscle pain may reflect the formation of new central nervous connections and may be another aspect of neuroplasticity.

III-C. Other forms of muscle pain

Every nerve lesion that affects primary afferent neurons that are involved in muscle nociception can lead to neurogenic muscle pain which is projected to the region supplied by the neurons. This type of muscle pain is often associated with cutaneous and visceral pain (or dys- and paresthesias) because of concomitant lesions of neurons supplying the skin and viscera. The causes of neurogenic muscle pain are multifold: interruption of peripheral nerves followed by neuroma formation, nerve inflammation, compression of dorsal roots by a herniated disk or a narrow spinal canal, radiculitis or radiculopathy, root avulsion, alcoholic and diabetic neuropathies.

Chronic axotomy distal to a DRG is followd by an increase in the synthesis of the neuropeptides galanin and vasoactive intestinal peptide in DRG cells which normally do not express these peptides. In contrast, SP is depleted in the ganglion cells (Villar et al. 1989; Xu et al. 1990). It is unclear, however, whether the changes in neuropeptide expression, which are followed by changes in neuropeptide content in the spinal cord, are causally related to the pain of nerve lesions.

Central muscle pain can occur as a direct sequel of injury to the spinal cord or higher central nervous centers. A theoretical mechanism, for which direct evidence is still lacking, would be that in the course of chronic muscle pain central nervous neurons are sensitized to such an extent that they become the source of central pain.

Another form of muscle pain for which a central nervous pathogenetic component has been discussed is fibromyalgia. The syndrome is characterized by a combination of widespread pain with tenderness of multiple points of the musculoskeletal system (American College of Rheumatology 1990). The mechanisms underlying the spontaneous pain and formation of tender points in muscle and tendinous insertions are unknown. There is evidence indicating that a sensitization of muscle nociceptors due to disturbances of the microcirculation may be of importance (Henriksson and Bengtsson 1991). Histological signs of an inflammation have not been found by most authors; the moth-eaten appearance of some muscle fibers has been assumed to be caused by local ischemia and spasms (Fassbender and Wegner 1973; Kalyan-Raman et al. 1984). This view is supported by the finding that the levels of high-energy phosphates in the muscles of fibromyalgia patients are lower than normal (Bengtsson et al. 1986). The painful muscles exhibit neither increased tension nor raised activity in the surface EMG (Zidar et al. 1990). Published data on the intramuscular pO_2 in patients with fibromyalgia (or generalized tendomyopathy as it is called in many European countries) (Müller 1991) are conflicting: both a trend to a decrease (Lund et al. 1986) and increase (Brückle et al. 1990) have been reported. This discrepancy may be partly due to the fact that Lund and coworkers used surface electrodes and Brückle and coworkers needle electrodes for measuring pO_2.

The beneficial effect of a sympathetic block on spontaneous pain and pain arising from tender points has been interpreted as indicating that sympathetic efferent activity may be a pathogenetic factor in fibromyalgia (Bengtsson and Bengtsson 1988). However,

recent microneurographic data have not supported the assumption that in fibromyalgia patients the sympathetic activity in muscle nerves is increased (Elam et al. 1992). The analgesic effect of a sympathetic block can therefore not be attributed to the reduction of an increased sympathetic activity but must be due to other reasons, e.g., hypersensitivity of blood vessels or nociceptors to normal levels of sympathetic activity and transmitters (see above).

The hypothesis that changes in the CNS may be relevant for the pathogenesis of fibromyalgia rests largely on the lack of pathological findings in routine laboratory tests. More special tests revealed that the cerebrospinal fluid level of SP is increased (Vaeroy et al. 1988) and the serum level of 5-HT decreased in fibromyalgia patients (Moldofsky 1982). As SP is considered to be a pain-promoting substance, and 5-HT is known to be a transmitter in the descending antinociceptive system (Basbaum and Fields 1984), these findings may be indicative of an altered processing of the pain information in central nervous pathways (for a discussion of possible pathogenetic factors of fibromyalgia, see Russell 1989; Henriksson and Bengtsson 1991).

Chronic muscle pain can also be due to the myofascial pain syndrome which resembles fibromyalgia in some respects. The syndrome is characterized by the presence of single or multiple trigger points in skeletal muscle and/or fascia which are palpable as localized muscle hardenings. Similar to the tender points in fibromyalgia, myofascial trigger points are tender to palpation, but upon pressure stimulation the latter exhibit additional features which are lacking in fibromyalgia, e.g., elicitation of a local twitch response, of referred pain, and of autonomic symptoms (Travell and Simons 1983, 1992). The presence of trigger points is the main feature that distinguishes myofascial pain from fibromyalgia (Simons 1988). The basic pathological process underlying the formation of a trigger point appears to be a local disturbance in the muscle tissue, often a trauma due to overload. The mechanisms that may lead to a chronic perpetuation of an acutely formed trigger point are discussed in Section III-D.1.

III-C.1. Section summary

Every nerve lesion that damages primary afferent neurons involved in muscle nociception can lead to neurogenic muscle pain which is projected to the region supplied by the neurons. As causes of neurogenic muscle pain, interruption or mechanical irritation of peripheral nerves, nerve inflammation, and alcoholic or diabetic neuropathies have to be considered. Fibromyalgia is characterized by a combination of widespread pain with tenderness of multiple points in

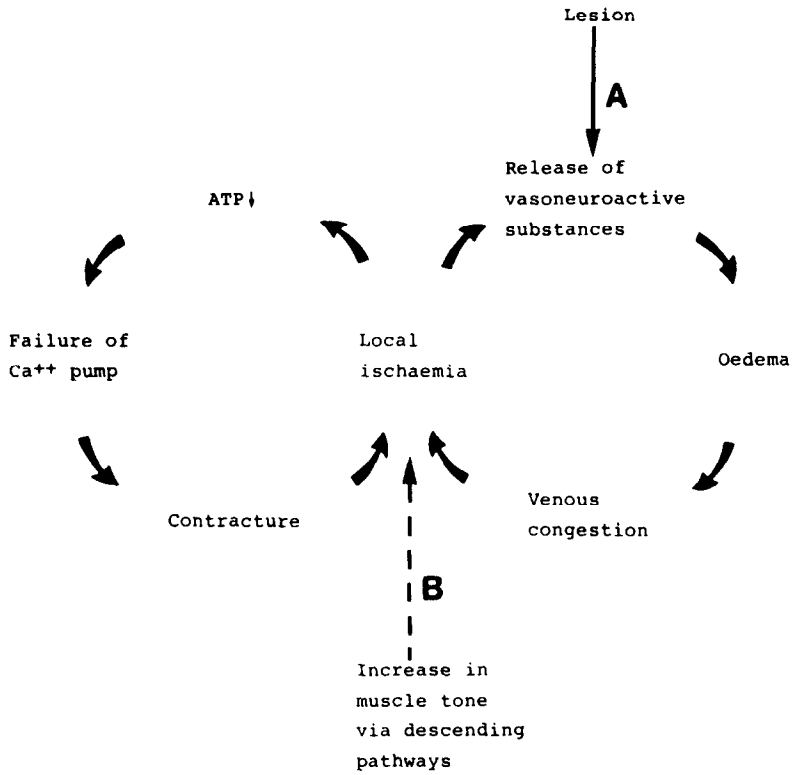

Fig. 16. Local vicious cycles in damaged muscle as a possible peripheral mechanism for chronic muscle pain. The right-hand cycle is assumed to be started by a tissue lesion which releases vasoneuroactive substances (path A). The central factor of the cycles is ischemia which can be produced by venous congestion, local contracture, and tonic activation of muscles by descending motor pathways (path B; modified from Simons 1988; Mense 1991).

the musculoskeletal system. Pathological alterations of the tissue at the tender points as well as altered processing of the pain information in central nervous pathways are being discussed as mechanisms underlying the disease. The myofascial pain syndrome is characterized by the presence of trigger points in skeletal muscle and/or fascia. Trigger points are also tender to palpation but, in contrast to the tender points of fibromyalgia, the former elicit local twitches, referred pain, and autonomic symptoms following local pressure stimulation.

III-D. Possible mechanisms for the transition from acute to chronic muscle pain

III-D.1. Chronic sensitization of peripheral nociceptors

Data obtained in behavioral experiments indicate that following a tissue lesion nociceptive nerve endings can maintain a state of subthreshold sensitization for prolonged periods of time (Nakamura-Craig and Smith 1989). In this state, minute amounts of SP, which are not sufficient for sensitizing nociceptors under normal conditions, can induce a long-lasting sensitization. A similar action has also been described for neurokinin A which is 10 times more potent than SP in this respect (Nakamura-Craig and Gill 1991).

A chronic sensitization of nociceptors can also be due to a persistent tissue lesion that constantly releases sensitizing substances. Such a mechanism may contribute to the maintenance of trigger points in skeletal muscle. A possible mechanism for the formation and maintenance of a trigger point is that a muscle lesion leads to ruptures of the sarcoplasmic reticulum and releases calcium from the intracellular stores. The increased calcium concentration causes sliding of the myosin and actin filaments; the result is a local contracture (myofilament activation without electrical activity) which has a high oxygen consumption and causes hypoxia. The hypoxia is followed by a drop in intracellular ATP which is required as an energy source by the calcium pump. If the function of the pump is impaired, intracellular calcium remains elevated, and the actin and myosin filaments are permanently activated. Instead of a rupture of the sarcoplasmic reticulum, local ischemia can also start the vicious cycle (left-hand cycle in Fig. 16).

An additional factor may be the traumatic or ischemic release of vasoneuroactive substances which produce a local edema that in turn compresses venules and enhances ischemia and hypoxia.

Hypoxia is known to be one of the main factors promoting the release of BKN from plasma proteins (right-hand cycle in Fig. 16). Thus, two vicious cycles can be constructed which are interconnected and perpetuate the contracture (modified after Travell and Simons 1983). Whether local reflex contractions via alpha- or gamma-motoneurons contribute to the maintenance of such a trigger point is an open question.

The above vicious cycle concept is largely hypothetical; the central role of ischemia, however, is supported by the recent finding that the oxygen tension inside myogeloses (which are probably equivalent to trigger points in muscle) is extremely low (Brückle et al. 1990). Thus, the chronic pain and tenderness of a trigger point may be due to a local focus of ischemia that continuously releases BKN and other vasoneuroactive substances which in turn activate and/or sensitize nociceptors.

III-D.2. Vicious cycles at the spinal level

The formation of a muscle pain–spasm–muscle pain vicious cycle as a cause of chronic muscle pain is an old clinical concept (Travell et al. 1942; Cobb et al. 1975). As stated in Section II-H, there are two main types of vicious cycle that have to be discussed as possible explanations of chronic pain, namely motor reflexes via alpha- or gamma-motoneurons (causing spasms) and sympathetic reflexes (leading to ischemia or sensitization of nociceptors). It has to be emphasized that most of the components of the cycles have not been tested experimentally and that available experimental data do not support the vicious cycle concept. This is particularly true for the alpha- and gamma-motor reflexes. A persisting muscle-to-muscle reflex via alpha-motoneurons has never been proven to exist in patients with painful muscle spasms, and results from animal experiments suggest that the gamma-activity to a damaged muscle is reduced rather than increased (see above).

There are further, more general, considerations that speak against a positive feedback mechanism via muscle nociceptors and motoneurons. A fact often overlooked is that according to the flexion reflex concept (Holmqvist and Lundberg 1961) a vicious cycle via alpha-motoneurons should be functional mainly in flexor muscles, because alpha-motoneurons of extensor muscles are inhibited by activation of nociceptors of the homonymous muscle (Paintal 1961). For extensor muscles, an activation of the gamma loop by muscle nociceptors can be postulated as a cause of reflex spasms but available experimental data do not support this assumption. The gamma system can also be activated by descending impulses in extrapyramidal motor pathways. These pathways are under the control of higher cortical centers and are likely to be more active under conditions of psychic stress. Via this connection psychogenic increases in muscle tone might occur. In those patients with tension headache whose facial muscles exhibit increased EMG activity, the pain may be due to such a mechanism.

In patients with temporomandibular dysfunction, the painful masticatory muscles have been reported not to

show increased EMG activity. Instead, the force of MVCs of the painful muscles was reduced (Lund et al. 1991). These data do not support the assumption that painful muscles are reflexly driven to higher activity. In their short review of pain mechanisms in masticatory muscles, Lund et al. (1991) arrive at the conclusion that, at least for temporomandibular pain, the vicious cycle model is incorrect.

One of the crucial assumptions of the vicious cycle concept, namely that a spastic muscle compresses its vasculature, is likewise questionable. Although there is compelling evidence that during MVC the high intramuscular pressure occludes the muscle arteries (Sylvest and Hvid 1959), moderate degrees of static exercise (up to 30% MVC) have been shown to lead to an increase in muscle blood flow in humans (Richardson 1981) and experimental animals (Hilton et al. 1978). Under these conditions the muscular pO_2 is likewise increased (Harrison et al. 1984). Recent data from patients show that the pO_2 inside muscles exhibiting increased tension may be higher than normal (Brückle et al. 1990). However, there are muscles (like the supraspinatus) which show significant reductions in blood flow during static contractions of as little as 16% of MVC (Järvholm et al. 1988).

For a long time, there have been clinical case reports describing muscle inhibitions rather than activations as a sequel to lesions of the musculoskeletal system. An example is the Chassaignac (1856) syndrome which is characterized by an acute paralysis of the arm muscles in children caused by a forceful traction to the upper extremity such as occurs when adults try to keep children from falling down. Reflex inhibitions of muscle groups can also be induced by lesions of joints, ligaments, and bones which must not necessarily be painful (DeAndrade et al. 1965; Brucini et al. 1981; Spencer et al. 1984). On the long-term scale, these inhibitions lead to atrophy of the affected muscle.

At present, no generally accepted concept seems to exist which could explain why muscles react with a spasm in one case of a peripheral lesion and with an inhibition in the other. Possible mechanisms are that postural muscles tend to become hyperactive, and phasic (locomotor) muscles atrophic (Lewit 1984), or that painful muscles are inhibited whereas those muscles that protect the damaged muscle from painful movements become hypertonic (Brügger 1984). Another possibility is that the spasms and involuntary EMG activity observed in some patients with muscle pain are not caused by reflexes at all but by a permanent activation of descending motor pathways because of psychic stress.

The hypothesis that increased sympathetic activity or reflexes contribute to muscle pain is an open question. At least in fibromyalgia patients such a mechanism does not seem to be present, since microneurographic data do not show a sympathetic overactivity (Elam et al. 1992).

III-D.3. Sensitization of central nervous neurons

In view of the well-established findings that dorsal horn neurons can be easily sensitized and that input from muscle via slowly conducting afferent fibers is particularly effective in this regard, it is likely that strong and long-lasting muscle pain leads to a sensitization of central nervous neurons. The sensitization is probably associated with increased expression of IEGs which in turn lead to changes in the protein synthesis of the cell (Morgan and Curran 1989) and to morphological changes (Gobel 1984). These events are likely to perpetuate the abnormal discharge behavior of the cells and to make an effective treatment more difficult.

Taken together, these data suggest that sensitized nociceptive neurons show plastic changes in their behavior, metabolism, and morphology. If the peripheral lesion persists for a prolonged period of time or occurs repeatedly, a maintained state of increased neuronal activity and sensitivity may result which may subjectively be perceived as chronic pain.

III-D.4. Disturbances of the descending antinociceptive system

This mechanism may be of particular importance for muscle pain, as evidence from animal experiments suggests that the nociceptive information from muscle is subjected to a much stronger descending inhibition than is the information from cutaneous nociceptors (Yu and Mense 1990a; Yu et al. 1991). The inhibition of dorsal horn neurons that process input from muscle nociceptors is tonically active; therefore, a pathological alteration of the antinociceptive system may lead to an increased activity and responsiveness of the neurons. Such changes might be perceived as muscle pain by patients. At present, this hypothesis rests solely on data obtained in animal experiments. A possible clinical example of muscle pain which may be partly due to this mechanism is the pain of fibromyalgia. It is not proven, however, that the decreased serum levels of 5-HT in fibromyalgia patients are an indication of an impaired function of the descending antinociceptive system.

III-D.5. Section summary

Following a tissue lesion nociceptive nerve endings have been reported to maintain a state of chronic subthreshold sensitization. Chronic sensitization of nociceptors can also be due to a persistent tissue lesion that constantly releases sensitizing substances. The two main types of vicious cycle that are being discussed as possible explanations of chronic pain, namely motor reflexes via alpha- or gamma-motoneurons and sympa-

thetic reflexes, are not supported by the available experimental data. The gamma system can also be directly activated by descending impulses in extrapyramidal motor pathways, e.g., under conditions of chronic psychic stress. The pain of muscle contraction headache may be due to such a mechanism. Strong and long-lasting muscle pain is likely to lead to a sensitization of central nervous neurons. The sensitization is associated with increased expression of IEGs which in turn lead to metabolic changes in the sensitized cell. If a peripheral lesion persists for a prolonged period of time or occurs repeatedly, a maintained state of central sensitization (hyperexcitability) may result which could subjectively be perceived as chronic pain. A pathological alteration of the descending antinociceptive system may be followed by a similar state of central hyperexcitability.

IV. Unresolved questions

IV-A. What does a muscle nociceptor look like?

Available data indicate that free nerve endings in deep somatic tissues show marked differences in their morphology (Andres et al. 1985; Düring and Andres 1990; Heppelmann et al. 1990). However, the questions as to which type of ending has a nociceptive function and whether there are different morphological types of muscle nociceptor cannot be answered. This problem could be solved in experiments in which single nociceptive afferent units are injected with a marker substance and reconstructed in the electron microscope.

IV-B. Where in the spinal cord do muscle group-IV fibers terminate?

Together with lamina I, lamina II is the main area of termination of cutaneous non-myelinated fibers, but lamina II does not appear to be a projection site for group-IV fibers from muscle, since it is free from labeling following application of HRP to a cat muscle nerve (Nyberg and Blomqvist 1984; Mense and Craig 1988). If one assumes that HRP labels all the spinal terminations of a muscle nerve, one has to conclude that cat muscle group-IV fibers terminate in laminae I and V, but not in lamina II. Muscle group-IV fibers have been reported to drive neurons in lamina I the axons of which do not project in the STT, whereas cells of origin of this tract do not receive input from muscle group-IV fibers (Craig and Kniffki 1985). This raises the question by what pathway the information from group-IV muscle nociceptors reaches higher-order central nervous centers in the cat. In the primate, STT cells driven by group-IV fibers from muscle have been found (Foreman et al. 1979a).

In an anesthetized experimental animal, the numerous non-myelinated afferent fibers of a muscle nerve (Mitchell and Schmidt 1983) have a surprisingly weak action on dorsal horn neurons. Out of several hundred cells with deep RFs recorded from in the cat and rat (Hoheisel and Mense 1990; Yu and Mense 1990a) only a few showed a muscle group-IV fiber input. In contrast, a large proportion of the dorsal horn neurons with cutaneous RFs exhibited C fiber-induced responses under identical experimental conditions. Possible explanations are that in anesthetized animals the group-IV fiber input from muscle is more susceptible to anesthetics than is that from the skin (a particularly strong action of barbiturates on group-IV input has been described by Wall (1967)) and/or that the muscle group-IV fiber input is tonically inhibited (Yu et al. 1991). It is also possible, however, that the efficacy of synaptic connections between muscle group-IV fibers and dorsal horn neurons is completely different from that of cutaneous non-myelinated fibers.

IV-C. How do higher central nervous centers extract the information on muscle nociception from dorsal horn neurons?

Subjectively, muscle pain can be clearly distinguished from cutaneous and visceral pain. However, pain from muscle does not seem to be due to activity in a specific set of central nervous neurons. In studies on dorsal horn neurons in anesthetized cats, an extremely small number of cells with exclusive input from muscle nociceptors were found, if any (Hoheisel and Mense 1989b, 1990). The bulk of the neurons receiving input from muscle nociceptors had additional input from other receptors in the skin and/or other deep somatic tissues. Of course, in animal experiments the anesthesia has a strong influence on the results. On the other hand, the assumption that in the non-anesthetized individual, neurons specific for muscle pain will be present appears to be unlikely since in awake, drug-free cats the proportion of dorsal horn neurons with presumably nociceptive properties (WDR cells) was found to be smaller than in lightly anesthetized animals (Collins 1987). Probably, the neuronal processing of nociceptive information from muscle at spinal and higher levels is highly complicated and not (only) based on the activation of muscle nociceptors and central nervous pathways specific for muscle pain.

Acknowledgements

The author wishes to thank Ms. B. Quencer for expert help with the figures. Particular thanks are due to my wife Inge who invested a lot of time in correcting the references.

References

Abrahams, V.C., Group III and IV receptors of skeletal muscle, Can. J. Physiol. Pharmacol., 64 (1986) 509–514.

Abrahams, V.C. and Swett, J.E., The pattern of spinal and medullary projections from a cutaneous nerve and a muscle nerve of the forelimb of the cat: a study using the transganglionic transport of HRP, J. Comp. Neurol., 246 (1986) 70–84.

Abrahams, V.C., Richmond, F.J.R. and Keane, J., Projections from C2 and C3 nerves supplying muscles and skin of the cat neck: a study using transganglionic transport of horseradish peroxidase, J. Comp. Neurol., 230 (1984) 142–154.

Amano, N., Hu, J.W. and Sessle, B.J., Responses of neurons in feline trigeminal subnucleus caudalis (medullary dorsal horn) to cutaneous, intraoral, and muscle afferent stimuli, J. Neurophysiol., 55 (1986) 227–243.

American College of Rheumatology, Wolfe et al., Critera for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee, Arth. Rheum., 33 (1990) 160–172.

Ammann, B., Gottschall, J. and Zenker, W., Afferent projections from the rat longus capitis muscle studied by transganglionic transport of HRP, Anat. Embryol., 166 (1983) 275–289.

Andres, K.H., von Düring, M. and Schmidt, R.F., Sensory innervation of the Achilles tendon by group III and IV afferent fibers, Anat. Embryol., 172 (1985) 145–156.

Angaut-Petit, D., The dorsal column system. I. Existence of long ascending postsynaptic fibres in the cat's fasciculus gracilis, Exp. Brain Res., 22 (1975) 457–470.

Ansell, B.M. (Ed.), Inflammatory Disorders of Muscle. Clinics in Rheumatic Diseases, Vol. 10, Saunders, London, 1984.

Appelberg, B., Hulliger, M., Johansson, H. and Soika, P., Actions on gamma-motoneurones elicited by electrical stimulation of group I muscle afferent fibres in the hind limb of the cat, J. Physiol., 335 (1983a) 237–253.

Appelberg, B., Hulliger, M., Johansson, H. and Sojka, P., Actions on gamma-motoneurones elicited by electrical stimulation of group II muscle afferent fibres in the hind limb of the cat, J. Physiol., 335 (1983b) 255–273.

Appelberg, B., Hulliger, M., Johansson, H. and Sojka, P., Actions on gamma-motoneurones elicited by electrical stimulation of group III muscle afferent fibres in the hind limb of the cat, J. Physiol., 335 (1983c) 275–292.

Armstrong, R.B., Ogilvie, R.W. and Schwane, J.A., Eccentric exercise-induced injury to rat skeletal muscle, J. Appl. Physiol., 54 (1983) 80–93.

Arvidsson, J. and Raappana, P., An HRP study of the central projections from primary sensory neurons innervating the rat masseter muscle, Brain Res., 480 (1989) 111–118.

Ashworth, B., Preliminary trial of carisoprodol in multiple sclerosis, Practitioner, 192 (1964) 540–542.

Asmussen, E., Observation on experimental muscular soreness, Acta Rheumatol. Scand., 2 (1956) 109–116.

Bakker, D.A., Richmond, F.J.R. and Abrahams, V.C., Central projections from cat suboccipital muscles: a study using transganglionic transport of horseradish peroxidase, J. Comp. Neurol., 228 (1984) 409–421.

Barabé, J., Caranikas, S., D'Orléans-Juste, P. and Regoli, D., New agonist and antagonist analogues of bradykinin, Can. J. Physiol. Pharmacol., 62 (1984) 627–629.

Barasi, S. and Lynn, B., Effects of sympathetic stimulation on mechanoreceptive and nociceptive afferent units from the rabbit pinna, Brain Res., 378 (1986) 21–27.

Barnes, P.J., Brown, M.J., Dollery, C.T., Fuller, R.W., Heavey, D.J. and Ind, P.W., Histamine is released from skin by substance P but does not act as the final vasodilator in the axon reflex, Br. J. Pharmacol., 88 (1986) 741–745.

Basbaum, A.I. and Fields, H.L., Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry, Annu. Rev. Neurosci., 7 (1984) 309–338.

Basbaum, A.J. and Levine, J.D., The contribution of the nervous system to inflammation and inflammatory disease, Can. J. Physiol. Pharmacol., 69 (1991) 647–651.

Beck, P.W. and Handwerker, H.O., Bradykinin and serotonin effects on various types of cutaneous nerve fibres, Pflüger's Arch., 347 (1974) 209–222.

Bengtsson, A. and Bengtsson, M., Regional sympathetic blockade in primary fibromyalgia, Pain, 33 (1988) 161–167.

Bengtsson, A., Hendriksson, K.G. and Larsson, I., Reduced high-energy phospate levels in the painful muscles of patients with primary fibromyalgia, Arthr. Rheum., 29 (1986) 817–821.

Bennet, G.J., Nishikawa, N., Lu, G.-W., Hoffert, M.J. and Dubner, R., The morphology of dorsal column postsynaptic spinomedullary neurons in the cat, J. Comp. Neurol., 224 (1984) 568–578.

Berberich, P., Hoheisel, U. and Mense, S., Effects of a carrageenan-induced myositis on the discharge properties of group III and IV muscle receptors in the cat, J. Neurophysiol., 59 (1988) 1395–1409.

Besson, J.M. and Chaouch, A., Peripheral and spinal mechanisms of nociception, Physiol. Rev., 67 (1987) 67–186.

Bessou, P. and Laporte, Y., Activation des fibres afférentes amyéliniques d'origine musculaire, Compt. Rend. Soc. Biol. (Paris), 152 (1958) 1587–1590.

Bessou, P. and Laporte, Y., Activation des fibres afférentes myélinisées de petit calibre d'origine musculaire (fibres du groupe III), J. Physiol. (Paris), 52 (1960) 19–20.

Bessou, P. and Perl, E.R., Response of cutaneous sensory units with unmyelinated fibres to noxious stimuli, J. Neurophysiol., 32 (1969) 1025–1043.

Bogduk, N., Lumbar dorsal ramus syndrome, Med. J. Aust., 2 (1980) 537–541.

Brain, S.D., Williams, T.J., Tippins, J.R., Morris, H.R. and MacIntyre, I., Calcitonin gene-related peptide is a potent vasodilator, Nature, 313 (1985) 54–56.

Bravo, R., Growth factor inducible genes in fibroblasts. In: A. Habenicht (Ed.), Growth Factors, Differentiation Factors and Cytokines, Springer, Berlin, 1990, pp. 324–343.

Brimijoin, S., Lundberg, J.M., Brodin, E., Hökfelt, T. and Nilsson, G., Axonal transport of substance P in the vagus and sciatic nerves of the guinea pig, Brain Res., 191 (1980) 443–457.

Brochocki, G., Die schmerzhaften Muskelkontrakturen bei rheumatischen Erkrankungen und deren Behandlung. Praxis (Schweizerische Rundschau für Medizin), 31 (1962) 790–793.

Brock, L.G., Eccles, J.C. and Rall, W., Experimental investigations on the afferent fibres in muscle nerves, Proc. R. Soc. (Lond.) B, 138 (1951) 453–475.

Broton, J.G. and Sessle, B.J., Reflex excitation of masticatory muscles induced by algesic chemicals applied to the temporomandibular joint of the cat, Arch. Oral Biol., 33 (1988) 741–747.

Brown, A.G., Ascending and long spinal pathways: dorsal columns, spinocervical tract and spinothalamic tract. In: A. Iggo (Ed.), Handbook of Sensory Physiology, Vol. 2, Somatosensory System, Springer, Heidelberg, 1973, pp. 315–338.

Brown, A.G., Organization in the Spinal Cord, The Anatomy and Physiology of Identified Neurones, Springer, Heidelberg, 1981.

Brown, A.G., Rose, P.K. and Snow, P.J., The morphology of hair follicle afferent fibre collaterals in the spinal cord of the cat, J. Physiol., 272 (1977) 779–797.

Brucini, M., Duranti, R., Galletti, R., Pantaleo, T. and Zucchi, P.L., Pain thresholds and electromyographic features of periarticular muscles in patients with osteoarthritis of the knee, Pain, 10 (1981) 57–66.

Brückle, W., Suckfüll, M., Fleckenstein, W., Weiss, C. and Müller, W., Gewebe-pO_2-Messung in der verspannten Rückenmuskulatur (M. erector spinae), Z. Rheumatol., 49 (1990) 208–216.

Brügger, A., Neurologische und morphologische Grundlagen der sogenannten rheumatischen Schmerzen – ein Beitrag zum Verständnis der Funktionskrankheiten. In: M. Berger, F. Gerstenbrand and K. Lewit (Eds.), Schmerzstudien 6, Schmerz und Bewegungssystem, Fischer, Stuttgart, 1984, pp. 56–79.

Brushart, T.M and Mesulam, M.-M., Transganglionic demonstration of central sensory projections from skin and muscle with HRP-lectin conjugates, Neurosci. Lett., 17 (1980) 1–6.

Brushart, T.M., Henry, E.W. and Mesulam, M.-M., Reorganization of muscle afferent projection accompanies peripheral nerve regeneration, Neuroscience, 6 (1981) 2053–2061.

Buck, S.H., Walsh, J.H., Yamamura, H.I. and Burks, T.F. Neuropeptides in sensory neurons, Life Sci., 30 (1982) 1857–1866.

Burgess, G.M., Mullaney, I., McNeil, M., Dunn, P.M. and Rang, H.P., Second messengers involved in the mechanisms of bradykinin on sensory neurones on culture, J. Neurosci., 9 (1989) 3314–3325.

Burke, D., Critical examination of the case for or against fusimotor involvement in disorders of muscle tone. In: J.E. Desmedt (Ed.), Advances in Neurology, Vol. 39, Motor Control Mechanisms in Health and Disease, Raven Press, New York, 1983, pp. 133–150.

Burstein, R., Cliffer, K.D. and Giesler, G.J., Cells of origin of the spinohypothalamic tract in the rat, J. Comp. Neurol., 291 (1990) 329–344.

Caldwell, P.C., Intracellular pH, Int. Rev. Cytol., 5 (1956) 229–277.

Calverley, R.K.S. and Jones, D.G., Contributions of dendritic spines and perforated synapses to synaptic plasticity, Brain Res. Rev., 15 (1990) 215–249.

Calvino, B., Villanueva, L. and Le Bars, D., Dorsal horn (convergent) neurones in the intact anaesthetized arthritic rat. I. Segmental excitatory influences, Pain, 28 (1986) 81–98.

Cameron, A.A., Leah, J.D. and Snow, P.J., The coexistence of neuropeptides in feline sensory neurons, Neuroscience, 27 (1988) 969–979.

Carstens, E. and Trevino, D.L., Laminar origins of spinothalamic projections in the cat as determined by the retrograde transport of horseradish peroxidase, J. Comp. Neurol., 182 (1978) 151–166.

Casey, K.L. and Morrow, T.J., Ventral posterior thalamic neurons differentially responsive to noxious stimulation of the awake monkey, Science, 221 (1983) 675–677.

Cavanagh, P.R., On 'muscle action' vs. 'muscle contraction', J. Biomech., 21 (1988) 69.

Cervero, F., Somatic and visceral inputs to the thoracic spinal cord of the cat: effects of noxious stimulation of the biliary system, J. Physiol., 337 (1983) 51–67.

Cervero, F. and Connell, L.A., Fine afferent fibers from viscera do not terminate in the substantia gelatinosa of the thoracic spinal cord, Brain Res., 294 (1984) 370–374.

Cervero, F., Iggo, A. and Ogawa, H., Nociceptor-driven dorsal horn neurones in the lumbar spinal cord of the cat, Pain, 2 (1976) 5–24.

Cervero, F., Schaible, H.-G. and Schmidt, R.F., Tonic descending inhibition of spinal cord neurones driven by joint afferents in normal cats and in cats with an inflammed knee joint, Exp. Brain Res., 83 (1991) 675–678.

Chang, H.-T., Neurophysiological interpretation of acupuncture analgesia, Endeavour, 4 (1980) 92–96.

Chassaignac, C.M.E., De la paralysie douloureuse des jeunes enfants, Arch. Gén. Méd., 5, Ser. I, (1856) 653–669.

Chiang, C.-Y., Chang, C.T., Chu, H.-L. and Yang, L.F., Peripheral afferent pathway for acupuncture analgesia, Sci. Sin., 16 (1973) 210–217.

Clemmesen, S., Some studies on muscle tone, Proc. R. Soc. Med., 44 (1951) 637–646.

Cobb, C.R., DeVries, H.A., Urban, R.T., Luekens, C.A. and Bagg, R.J., Electrical activity in muscle pain, Am. J. Phys. Med., 54 (1975) 80–87.

Coderre, T.J., Basbaum, A.I. and Levine, J.D., Neural control of vascular permeability: interactions between primary afferents, mast cells, and sympathetic efferents, J. Neurophysiol., 62 (1989) 48–58.

Coffman, J.D., The effect of aspirin on pain and hand blood flow responses to intra-arterial injection of bradykinin in man, Clin. Pharmacol. Ther., 7 (1966) 26–37.

Coggeshall, R.E. and Ito, H., Sensory fibres in ventral roots L7 and S1 in the cat, J. Physiol., 267 (1977) 215–235.

Coggeshall, R.E., Maynard, C.W. and Langford, L.A., Unmyelinated sensory and preganglionic fibers in rat L6 and S1 ventral spinal roots, J. Comp. Neurol., 193 (1980) 41–47.

Collins, J.G., A descriptive study of spinal dorsal horn neurons in the physiologically intact, awake, drug free cat, Brain Res., 416 (1987) 34–42.

Couture, R. and Kérouac, R., Plasma protein extravasation induced by mammalian tachykinins in rat skin: influence of anaesthetic agents and acetylcholine antagonist, Br. J. Pharmacol., 91 (1987) 265–273.

Craig, A.D. and Kniffki, K.-D., Spinothalamic lumbosacral lamina I cells responsive to skin and muscle stimulation in the cat, J. Physiol., 365 (1985) 197–221.

Cuello, A.C., Peptides as neuromodulators in primary sensory neurons, Neuropharmacology, 26 (1987) 971–979.

DeAndrade, J.R., Grant, C. and Dixon, A.St.J., Joint distension and reflex muscle inhibition in the knee, J. Bone Joint Surg., 47 (1965) 313–322.

DeVere, R. and Bradley, W.G., Polymyositis: its presentation, morbidity and mortality, Brain, 98 (1975) 637–666.

Devor, M., Wall, P.D. and McMahon, S.B., Dichotomizing somatic nerve fibers exist in rats but they are rare, Neurosci. Lett., 49 (1984) 187–192.

DeVries, H.A., Quantitative electromyographic investigation of the spasm theory of muscle pain, Am. J. Phys. Med., 45 (1966) 119–134.

Dickenson, A.H. and Sullivan, A.F., NMDA receptors and central hyperalgesic states, Pain, 46 (1991) 344–345.

Diehl, B., Hoheisel, U. and Mense, S., Histological and neurophysiological changes induced by carrageenan in skeletal muscle of cat and rat, Agents Actions, 25 (1988) 210–213.

Dietrichson, P., Tonic ankle reflex in Parkinsonian rigidity and in spasticity, Acta Neurol. Scand., 47 (1971) 163–182.

Digiesi, V., Bartoli, V. and Dorigo, B., Effect of a proteinase inhibitor on intermittent claudication or on pain at rest in patients with peripheral arterial disease, Pain, 1 (1975) 385–389.

DiRosa, M., Giroud, J.P. and Willoughby, D.A., Studies of the mediators of the acute inflammatory response induced in rats in different sites by carrageenan and turpentine, J. Pathol., 104 (1971) 15–29.

Dong, W.K., Ryu, H. and Wagman, I.H., Nociceptive responses of neurons in medial thalamus and their relationship to spinothalamic pathways, J. Neurophysiol., 41 (1978) 1592–1613.

Dorpat, T.L. and Holmes, T.H., Backache of muscle tension origin. In: W.S. Kroger (Ed.), Psychosomatic Obstetrics, Gynecology and Endocrinology, CC Thomas, Springfield, IL, 1962, pp. 425–436.

Dougherty, P.M. and Willis, W.D., Enhancement of spinothalamic neuron responses to chemical and mechanical stimuli following combined micro-iontophoretic application of *N*-methyl-D-aspartic acid and substance P, Pain, 47 (1991) 85–93.

Douglas, A.J., Walsh, E.G., Wright, G.W. and Edmond, P., Muscle tone around the human knee in paraplegia, Quart. J. Exp. Physiol., 74 (1989) 897–905.

Dragunow, M., Currie, R.W., Faull, R.L.M., Robertson, H.A. and Jansen, K., Immediate-early genes, kindling and long-term potentiation, Neurosci. Biobehav. Rev., 13 (1989) 301–313.

Draisci, G. and Iadarola, M.J., Temporal analysis of increases in

c-*fos* preprodynorphin and preproenkephalin mRNAs in rat spinal cord, Mol. Brain Res., 6 (1989) 31–37.

Dreyer, D.A., Schneider, R.J., Metz, C.B. and Whitsel, B.L., Differential contributions of spinal pathways to body representation in postcentral gyrus of *Macaca mulatta*, J. Neurophysiol., 37 (1974) 119–145.

Drummond, P.D., Finch, P.M. and Smythe, G.A., Reflex sympathetic dystrophy: the significance of differing plasma catecholamine concentrations in affected and unaffected limbs, Brain, 114 (1991) 2025–2036.

Dubner, R., Hyperalgesia and expanded receptive fields, Pain, 48 (1992) 3–4.

Dubner, R. and Bennett, G.J., Spinal and trigeminal mechanisms of nociception, Annu. Rev. Neurosci., 6 (1983) 381–418.

Dubner, R. and Ruda, M.A., Activity-dependent neuronal plasticity following tissue injury and inflammation, Trends Neurol. Sci., 15 (1992) 96–103.

Dubner, R., Kenshalo, D.R., Maixner, W., Bushnell, M.C. and Oliveras, J.-L., The correlation of monkey medullary dorsal horn neuronal activity and the perceived intensity of noxious heat stimuli, J. Neurophysiol., 62 (1989) 450–457.

Düring, M. von and Andres, K.H., Topography and ultrastructure of group III and IV nerve terminals of the cat's gastrocnemius-soleus muscle. In: W. Zenker and W.L. Neuhuber (Eds.), The Primary Afferent Neuron, Plenum Press, New York, 1990, pp. 35–41.

Duggan, A.W., Hendry, I.A., Morton, C.R., Hutchison, W.D. and Zhao, Z.Q., Cutaneous stimuli releasing immunoreactive substance P in the dorsal horn of the cat, Brain Res., 451 (1988) 261–273.

Duggan, A.W., Hope, P.J., Lang, C.W. and Williams C.A., Sustained isometric contraction of skeletal muscle results in release of immunoreactive neurokinins in the spinal cord of the anesthetized cat, Neurosci. Lett., 122 (1991) 191–194.

Eccles, R.M. and Lundberg, A., Synaptic actions in motoneurones by afferents which may evoke the flexion reflex, Arch. Ital. Biol., 97 (1959) 199–221.

Eccles, J.C., Eccles, R.M. and Lundberg, A., Synaptic actions on motoneurones caused by impulses in Golgi tendon organ afferents, J. Physiol., 138 (1957) 227–252.

Elam, M., Johansson, G. and Wallin, B.G., Do patients with primary fibromyalgia have and altered muscle sympathetic nerve activity?, Pain, 48 (1992) 371–375.

Ellaway, P.H., Murphy, P.R. and Tripathi, A., Closely coupled excitation of gamma-motoneurones by group III muscle afferents with low mechanical threshold in the cat, J. Physiol., 331 (1982) 481–498.

Emre, M. and Mathies, H. (Eds.), Muscle Spasms and Pain, Parthenon, Park Ridge, 1988.

Fagius, J., Karhuvaara, S. and Sundlöf, G., The cold pressor test: effects on sympathetic nerve activity in human muscle and skin nerve fascicles, Acta Physiol. Scand., 137 (1989) 325–334.

Fassbender, H.G. and Wegner, K., Morphologie und Pathogenese des Weichteilrheumatismus, Z. Rheumaforschung, 32 (1973) 355–374.

Feinstein, B., Langton, J.N.K., Jameson, R.M. and Schiller, F., Experiments on pain referred from deep somatic tissues, J. Bone Joint Surg., 36 (1954) 981–997.

Ferrell, W.R., Wood, L. and Baxendale, R.H., The effect of acute joint inflammation on flexion reflex excitability in the decerebrate, low-spinal cat, Quart. J. Exp. Physiol., 73 (1988) 95–102.

Fields, H.L., Clanton, C.H. and Anderson, S.D., Somatosensory properties of spinoreticular neurons in the cat, Brain Res., 120 (1977) 49–66.

Fishbain, D.A., Goldberg, M., Meagher, B.R., Steele, R. and Rosomoff, H., Male and female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria, Pain, 26 (1986) 181–197.

Fjällbrant, N. and Iggo, A., The effect of histamine, 5-hydroxytryptamine and acetylcholine on cutaneous afferent fibres, J. Physiol., 156 (1961) 578–590.

Fock, S. and Mense, S., Excitatory effects of 5-hydroxytryptamine, histamine, and potassium ions on muscular group IV afferent units: a comparison with bradykinin. Brain Res., 105 (1976) 459–469.

Fontaine, B., Klarsfeld, A., Hökfelt, T. and Changeux, J.P., Calcitonin gene-related peptide, a peptide present in spinal cord motoneurons, increases the number of acetylcholine receptors in primary cultures of chick embryo myotubes, Neurosci. Lett., 71 (1986) 59–65.

Foreman, R.D., Kenshalo, D.R., Schmidt, R.F. and Willis, W.D., Field potentials and excitation of primate spinothalamic neurones in response to volleys in muscle afferents, J. Physiol., 286 (1979a) 197–213.

Foreman, R.D., Schmidt, R.F. and Willis, W.D., Effects of mechanical and chemical stimulation of fine muscle afferents upon primate spinothalamic tract cells, J. Physiol., 286 (1979b) 215–231.

Foreman R.D., Blair R.W. and Weber, R.N., Viscerosomatic convergence onto T2-T4 spinoreticular, spinoreticular-spinothalamic, and spinothalamic tract neurons in the cat, Exp. Neurol., 85 (1984) 597–619.

Franco-Cereceda, A., Saria, A. and Lundberg, J.M., Differential release of calcitonin gene-related peptide and neuropeptide Y from the isolated heart by capsaicin, ischaemia, nicotine, bradykinin and ouabain, Acta Physiol. Scand., 135 (1989) 173–187.

Franz, M. and Mense, S., Muscle receptors with group IV afferent fibres responding to application of bradykinin, Brain Res., 92 (1975) 369–383.

Freeman, M.A.R. and Wyke, B., Articular reflexes at the ankle joint: an electromyographic study of normal and abnormal influences of ankle-joint mechanoreceptors upon reflex activity in the leg muscles, Br. J. Surg., 54 (1967) 990–1001.

Frenk, H., Bossut, D., Urca, G. and Mayer, D.J., Is substance P a primary afferent neurotransmitter for nociceptive input?. I. Analysis of pain-related behaviors resulting from intrathecal administration of substance P and 6 excitatory compounds, Brain Res., 455 (1988) 223–231.

Fricton, J.R., Myofascial pain syndromes: characteristics and epidemiology. In: J.R. Fricton and A.A. Awad (Eds.), Myofascial Pain and Fibromyalgia, Adv. Pain Res. Ther., Vol. 17, 1990, pp. 107–127.

Fridén, J., Sfakianos, P.N., Hargens, A.R. and Akeson, W.H., Residual muscular swelling after repetitive eccentric contractions, J. Orthop. Res., 6 (1988) 493–498.

Gamse, R. and Saria, A., Potentiation of tachykinin-induced plasma protein extravasation by calcitonin gene-related peptide, Eur. J. Pharmacol., 114 (1985) 61–66.

Gardner, E., Reflex muscular responses to stimulation of articular nerves in the cat, Am. J. Physiol., 161 (1950) 133–141.

Garry, M.G., Miller, K.E. and Seybold, V.S., Lumbar dorsal root ganglia of the cat: a quantitative study of peptide immunoreactivity and cell size, J. Comp. Neurol., 284 (1989) 36–47.

Garthwaite, J., Glutamate, nitric oxide and cell-cell signalling in the nervous system, Trends Neurol. Sci., 14 (1991) 60–67.

Gasser, H.S. and Grundfest, H., Axon diameters in relation to the spike dimensions and the conduction velocity im mammalian A fibers, Am. J. Physiol., 127 (1939) 393–414.

Gautron, M. and Guilbaud, G. Somatic responses of ventrobasal thalamic neurones in polyarthritic rats, Brain Res. 237 (1982) 459–471.

Gebhart, G.F. and Ness, T.J., Central mechanisms of visceral pain, Can. J. Physiol. Pharmacol., 69 (1991) 627–634.

Gobel, S., An electron microscopic analysis of the trans-synaptic effects of peripheral nerve injury subsequent to tooth pulp extirpations on neurons in lamina I and II of the medullary dorsal horn, J. Neurosci., 4 (1984) 2281–2290.

Gomazkow, O.A., Das Kallikrein-Kinin-System bei Myokardischämie und Herzinfarkt – Experimentelle Untersuchungen. In: D. Gross et al. (Eds.), Ischämie-Morphologie, Biochemie, Experimentelle Parmakologie, Klinik und Therapie, Schattauer, Stuttgart, 1975, pp. 101–112.

Gottschall, J., Zenker, W., Neuhuber, W., Mysicka, A. and Müntener, M., The sternomastoid muscle of the rat and its innervation. Muscle fiber composition, perikarya and axons of efferent and afferent neurons, Anat. Embryol., 160 (1980) 285–300.

Granit, R., Reflex self-regulation of muscle contraction and autogenetic inhibition, J. Neurophysiol., 13 (1950) 351–372.

Grassi, C. and Passatore, M., Action of the sympathetic system on skeletal muscle, Ital. J. Neurol. Sci., 9 (1988) 23–28.

Grigg, P., Schaible, H.-G. and Schmidt, R.F., Mechanical sensitivity of group III and IV afferents from posterior articular nerve in normal and inflamed cat knee, J. Neurophysiol., 55 (1986) 635–643.

Guilbaud, G., Peripheral and central electrophysiological mechanisms of joint and muscle pain. In: R. Dubner, G.F. Gebhart and M.R. Bond (Eds.), Proc. Vth World Congress on Pain, Elsevier, Amsterdam, 1988, pp. 201–215.

Guilbaud, G., Central neurophysiological processing of joint pain on the basis of studies performed in normal animals and in models of experimental arthritis, Can. J. Physiol. Pharmacol., 69 (1991) 637–646.

Guilbaud, G., Caille, D., Besson, J.M. and Benelli, I.G., Single units activities in ventral posterior and posterior group thalamic nuclei during nociceptive and non nociceptive stimulations in the cat, Arch. Ital. Biol., 115 (1977) 38–56.

Guilbaud, G., Peschanski, M., Gautron, M. and Binder, D., Neurones responding to noxious stimulation in VB complex and caudal adjacent regions in the thalamus of the rat, Pain, 8 (1980) 303–318.

Guilbaud, G., Benoist, J.M., Eschalier, A., Kayser, V., Gautron, M. and Attal, N., Evidence for central phenomena participating in the changes of responses of ventrobasal thalamic neurons in arthritic rats, Brain Res., 484 (1989) 383–388.

Häbler, H.J., Jänig, W. and Koltzenburg, M., A novel type of unmyelinated chemosensitive nociceptor in the acutely inflamed urinary bladder, Agents Actions, 25 (1988) 219–221.

Haley, J., Ketchum, S. and Dickenson, A., Peripheral kappa opioid modulation of the formalin response: an electrophysiological study in the rat, Eur. J. Pharmacol., 191 (1990) 437–446.

Handwerker, H.O. and Reeh, P.W., Pain and inflammation. In: M.R. Bond, I.E. Charlton and C.J. Woolf (Eds.), Proc. VIth World Congress on Pain, Elsevier, Amsterdam, 1991, pp. 59–70.

Handwerker, H.O., Kilo, S. and Reeh, P.W., Unresponsive afferent nerve fibres in the sural nerve of the rat, J. Physiol., 435 (1991) 229–242.

Hanson, J., Hypoglossal high threshold afferents projecting to the secondary somatosensory area in the cat, Arch. Ital. Biol., 123 (1985) 63–68.

Hardy, T.L., Bertrand, G. and Thompson, C.J., Position and organization of thalamic cellular activity during diencephalic recording. II. Joint- and muscle-evoked activity, Appl. Neurophysiol., 43 (1980) 28–36.

Harpuder, K. and Stein, I., Studies on the nature of pain arising from an ischemic limb, Am. Heart J., 25 (1943) 429–448.

Harrison, D.K., Höper, J., Günther, H., Vogel, H., Frank, K.H., Brunner, M., Ellermann, R. and Kessler, M., Microcirculation and pO_2 in skeletal muscle during respiratory hypoxia and stimulation, Adv. Exp. Med. Biol., 169 (1984) 477–485.

Hassler, R., Wechselwirkungen zwischen dem System der schnellen Schmerzempfindung und dem des langsamen, nachhaltigen Schmerzgefühles, Langenbecks Arch. Chir., 342 (1976) 47–61.

He, L., Involvement of endogenous opioid peptides in acupuncture analgesia, Pain, 31 (1987) 99–121.

He, X., Proske, U., Schaible, H.-G. and Schmidt, R.F., Acute inflammation of the knee joint in the cat alters responses of flexor motoneurons to leg movements, J. Neurophysiol., 59 (1988) 326–340.

Helliwell, P.S., Howe, A. and Wright, V., Lack of objective evidence of stiffness in rheumatoid arthritis, Annu. Rheum. Dis., 47 (1988) 754–758.

Hellon, R.F. and Mitchell, D., Characteristics of neurones in the ventro-basal thalamus of the rat which respond to noxious stimulation of the tail, J. Physiol., 250 (1975) 29–30.

Henriksson, K.G. and Bengtsson, A., Fibromyalgia – a clinical entity?, Can. J. Physiol. Pharmacol., 69 (1991) 672–677.

Henry, J.L., Effects of substance P on functionally identified units in cat spinal cord, Brain Res., 114 (1976) 439–451.

Heppelmann, B., Messlinger, K., Neiss, W.F. and Schmidt, R.F., Ultrastructural three-dimensional reconstruction of group III and group IV sensory nerve endings ('free nerve endings') in the knee joint capsule of the cat: evidence for multiple receptive sites, J. Comp. Neurol., 292 (1990) 103–116.

Hertel, H.-C., Howaldt, B. and Mense, S., Responses of group IV and group III muscle afferents to thermal stimuli, Brain Res., 113 (1976) 201–205.

Hilton, S.M., Hudlická, O. and Marshall, J.M., Possible mediators of functional hyperaemia in skeletal muscle, J. Physiol., 282 (1978) 131–147.

Hnik, P., Holas, M., Krekule, I., Kriz, N., Mejsnar, J., Smiesko, V., Ujec, E. and Vyskocil, F., Work-induced potassium changes in skeletal muscle and effluent venous blood assessed by liquid ion-exchanger microelectrodes, Pflüger's Arch., 362 (1976) 85–94.

Hockaday, J.M. and Whitty, C.W.M., Patterns of referred pain in the normal subject, Brain, 90 (1967) 481–496.

Hoheisel, U. and Mense, S., Morphological and cytochemical properties of physiologically identified dorsal root ganglion cells in the rat, Pflüger's Arch., 413 (1989a) R27.

Hoheisel, U. and Mense S., Long-term changes in discharge behaviour of cat dorsal horn neurones following noxious stimulation of deep tissues, Pain, 36 (1989b) 239–247.

Hoheisel, U. and Mense, S., Response behaviour of cat dorsal horn neurones receiving input from skeletal muscle and other deep somatic tissues, J. Physiol., 426 (1990) 265–280.

Hoheisel, U., Lehmann-Willenbrock, E. and Mense, S., Termination patterns of identified group II and III afferent fibres from deep tissues in the spinal cord of the cat, Neuroscience, 28 (1989) 495–507.

Hökfelt, T., Johansson, O., Ljungdahl, Å., Lundberg, J.M. and Schultzberg, M., Peptidergic neurones, Nature, 284 (1980) 515–521.

Holmqvist, B. and Lundberg, A., Differential supraspinal control of synaptic actions evoked by volleys in the flexion reflex afferents in alpha motoneurones, Acta Physiol. Scand., 54, Suppl. 186 (1961) 1–51.

Holzer, P., Local effector functions of capsaicin-sensitive sonsory nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides, Neuroscience, 24 (1988) 739–768.

Hong, S.K., Kniffki, K.D. and Schmidt, R.F., Reflex discharges of extensor and flexor gamma motoneurones by chemically induced muscle pain, Pain, Abst. 1 (1978) 58.

Hong, S.K., Kniffki, K.-D., Mense, S., Schmidt, R.F. and Wendisch, M., Descending influences on the responses of spinocervical tract neurones to chemical stimulation of fine muscle afferents, J. Physiol., 290 (1979) 129–140.

Hore, J., Preston, J.B., Durkovic, R.G. and Cheney, P.D., Responses of cortical neurons (areas 3a and 4) to ramp stretch of hind limb muscles in the baboon, J. Neurophysiol., 39 (1976) 484–500.

Hough, T., Ergographic studies in muscular soreness, Am. J. Physiol., 7 (1902) 76–92.

Howell, J.N., Chila, A.G., Ford, G., David, D. and Gates, T., An electromyographic study of elbow motion during postexercise muscle soreness, J. Appl. Physiol., 58 (1985) 1713–1718.

Hu, J.W., Sessle, B.J., Raboisson, P., Dallel, R. and Woda, A., Stimulation of craniofacial muscle afferents induces prolonged facilitatory effects in trigeminal nociceptive brain-stem neurones, Pain, 48 (1992) 53–60.

Huang, C.-S., Hiraba, H. and Sessle, B.J., Input-output relationships of the primary face motor cortex in the monkey (*Macaca fascicularis*), J. Neurophysiol., 61 (1989) 350–362.

Hunt, S.P., Pini, A. and Evan, G., Induction of c-*fos*-like protein in spinal cord neurons following sensory stimulation, Nature, 328 (1987) 632–634.

Hylden, J.L.K., Hayashi, H., Dubner, R. and Bennett, G.J., Physiology and morphology of the lamina I spinomesencephalic projection, J. Comp. Neurol., 247 (1986) 505–515.

Hylden, J.L.K., Nahin, R.L., Traub, R.J. and Dubner, R., Expansion of receptive fields of spinal lamina I projection neurons in rats with unilateral adjuvant-induced inflammation: the contribution of dorsal horn mechanisms, Pain, 37 (1989) 229–243.

Ialenti, A., Ianaro, A., Moncada, S. and Di Rosa, M., Modulation of acute inflammation by endogenous nitric oxide, Eur. J. Pharmacol., 211 (1992) 177–182.

Ichikawa, H., Nishikawa, S., Wakisaka, S., Matsuo, S., Takano, Y. and Akai, M., Occurrence of substance P-like immunoreactive nerve fibers in Krause corpuscles of the dog's tongue, Acta Anat., 131 (1988) 215–217.

Iggo, A., Non-myelinated afferent fibres from mammalian skeletal muscle, J. Physiol., 155 (1961) 52–53.

Iggo, A., Cutaneous thermoreceptors in primates and sub-primates, J. Physiol., 200 (1969) 403–430.

Inman, V.T. and Saunders, J.B., de C.M., Referred pain from skeletal structures, J. Nerv. Ment. Dis., 99 (1944) 660–667.

Ishida-Yamamoto, A. and Tohyama, M., Calcitonin gene-related peptide in the nervous tissue, Prog. Neurobiol., 33 (1990) 335–386.

Iwamura, Y., Kniffki, K.-D., Mizumura, K. and Wilberg, K., Responses of feline SI neurones to noxious stimulation of muscle and tendon, Pain, 1 (1981) 213.

Iwata, K., Itoga, H., Ikukawa, A., Hanashima, N., and Sumino, R., Distribution and response characteristics of masseteric nerve-driven neurons in two separate cortical projection areas of cats, Brain Res., 342 (1985) 179–182.

Järvholm, U., Styf, J., Suurkula, M. and Herberts, P., Intramuscular pressure and muscle blood flow in supraspinatus, Eur. J. Appl. Physiol., 58 (1988) 219–224.

Jennische, E., Hagberg, H. and Haljamäe, H., Extracellular potassium concentration and membrane potential in rabbit gastrocnemius muscle during tourniquet ischemia, Pflüger's Arch., 392 (1982) 335–339.

Jessen, C., Feistkorn, G. and Nagel, A., Temperature sensitivity of skeletal muscle in the conscious goat, J. Appl. Physiol., 54 (1983) 800–886.

Jinnai, K., Chihara, K., Kanda, F., Tada, K. and Fujita, T., Calcitonin gene-related peptide enhances spontaneous acetylcholine release from the rat motor nerve terminal, Neurosci. Lett., 103 (1989) 64–68.

Joekes, A.M., Cramp: a review, J.R. Soc. Med., 75 (1982) 546–549.

Jones, A.K.P., Brown, W.D., Friston, K.J., Qi, L.Y. and Frackowiak, R.S.J., Cortical and subcortical localization of response to pain in man using positron emission tomography, Proc. R. Soc. (Lond.) B, 244 (1991) 39–44.

Jones, D.A., Newham, D.J. and Clarkson, P.M., Skeletal muscle stiffness and pain following eccentric exercise of the elbow flexors, Pain, 30 (1987) 233–242.

Jones, D.A., Newham, D.J. and Torgan, C., Mechanical influences on long-lasting human muscle fatique and delayed-onset pain, J. Physiol., 412 (1989) 415–427.

Jose, P.J., Page, D.A., Wolstenholme, B.E., Williams, T.J. and Dumonde, D.C., Bradykinin-stimulated prostaglandin E_2 production of endothelial cells and its modulation by antiinflammatory compounds, Inflammation, 5 (1981) 363–378.

Ju, G., Hökfelt, T., Brodin, E., Fahrenkrug, J., Fischer, J.A., Frey, P., Primary sensory neurons of the rat showing calicitonin gene-related peptide immunoreactivity and their relation to substance P, somatostatin-, galanin-, vasoactive intestinal polypeptide- and cholecystokinin-immunoreactive ganglion cells, Cell Tissue Res., 247 (1987) 417–431.

Kalia, M., Mei, S.S. and Kao, F.F., Central projections from ergoreceptors (C fibers) in muscle involved in cardiopulmonary responses to static exercise, Circ. Res., 48 (1981) 48–62.

Kalyan-Raman, U.P., Kalyan-Raman, K., Yunus, M.B. and Masi, A.T., Muscle pathology in primary fibromyalgia syndrome: a light microscopic, histochemical, and ultrastructural study, J. Rheumatol., 11 (1984) 808–813.

Kao, F.F., An experimental study of the pathway involved in exercise hyperpnoea employing cross-circulation techniques. In: D.J.C. Cunningham, and B.B. Lloyd (Eds.), The Regulation of Human Respiration, Blackwell, Oxford, 1963, pp. 461–502.

Kaufman, M.P., Iwamoto, G.A., Longhurst, J.C. and Mitchell, J.H., Effects of capsaicin and bradykinin on afferent fibers with endings in skeletal muscle, Circ. Res., 50 (1982) 133–139.

Kaufman, M.P., Longhurst, J.C., Rybicki, K.J., Wallach, J.H. and Mitchell, J.H., Effects of static muscular contraction on impulse activity of groups III and IV afferents in cats, J. Appl. Physiol., 55 (1983) 105–112.

Kaufman, M.P., Waldrop T.G., Rybicki, K.J., Ordway, G.A. and Mitchell, J.H, Effects of static and rhythmic twich contractions on the discharge of group III an IV muscle afferents, Cardiovasc. Res., 18 (1984a) 663–668.

Kaufman, M.P., Rybicki, K.J., Waldrop, T.G. and Ordway, G.A., Effect of ischemia on responses of group III and IV afferents to contraction, J. Appl. Physiol., 57 (1984b) 644–650.

Kellgren, J.H., Observations on referred pain arising from muscle, Clin. Sci., 3 (1938) 175–190.

Kellstein, D.E., Price, D.D., Hayes, R.L. and Mayer, D.J., Evidence that substance P selectively modulates C-fiber-evoked discharges of dorsal horn nociceptive neurons, Brain Res., 526 (1990) 291–298.

Kenins, P., The functional anatomy of the receptive fields of rabbit C polymodal nociceptors, J. Neurophysiol., 59 (1988) 1098–1115.

Kenshalo, D.R. and Isensee, O., Responses of primate SI cortical neurons to noxious stimuli, J. Neurophysiol., 50 (1983) 1479–1496.

Kenshalo, D.R., Chudler, E.H., Anton, F. and Dubner, R., SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation, Brain Res., 454 (1988) 378–382.

Kieschke, J., Mense, S. and Prabhakar, N.R., Influence of adrenaline and hypoxia on rat muscle receptors in vitro. In: W. Hamann and A. Iggo (Eds.), Prog. Brain Res., Vol. 74, Elsevier, Amsterdam, 1988, pp. 91–97.

Kniffki, K.-D. and Mizumura, K., Responses of neurons in VPL and VPL-VL region of the cat to algesic stimulation of muscle and tendon, J. Neurophysiol., 49 (1983) 649–661.

Kniffki, K.-D., Mense, S. and Schmidt, R.F., Responses of group IV afferent units from skeletal muscle to stretch, contraction and chemical stimulation, Exp. Brain Res., 31 (1978) 511–522.

Kniffki, K.-D., Schomburg, E.D. and Steffens H., Synaptic effects from chemically activated fine muscle afferents upon alpha-motoneurones in decerebrate and spinal cats, Brain Res., 206 (1981) 361–370.

Kocher, L., Anton, F., Reeh, P.W. and Handwerker, H.O., The effect of carrageenan-induced inflammation on the sensitivity of unmyelinated skin nociceptors in the rat, Pain, 29 (1987) 363–373.

Koerber, H.R. and Brown, P.B., Projections of two hindlimb cuta-

neous nerves to cat dorsal horn, J. Neurophysiol., 44 (1980) 259–269.

Kow, L.-M. and Pfaff, D.W., Neuromodulatory actions of peptides, Annu. Rev. Pharmacol. Toxicol., 28 (1988) 163–188.

Kruger, L., Morphological correlates of 'free' nerve endings – a reappraisal of thin sensory axon classification. In: R.F. Schmidt, H.-G. Schaible and C. Vahle-Hinz (Eds.), Fine Afferent Nerve Fibers and Pain, VCH, Weinheim, 1987, pp. 1–13.

Kruger, L., Silverman, J.D., Mantyh, P.W., Sternini, C. and Brecha, N.C., Peripheral patterns of calcitonin-gene-related peptide general somatic sensory innervation: cutaneous and deep terminations, J. Comp. Neurol., 280 (1989) 291–302.

Kuipers, H., Keizer, H.A., Verstappen, F.T.J. and Costill, D.L., Influence of prostaglandin-inhibiting drug on muscle soreness after eccentric work, Int. J. Sports Med., 6 (1985) 336–339.

Kumazawa, T. and Mizumura, K., Thin-fibre receptors responding to mechanical, chemical and thermal stimulation in the skeletal muscle of the dog, J. Physiol., 273 (1977) 179–194.

Kumazawa, T., Mizumara, K. and Sato, J., Thermally potentiated responses to algesic substances of visceral nociceptors, Pain, 28 (1987) 255–264.

Kuo, D.C., Nadelhaft, I., Hisamitsu, T. and deGroat, W.C., Segmental distribution and central projections of renal afferent fibers in the cat studied by transganglionic transport of horseradish peroxidase, J. Comp. Neurol., 216 (1983) 162–174.

Kuraishi, Y., Nanayama, T., Ohno, H., Fujii, N., Otaka, A., Yajima, H. and Satoh, M., Calcitonin gene-related peptide increases in the dorsal root ganglia of adjuvant arthritic rat, Peptides, 10 (1989) 447–452.

Lam, F.Y. and Ferrell, W.R., Mediators of substance P-induced inflammation in the rat knee joint, Agents Actions, 31 (1990) 298–307.

Lamour, Y., Willer, J.C. and Guilbaud, G., Rat somatosensory (Sm I) cortex. I. Characteristics of neuronal responses to noxious stimulation and comparison with responses to non-noxious stimulation, Exp. Brain Res., 49 (1983a) 35–45.

Lamour, Y., Guilbaud, G. and Willer, J.C., Rat somatosensory (Sm I) cortex. II. Laminar and columnar organization of noxious and non-noxious inputs, Exp. Brain Res., 49 (1983b) 46–54.

Lamour, Y., Willer, J.C. and Guilbaud, G., Altered properties and laminar distribution of neuronal responses to peripheral stimulation in the Sm I cortex of the arthritic rat, Brain Res., 273 (1983c) 183–187.

Lanari, A., Muchnik, S., Rey, N. and Semeniuk, G., Muscular cramp mechanism, Medicina, 33 (1973) 235–240.

Langford, L.A., Unmyelinated axon ratios in cat motor, cutaneous and articular nerves, Neurosci. Lett., 40 (1983) 19–22.

Layzer, R.B., Neuromuscular Manifestations of Systemic Disease, Davis, Philadelphia, PA, 1985.

Layzer, R.B. and Rowland, L.P., Cramps, N. Engl. J. Med., 285 (1971) 31–40.

Leah, J.D., Cameron, A.A. and Snow, P.J., Neuropeptides in physiologically indentified mammalian sensory neurones, Neurosci. Lett., 56 (1985) 257–263.

Lee, Y., Takami, K., Kawai, Y., Girgis, S., Hillyard, C.J., MacIntyre, I., Emson, P.C. and Tohyama, M., Distribution of calcitonin gene-related peptide in the rat peripheral nervous system with reference to its coexistence with substance P, Neuroscience, 15 (1985) 1227–1237.

Le Greves, P., Nyberg, F., Terenius, L. and Hökfelt, T., Calcitonin gene-related peptide is a potent inhibitor of substance P degradation, Eur. J. Pharmacol., 115 (1985) 309–311.

Lembeck, F. and Holzer, P., Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation, Naunyn-Schmiedeberg's Arch. Pharmacol., 310 (1979) 175–183.

Lembeck, F., Donnerer, J. and Colpaert, F.C., Increases of substance P in primary afferent nerves during chronic pain, Neuropeptides, 1 (1981) 175–180.

Levine, J.D. and Taiwo, Y.O., Involvement of the mu-opiate receptor in peripheral analgesia, Neuroscience, 32 (1989) 571–575.

Levine, J.D., Taiwo, Y.O., Collins, S.D. and Tam, J.K., Noradrenaline hyperalgesia is mediated through interaction with sympathetic postganglionic neurone terminals rather than activation of primary afferent nociceptors, Nature, 323 (1986) 158–160.

Lewis, T., Pain, Macmillan, London, 1942.

Lewis, T., Pickering, G.W. and Rothschild, P., Observations upon muscular pain in intermittent claudication, Heart, 15 (1931) 359–383.

Lewit, K., Muskelfehlsteuerung und Schmerz. In: M. Berger, F. Gerstenbrand and K. Lewit (Eds.), Schmerzstudien 6, Schmerz und Bewegungssystem, Fischer, Stuttgart, 1984, pp. 88–97.

Light, A.R. and Perl, E.R., Spinal termination of functionally identified primary afferent neurons with slowly conducting myelinated fibers, J. Comp. Neurol., 186 (1979) 133–150.

Light, A.R., Trevino, D.L. and Perl, E.R., Morphological features of functionally defined neurons in the marginal zone and substantia gelatinosa of the spinal dorsal horn, J. Comp. Neurol., 186 (1979) 151–171.

Lindahl, O., Experimental skin pain induced by injection of water-soluble substances in humans, Acta Physiol. Scand., 51, Suppl. 179 (1961) 1–90.

Lloyd, D.P.C., Neuron patterns controlling transmission of ipsilateral hind limb reflexes in cat, J. Neurophysiol., 6 (1943) 293–315.

Lotz, M., Carson, D.A. and Vaughan, J.H., Substance P activation of rheumatoid synoviocytes: neural pathway in pathogenesis of arthritis, Science, 235 (1987) 893–895.

Lund, J.P., Donga, R., Widmer, C.G. and Stohler, C.S., The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity, Can. J. Physiol. Pharmacol., 69 (1991) 683–694.

Lund, M., Bengtsson, A. and Thorborg, P., Muscle tissue oxygen pressure in primary fibromyalgia, Scand. J. Rheumatol., 15 (1986) 165–173.

Macefield, G., Gandevia, S.C. and Burke, D., Perceptual responses to microstimulation of single afferents innervating joints, muscles, and skin of the human hand, J. Physiol., 429 (1990) 113–129.

MacKenzie, J., Symptoms and Their Interpretation, Shaw and Sons, London, 1909.

Magni, G., Caldieron, C., Luchini, S.R. and Merskey, H., Chronic musculoskeletal pain and depressive symptoms in the general population. An analysis of the 1st National Health and Nutrition Examination Survey Data, Pain, 43 (1990) 299–307.

Mallart, A., Thalamic projection of muscle nerve afferents in the cat, J. Physiol., 194 (1968) 337–353.

Marchettini, P., Muscle pain, animal and human experimental and clinical studies. In: AAEM International Symposium on Neuropathic Pain, Johnson, Rochester, NY, 1992, pp. 39–44.

Marfurt, C.F., The central projections of trigeminal primary afferent neurons in the cat as determined by the transganglionic transport of horseradish peroxidase, J. Comp. Neurol., 203 (1981) 785–798.

Marshall, J., Sensory disturbances in cortical wounds with special reference to pain, J. Neurol. Neurosurg. Psychiat., 14 (1951) 187–204.

Marx, J.L., The fos gene as a 'master switch', Science, 237 (1987) 854–856.

Maunz, R.A., Pitts, N.G. and Peterson, B.W., Cat spinoreticular neurons: locations, responses, and changes in responses during repetitive stimulation, Brain Res., 148 (1978) 365–379.

McCarson, K.E. and Goldstein, B.D., Release of substance P into the superfical dorsal horn following nociceptive activation of the hindpaw of the rat, Brain Res., 568 (1991) 109–115.

McGlynn, G.H., Laughlin, N.T. and Rowe, V., Effect of electromyo-

graphic feedback and static stretching on artifically induced muscle soreness, Am. J. Phys. Med., 58 (1979) 139–148.

McMahon, S.B. and Wall, P.D., The distribution and central termination of single cutaneous and muscle unmyelinated fibers in rat spinal cord, Brain Res., 359 (1985) 39–48.

McMahon, S.B., Sykova, E., Wall, P.D., Woolf, C.J. and Gibson, S.J., Neurogenic extravasation and substance P levels are low in muscle as compared to skin in the rat hindlimb, Neurosci. Lett., 52 (1984) 235–240.

Menétrey, D., Giesler, G.J. and Besson, J.M., An analysis of response properties of spinal cord dorsal horn neurones to nonnoxious and noxious stimuli in the spinal rat, Exp. Brain Res., 27 (1977) 15–33.

Menétrey, D., Chaouch, A. and Besson, J.M., Location and properties of dorsal horn neurons at origin of spinoreticular tract in lumbar enlargement of the rat, J. Neurophysiol., 44 (1980) 862–877.

Mense, S., Nervous outflow from skeletal muscle following chemical noxious stimulation, J. Physiol., 267 (1977) 75–88.

Mense, S., Sensitization of group IV muscle receptors to bradykinin by 5-hydroxytryptamine and prostaglandin E_2, Brain Res., 225 (1981) 95–105.

Mense, S., Reduction of the bradykinin-induced activation of feline group III and IV muscle receptors by acetylsalicylic acid, J. Physiol., 326 (1982) 269–283.

Mense, S., Slowly conducting afferent fibers from deep tissues: neurobiological properties and central nervous actions, Prog. Sens. Physiol., 6 (1986) 139–219.

Mense, S., Structure-function relationships in identfied afferent neurones, Anat. Embryol., 181 (1990) 1–17.

Mense, S., Auslösende Faktoren des Muskelschmerzes unter besonderer Berücksichtigung der Ischämie. In: Ch. Maier and J. Wawersik (Eds.), Schmerztherapie bei Ischämischen Krankheiten, Schmerzstudien 9, Fischer, Stuttgart, 1991, pp. 45–56.

Mense, S. and Craig, A.D., Spinal and supraspinal terminations of primary afferent fibers from the gastrocnemius-soleus muscle in the cat, Neuroscience, 26 (1988) 1023–1035.

Mense, S. and Hoheisel, U., Influence of leukotriene D_4 on the discharges of slowly conducting afferent units from normal and inflamed muscle in the rat, Pflüger's Arch., 415, Suppl. 1 (1990) R105.

Mense, S. and Meyer, H., Response properties of group III and IV receptors in the Achilles tendon of the cat, Pflüger's Arch., 389 (1981) R25.

Mense, S. and Meyer, H., Different types of slowly conducting afferent units in cat skeletal muscle and tendon, J. Physiol., 363 (1985) 403–417.

Mense, S. and Meyer, H., Bradykinin-induced modulation of the response behaviour of different types of feline group III and IV muscle receptors, J. Physiol., 398 (1988) 49–63.

Mense, S. and Skeppar, P., Discharge behaviour of feline gamma-motoneurones following induction of an artificial myositis, Pain, 46 (1991) 201–210.

Mense, S. and Stahnke, M., Responses in muscle afferent fibres of slow conduction velocity to contractions and ischaemia in the cat, J. Physiol., 342 (1983) 383–397.

Mense, S., Light, A.R. and Perl, E.R., Spinal terminations of subcutaneous high-threshold mechanoreceptors. In: A.G. Brown and M. Réthelyi (Eds.), Spinal Cord Sensation, Scottish Academic Press, Edinburgh, 1981, pp. 79–86.

Merighi, A., Kar, S., Gibson, S.J., Ghidella, S., Gobetto, A., Peirone, S.M. and Polak, J.M., The immunocytochemical distribution of seven peptides in the spinal cord and dorsal root ganglia of horse and pig, Anat. Embryol., 181 (1990) 271–280.

Mertens, H.G. and Ricker, K., Übererregbarkeit der gamma-Motoneurone beim 'Stiff-man'-Syndrom, Kli. Wo., 46 (1968) 33–42.

Meyer, R.A. and Campbell, J.N., A novel electrophysiological technique for locating cutaneous nociceptive and chemospecific receptors, Brain Res. 441, (1988) 81–86.

Mitchell, J.H. and Schmidt, R.F., Cardiovascular reflex control by afferent fibers from skeletal muscle receptors. In: J.T. Shepherd and F.M. Abboud (Eds.), Handbook of Physiology, Section 2, The Cardiovascular System, Vol. III, Peripheral Circulation and Organ Blood Flow, Part 2, American Physiological Society, Bethesda, MD, 1983, pp. 623–658.

Molander, C. and Grant, G., Spinal cord projections from hindlimb muscle nerves in the rat studied by transganglionic transport of horseradish peroxidase, wheat germ agglutinin conjugated horseradish peroxidase, or horseradish peroxidase with dimethylsufoxide, J. Comp. Neurol., 260 (1987) 246–255.

Molander, C., Ygge, I. and Dalsgaard, C.-J., Substance P-, somatostatin-, and calcitonin gene-related peptide-like immunoreactivity and fluoride resistant acid phosphatase-activity in relation to retrogradely labeled cutaneous, muscular and visceral primary sensory neurons in the rat, Neurosci. Lett., 74 (1987) 37–42.

Moldofsky, H., Rheumatic pain modulation syndromes: the interrelationships between sleep, central nervous system, serotonin and pain, Adv. Neurol. 33 (1982) 51–57.

Moncada, S., Palmer, R.M.R. and Higgs, E.A., Nitric oxide: physiology, pathophysiology and pharmacology, Pharmacol. Rev., 43 (1991) 109–142.

Moore, R.M., Moore, R.E and Singleton, A.O., Experiments on the chemical stimulaton of pain-endings associated with small blood-vessels, Am. J. Physiol., 107 (1934) 594–602.

Morgan, I.T. and Curran, T., Stimulus-transcription coupling in neurones: role of cellular immediate-early genes, Trends Neurol. Sci., 12 (1989) 459–462.

Morley, J.E., Kay, N.E., Solomon, G.F. and Plotnikoff, N.P., Neuropeptides: conductors of the immune orchestra, Life Sci., 41 (1987) 527–544.

Mountcastle, V.B. and Powell, T.P.S., Central nervous mechanisms subserving position sense and kinesthesia, Bull. Johns Hopkins Hosp., 105 (1959) 173–200.

Müller, W. (Ed.), Generalisierte Tendomyopathie (Fibromyalgie), Steinkopff, Darmstadt, 1991.

Nadelhaft, I., Roppolo, J., Morgan, C. and deGroat, W.C., Parasympathetic preganglionic neurons and visceral primary afferents in monkey sacral spinal cord revealed following application of horseradish peroxidase to pelvic nerve, J. Comp. Neurol., 216 (1983) 36–52.

Nakahara, M., The effect of a tourniquet on the kinin-kininogen system in blood and muscle, Thromb. Diathes. Haemorrh., 26 (1971) 264–274.

Nakamura, Y., Nagashima, H. and Mori, S., Bilateral effects of the afferent impulses from the masseteric muscle on the trigeminal motoneuron of the cat, Brain Res., 57 (1973) 15–27.

Nakamura-Craig, M. and Gill, B.K., Effect of neurokinin A, substance P and calcitonin gene-related peptide in peripheral hyperalgesia in the rat paw, Neurosci. Lett., 124 (1991) 49–51.

Nakamura-Craig, M. and Smith, T.W., Substance P and peripheral inflammatory hyperalgesia, Pain, 38 (1989) 91–98.

Nazruddin, Suemune, S., Shirana, Y., Yamauchi, K. and Shigenaga, Y., The cells of origin of the hypoglossal afferent nerves and central projections in the cat, Brain Res., 490 (1989) 219–235.

New, H.V. and Mudge, A.W., Calcitonin gene-related peptide regulates muscle acetylcholine receptor synthesis, Nature, 323 (1986) 809–811.

Nicoll, R.A., Schenker, C. and Leeman, S.E., Substance P as a transmitter candidate, Annu. Rev. Neurosci., 3 (1980) 227–268.

Nishimori, T., Sera, M., Suemune, S., Yoshida, A., Tsuru, K., Tsuiki, Y., Akisaka, T., Okamoto, T., Dateoka, Y. and Shigenaga, Y., The distribution of muscle primary afferents from the masseter

nerve to the trigeminal sensory nuclei, Brain Res., 372 (1986) 375–381.

Noguchi, K., Senba, E., Morita, Y., Sato, M. and Tohyama, M., Co-expression of alpha-CGRP and beta-CGRP mRNAs in the rat dorsal root ganglion cells, Neurosci. Lett., 108 (1990) 1–5.

Noth, J. and Thilmann, A., Autogenetic excitation of extensor gamma-motoneurones by group II muscle afferents in the cat, Neurosci. Lett., 17 (1980) 23–26.

Nyberg, G. and Blomqvist, A., The central projection of muscle afferent fibres to the lower medulla and upper spinal cord: an anatomical study in the cat with the transganglionic transport method, J. Comp. Neurol., 230 (1984) 99–109.

O'Brien, C., Woolf, C.J., Fitzgerald, M., Lindsay, R.M. and Molander, C., Differences in the chemical expression of rat primary afferent neurons which innervate skin, muscle or joint, Neuroscience, 32 (1989) 493–502.

Öhlén, A., Lindblom, L., Staines, W., Hökfelt, T., Cuello, A.C., Fischer, J.A. and Hedqvist, P., Substance P and calcitonin gene-related peptide: immunohistochemical localisation and microvascular effects in rabbit skeletal muscle, Naunyn-Schmiedeberg's Arch. Pharmacol., 336 (1987) 87–93.

Öhlén, A., Wiklund, N.P., Persson, M.G. and Hedqvist, P., Calcitonin gene-related peptide desensitizes skeletal muscle arterioles to substance P in vivo, Br. J. Pharmacol., 95 (1988) 673–674.

O'Leary, J., Heinbecker, P. and Bishop, G.H., Analysis of function of a nerve to muscle, Am. J. Physiol., 110 (1935) 636–658.

Padawer, W.J. and Levine, F.M., Exercise-induced analgesia: fact or artifact?, Pain, 48 (1992) 131–135.

Paintal, A.S., Functional analysis of group III afferent fibres of mammalian muscles, J. Physiol., 152 (1960) 250–270.

Paintal, A.S., Participation by pressure-pain receptors of mammalian muscles in the flexion reflex, J. Physiol., 156 (1961) 498–514.

Pedersen-Bjergaard, U., Bogeskov Nielsen, L., Jensen, K., Edvinsson, L., Jansen, I. and Olesen, J., Algesia and local responses induced by neurokinin A and substance P in human skin and temporal muscle, Peptides, 10 (1991a) 1147–1152.

Pedersen-Bjergaard, U., Bogeskov Nielsen, L., Jensen, K., Edvinsson, L., Jansen, I. and Olesen, J., Calcitonin gene-related peptide, neurokinin A and substance P: effects on nociception and neurogenic inflammation in human skin and temporal muscle, Peptides, 12 (1991b) 333–337.

Perl, E.R., Afferent basis of nociception and pain: evidence from the characteristics of sensory receptors and their projections to the spinal dorsal horn. In: J.J. Bonica (Ed.), Pain, Raven Press, New York, 1980, pp. 19–45.

Perl, E.R., Pain and nociception. In: I. Darian-Smith (Ed.), Handbook of Physiology, Section 1, The Nervous System, Vol. III, Part 2, Am. Physiol. Soc., Bethesda, MD, 1984, pp. 915–975.

Pickering, G.W. and Wayne, E.J., Observations on angina pectoris and intermittent claudication in anaemia, Clin. Sci., 1 (1933-34) 305–325.

Pierau, F.-K., Fellmer, G. and Taylor, D.C.M., Somato-visceral convergence in cat dorsal root ganglion neurones demonstrated by double-labeling with fluorescent tracers, Brain Res., 321 (1984) 63–70.

Piper, P.J., Formation and actions of leukotrienes, Physiol. Rev., 64 (1984) 744–761.

Pomeranz, B., Wall, P.D. and Weber, W.V., Cord cells responding to fine myelinated afferents from viscera, muscle and skin, J. Physiol., 199 (1968) 511–532.

Popper, P. and Micevych, P.E., Localization of calcitonin gene-related peptide and its receptors in an striated muscle, Brain Res., 496 (1989) 189–186.

Randic, M. and Miletic, V., Effect of substance P in cat dorsal horn neurones activated by noxious stimuli, Brain Res., 128 (1977) 164–169.

Reinert, A., Vitek, M. and Mense, S., Effects of substance P on the activity of high- and low-threshold mechanosensitive receptors of the rat diaphragm in vitro, Pflüger's Arch., 420 (1992) R47.

Richardson, D., Blood flow response of human calf muscles to static contractions at various percentages of MVC, J. Appl. Physiol., 51 (1981) 929–933.

Richmond, F.J.R., Anstee, G.C.B., Sherwin, E.A. and Abrahams, V.C., Motor and sensory fibres of neck muscle nerves in the cat, Can. J. Physiol. Pharmacol., 54 (1976) 294–304.

Roberts, W.J. and Elardo, S.M., Sympathetic activation of A-delta nociceptors, Somatosens. Res., 3 (1985) 33–44.

Robinson, L.R., AAEM Case Report No. 22: Polymyositis, Muscle and Nerve, 14 (1991) 310–315.

Rodbard, S., Pain associated with muscular activity, Am. Heart J., 90 (1975) 84–92.

Roland, P., Cortical representation of pain, Trends Neurol. Sci., 15 (1992) 3–5.

Round, J.M., Jones, D.A. and Cambridge, G., Cellular infiltrates in human skeletal muscle: exercise induced damage as a model for inflammatory disease?, J. Neurol. Sci., 82 (1987) 1–11.

Ruch, T.C., Visceral sensation and referred pain. In: J.F. Fulton (Ed.), Howell's Textbook of Physiology, 16th edn., Saunders, Philadelphia, PA, 1949, pp. 385–401.

Russell, I.J., Neurohormonal aspects of fibromyalgia syndrome, Rheum. Dis. Clin. N. Am., 15 (1989) 149–168.

Ryu, P.D., Gerber, G., Murase, K. and Randic, M., Calcitonin gene-related peptide enhances calcium current of rat dorsal root ganglion neurons and spinal excitatory synaptic transmission, Neurosci. Lett., 89 (1988) 305–312.

Sahlin, K., Harris, R.C., Nylind, B. and Hultman, E., Lactate content and pH in muscle samples obtained after dynamic exercise, Pflüger's Arch., 67 (1976) 143–149.

Samuelsson, B., Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation, Science, 220 (1983) 568–575.

Samuelsson, B., Dahlén, S.-E., Lindgren, J.Å., Rouzer, C.A. and Serhan, C.N., Leukotrienes and lipoxins: structures, biosynthesis and biological effects, Science, 237 (1987) 1171–1176.

Sandoz, P.A. and Zenker, W., Unmyelinated axons in a muscle nerve. Electron microscopic morphometry of the sternomastoid nerve in normal and sympathectomized rats, Anat. Embryol., 174 (1986) 207–213.

Sato, J. and Perl, E.R., Adrenergic excitation of cutaneous pain receptors induced by peripheral nerve injury, Science, 251 (1991) 1608–1610.

Satoh, M., Kuraishi, Y. and Kawamura, M., Effects of intrathecal antibodies to substance P, calcitonin gene-related peptide and galanin on repeated cold stress-induced hyperalgesia: comparison with carrageenan-induced hyperalgesia, Pain, 49 (1992) 273–278.

Schaible, H.-G. and Schmidt, R.F., Excitation and sensitization of fine articular afferents from cat's knee joint by prostaglandin E_2, J. Physiol., 403 (1988) 91–104.

Schaible, H.-G., Schmidt, R.F. and Willis, W.D., Convergent inputs from articular, cutaneous and muscle receptors onto ascending tract cells in the cat spinal cord, Exp. Brain Res., 66 (1987a) 479–488.

Schaible, H.-G., Schmidt, R.F. and Willis, W.D., Enhancement of responses of ascending tract cells in the cat spinal cord by acute inflammation of the knee joint, Exp. Brain Res., 66 (1987b) 489–499.

Schumann, H.J. and Berger, W., Überlastungsnekrosen der Herz- und Skelettmuskulatur bei kleinen Zugvögeln, Beitr. Vogelkd., 20 (1974) 301–309.

Schweizer, A., Brom, R., Glatt, M. and Bray, M.A., Leukotrienes reduce nociceptive responses to bradykinin, Eur. J. Pharmacol., 105 (1984) 105–112.

Sessle, J.B. and Hu, J.W., Mechanisms of pain arising from articular tissues, Can. J. Physiol. Pharmacol., 69 (1991) 617–626.

Shea, V.K. and Perl, E.R., Failure of sympathetic stimulation to affect responsiveness of rabbit polymodal nociceptors, J. Neurophysiol., 54 (1985) 513–519.

Sher, G.D., Cartmell, S.M., Gelgor, L. and Mitchell, D., Role of *N*-methyl-D-aspartate and opiate receptors in nociception during and after ischaemia in rats, Pain, 49 (1992) 241–248.

Shigena, Y., Sera, M., Nishimori, T., Suemune, S., Nishimura, M. Yoshida, A. and Tsuru, K., The central projection of masticatory afferent fibers to the trigeminal sensory nuclear complex and upper cervical spinal cord, J. Comp. Neurol., 268 (1988) 489–507.

Shyu, B.C., Andersson, S.A. and Thorén, P., Endorphin mediated increase in pain threshold induced by long-lasting exercise in rats, Life Sci., 10 (1982) 833–840.

Shyu, B.C., Andersson, S.A. and Thorén, P., Spontaneous running in wheels. A microprocessor assisted method for measuring physiological parameters during exercise in rodents, Acta Physiol. Scand., 121 (1984) 103–109.

Sicuteri, F., Vasoneuroactive substances and their implication in vascular pain. In: A.P. Friedman (Ed.), Res. Clin. Stud. Headache, Vol. 1, Karger, Basel, 1967, pp. 6–45.

Sicuteri, F., Franchi, G. and Fanciullacci, M., Bradichinina e dolore da ischemia, Settim. Med., 52 (1964) 127–139.

Simone, D.A., Caputi, G., Marchettini, P. and Ochoa, J., Muscle nociceptors identified in humans: intraneural recordings, microstimulation and pain, Soc. Neurosci. Abst. 17 (1991) 546.5.

Simons, D.G., Myofascial pain syndrome due to trigger points. In: J. Goodgold (Ed.), Rehabilitation Medicine, Ch. 45, Mosby, St. Louis, MO, 1988, pp. 686–723.

Sinclair, D.C., Weddell, G. and Feindel, W.H., Referred pain and associated phenomena, Brain, 71 (1948) 184–211.

Sirisko, M.A. and Sessle, B.J., Corticobulbar projections and orofacial muscle afferent inputs to neurones in primate sensorimotor cerebral cortex, Exp. Neurol., 82 (1983) 716–720.

Spencer, J.D., Hayes, K.C. and Alexander, I.J., Knee joint effusion and quadriceps reflex inhibition in man, Arch. Phys. Med. Rehab., 65 (1984) 171–177.

Spitzer, N.C., A developmental handshake: neuronal control of ionic currents and their control of neuronal differentiation, J. Neurobiol., 22 (1991) 659–673.

Stacey, M.J., Free nerve endings in skeletal muscle of the cat, J. Anat., 105 (1969) 231–254.

Staff, P.H., Clinical consideration in referred muscle pain and tenderness – connective tissue reactions, Eur. J. Appl. Physiol., 57 (1988) 369–372.

Staton, W.M., New approach to muscle soreness, Athletic J., 31 (1951) 24–61.

Stauber, W.T., Clarkson, P.M., Fritz, V.K. and Evans, W.J., Extracellular matrix disruption and pain after eccentric muscle action, J. Appl. Physiol., 69 (1990) 868–874.

Staunton, H.P, Taylor, S.H. and Donald, K.W., The effect of vascular occlusion on the pressor response to static muscular work, Clin. Sci., 27 (1964) 283–291.

Steen, K.H., Reh, P.W., Anton, F. and Handwerker, H.O., Protons selectively induce lasting excitation and sensitization to mechanical stimulation of nociceptors in rat skin in vitro, J. Neurosci., 12 (1992) 86–95.

Stein, C., Millan, M.J., Shippenberg, T.S. and Herz, A., Peripheral effect of fentanyl upon nociception in inflamed tissue of the rat, Neurosci. Lett., 84 (1988) 225–228.

Sugiura, Y., Lee, C.L. and Perl, E.R., Central projections of identified, unmyelinated (C) afferent fibers innervating mammalian skin, Science, 234 (1986) 358–361.

Sugiura, Y., Terui, N. and Hosoya, Y., Difference in distribution of central terminals between visceral and somatic unmyelinatd (C) primary afferent fibers, J. Neurophysiol., 62 (1989) 834–840.

Sylvest, O. and Hvid, N., Pressure measurements in human striated muscles during contraction, Acta Rheum. Scand., 5 (1959) 216–222.

Szolcsányi, J., Selective reponsiveness of polymodal nociceptors of the rabbit ear to capsaicin, bradykinin and ultra-violet irradiation, J. Physiol., 388 (1987) 9–24.

Taiwo, Y.O., Bjerknes, L.K., Goetzl, E.J. and Levine, J.D., Mediation of primary afferent peripheral hyperalgesia by the cAMP second messenger system, Neuroscience, 32 (1990) 577–580.

Takami, K., Kawai, Y., Uchida, S., Tomyama, M., Shiotani, Y., Yoshida, H., Emson, P.C., Girgis, S., Hillyard, C.J. and MacIntyre, I., Effect of calcitonin gene-related peptide on contraction of striated muscle in the mouse, Neurosci. Lett., 60 (1985) 227–230.

Takami, K., Hashimoto, K., Uchida, S., Tohyama, M. and Yosihda, H., Effects of calcitonin gene-related peptide on the cyclic AMP levels of isolated mouse diaphragm, Jpn J. Pharmacol., 42 (1986) 345–350.

Talbot, J.D., Marrett, S., Evans, A.C., Meyer, E., Bushnell, M.C. and Duncan, G.H., Multiple representations of pain in human cerebral cortex, Science, 251 (1991) 1355–1358.

Tanji, J. and Kato, M., The long-lasting effects of cutaneous and high threshold muscle afferent volleys on semitendinosus gammamotoneurones, Brain Res., 40 (1972) 523–526.

Taverner, D., Muscle spasm as a cause of somatic pain, Annu. Rheum. Dis., 13 (1954) 331–335.

Torebjörk, E., Nociceptor activation and pain, Phil. Trans. R. Soc. (Lond.) B, 308 (1985) 227–234.

Torebjörk, H.E. and Hallin, R.G., Identification of afferent C units in intact human skin nerves, Brain Res., 67 (1974) 387–403.

Torebjörk, H.E., Schady, W. and Ochoa, J., Sensory correlates of somatic afferent fibre activation, Hum. Neurobiol., 3 (1984a) 15–20.

Torebjörk, H.E., Ochoa, J.L. and Schady, W., Referred pain from intraneural stimulation of muscle fascicles in the median nerve, Pain, 18 (1984a) 145–156.

Travell, J. and Rinzler, S.H., The myofascial genesis of pain, Postgr. Med., 11 (1952) 425–434.

Travell, J.G. and Simons, D.G., Myofascial Pain and Dysfunction. The Trigger Point Manual, Williams and Wilkins, Baltimore, MD, 1983.

Travell, J.G. and Simons, D.G., Myofascial Pain and Dysfunction. The Trigger Point Manual, Vol. 2, The Lower Extremities, Williams and Wilkins, Baltimore, MD, 1992.

Travell, J., Rinzler, S.H. and Herman, M., Pain and disability of the shoulder and arm: treatment by intramuscular infiltration with procaine hydrochloride, J. Am. Med. Assoc., 120 (1942) 417–422.

Uchida, Y. and Ueda, H., Kininogen and kinin activity during local ischemia in man, Jpn Heart J., 10 (1969) 503–508.

Vaeroy, M., Helle, R., Forre, O., Kåss, E. and Terenius, L., Elevated CSF levels of substance P and high incidence of Raynaud's phenomenon in patients with fibromyalgia: new features for diagnosis, Pain, 33 (1988) 21–26.

Vecchiet, L., Giamberardino, M.A., Dragani, L., Galletti, R. and Albe-Fessard, D., Referred muscular hyperalgesia from viscera: clinical approach. In: S. Lipton et al. (Eds.), Advances in Pain Research and Therapy, Vol. 13, Raven Press, New York, 1990, pp. 175–182.

Villar, M.J., Cortés, R., Theodorsson, E., Wiesenfeld-Hallin, Z., Schalling, M., Fahrenkrug, J., Emson, P.C. and Hökfelt, T., Neuropeptide expression in rat dorsal root ganglion cells and spinal cord after peripheral nerve injury with special reference to galanin, Neuroscience, 33 (1989) 587–604.

Wall, P.D., The laminar organization of dorsal horn and effects of descending inpulses, J. Physiol., 188 (1967) 403–423.

Wall, P.D., The presence of ineffective synapses and circumstances

which unmask them, Phil. Trans. R. Soc. (Lond.) B, 278 (1977) 361–372.

Wall, P.D. and Woolf, C.J., Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat, J. Physiol., 356 (1984) 443–458.

Wall, P.D., Coderre, T.J., Stern, Y. and Wiesenfeld-Hallin, Z., Slow changes in the flexion reflex of the rat following arthritis or tenotomy, Brain Res., 447 (1988) 215–222.

Wallengren, J. and Håkanson, R., Effects of substance P, neurokinin A and calcitonin gene-related peptide in human skin and their involvement in sensory nerve-mediated responses, Eur. J. Pharmacol., 143 (1987) 267–273.

Weiner, I.H. and Weiner, H.L., Nocturnal leg muscle cramps, J. Am. Med. Assoc., 244 (1980) 2332–2333.

Weinreich, D. and Wonderlin, W.F., Inhibition of a calcium-dependent spike after-hyperpolarization increases excitability of rabbit visceral sensory neurones, J. Physiol., 394 (1987) 415–427.

Wiberg, M. and Blomqvist, A., The spinomesencephalic tract in the cat: its cells of origin and termination pattern as demonstrated by the intraaxonal transport method, Brain Res., 291 (1984) 1–18.

Wiesendanger, M., Input from muscle and cutaneus nerves of the hand and forearm to neurones of the precentral gyrus of baboons and monkeys, J. Physiol., 228 (1973) 203–219.

Willis, W.D., The pain system. In: Ph.L. Gildenberg (Ed.), Pain and Headache, Vol. 8, Karger, Basel, 1985a.

Willis, W.D., Nociceptive pathways: anatomy and physiology of nociceptive ascending pathways, Phil. Trans. R. Soc. (Lond.) B, 308 (1985b) 253–268.

Wood, J.N., Bevan, S.J., Coote, P.R., Dunn, P.M., Harmar, A., Hogan, P., Latchman, D.S., Morrison, C., Rougon, G., Theveniau, M. and Wheatley, S., Novel cell lines display properties of nociceptive sensory neurons, Proc. R. Soc. (Lond.) B, 241/1302 (1990) 187–194.

Woolf, C.J. and Thompson, S.W.N., The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain hypersensitivity states, Pain, 44 (1991) 293–299.

Woolf, C.J. and Wall, P.D., Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat, J. Neurosci., 6 (1986) 1433–1442.

Woolf, C.J. and Wiesenfeld-Hallin, Z., Substance P and calcitonin gene-related peptide synergistically modulate the gain of the nociceptive flexor withdrawal reflex in the rat, Neurosci. Lett, 66 (1986) 226–230.

Xu, X.J., Wiesenfeld-Hallin, Z., Villar, M.J., Fahrenkrug, J. and Hökfelt, T., On the role of galanin, substance P and other neuropeptides in primary sensory neurons of the rat: studies on spinal reflex excitability and peripheral axotomy, Eur. J. Neurosci., 2 (1990) 733–743.

Yaksh, T.L., Substance P release from knee joint afferent terminals: modulation by opioids, Brain Res., 458 (1988) 319–324.

Ygge, J., Central projections of the rat radial nerve investigated with transganglionic degeneration and transganglionic transport of horseradish peroxidase, J. Comp. Neurol., 279 (1989) 199–211.

Yoss, R.E., Studies of the spinal cord. Part 3. Pathways for deep pain within the spinal cord and brain, Neurology, 3 (1953) 163–175.

Young, S.W., Wamsley, J.K., Zarbin, M.A. and Kuhar, M.J., Opioid receptors undergo axonal flow, Science, 210 (1980) 76–78.

Yu, X.-M. and Mense, S., Response properties and descending control of rat dorsal horn neurons with deep receptive fields, Neuroscience, 39 (1990a) 823–831.

Yu, X.-M. and Mense, S., Somatotopical arrangement of rat spinal dorsal horn cells processing input from deep tissues, Neurosci. Lett., 108 (1990b) 43–47.

Yu, X.-M., Hua, M. and Mense, S., The effects of intracerebroventricular injection of naloxone, phentolamine and methysergide on the transmission of nociceptive signals in rat dorsal horn neurones with convergent cutaneous-deep input, Neuroscience, 44 (1991) 715–723.

Zenker, W., Sandoz, P.A. and Neuhuber, W., The distribution of anterogradely labeled I-IV primary afferents in histochemically defined compartments of the rat's sternomastoid muscle, Anat. Embryol., 177 (1988) 235–243.

Zidar, J., Bäckman, E., Bengtsson, A. and Henriksson, K.G., Quantitative EMG and muscle tension in painful muscles in fibromyalgia, Pain, 40 (1990) 229–254.

Zieglgänsberger, W. and Tulloch, I.F., Effects of substance P on neurones in the dorsal horn of the spinal cord of the cat, Brain Res., 166 (1979) 273–282.