Peripheral and Central Sensitization in Musculoskeletal Pain Disorders: An Experimental Approach

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This report provides a brief introduction to the manifestations of peripheral and central sensitization involved in musculoskeletal pain disorders. It has become increasingly evident that muscle hyperalgesia, referred pain, referred hyperalgesia, and widespread hyperalgesia play an important role in chronic musculoskeletal pain. A better understanding of the involved basic mechanisms and better methods to assess muscle pain in the clinic may provide new possibilities for designing rational therapies and for targeting the pharmacologic intervention optimally. Peripheral sensitization plays an important role for increased sensitivity of deep tissue. However, central sensitization may be equally important but less addressed. Quantitative sensory testing provides the possibility to evaluate these manifestations in a standardized way in patients with musculoskeletal pain or in healthy volunteers (*eg*, experimentally induced referred pain can be used to assess the potential involvement of central sensitization in musculoskeletal pain conditions). Central sensitization may play a role in the persistence, amplification, and spread of pain. Interventions should take this aspect into consideration.

Introduction

Musculoskeletal pain is a common complaint during patient-physician encounters. Moreover, the drugs available in the treatment of musculoskeletal pain conditions are not optimal [1]. Therefore, deep pain is a diagnostic and therapeutic problem. Further insights into the peripheral and central neurophysiologic mechanisms are necessary to improve diagnosis and therapy, and to implement a mechanism-based approach. This report discusses the possible involvement of peripheral sensitization versus central sensitization underlying deep tissue hyperalgesia and referred pain. This report also provides examples of how these mechanisms can be assessed under experimental conditions or in patients with musculoskeletal pain. However, this report does not discuss in detail the complicated pathophysiologic mechanisms involved in acute and chronic muscle pain. The terminology "hyperalgesia" is used for pain evoked by normally non-nociceptive or nociceptive stimuli (including allodynia).

Musculoskeletal pain disorders are often accompanied by local and referred changes in somatosensory sensitivity. However, most experimental pain research has been conducted on cutaneous pain, although deep tissue pain is far more clinically important. In contrast to sharp, localized characteristics of cutaneous pain, muscle pain is described as aching and cramping, with diffuse and referred localization. Kellgren [2] was one of the pioneers to experimentally study the characteristics of muscle pain and the locations of referred pain to selective activation of specific muscle groups. Firm neurophysiologically based explanations for referred pain do not exist, but wide dynamic range neurons and nociceptive-specific neurons in the spinal cord and in the brain stem receive convergent afferent input from the skin, muscles, joints, and viscera. This may cause misinterpretation of the afferent information coming from muscle afferents when reaching higher levels in the central nervous system and thus be one reason for the diffuse and referred characteristics.

The sensation of acute muscle pain results from the activation of group III (Aδ-fiber) and group IV (C-fiber) polymodal muscle nociceptors. The nociceptors can be sensitized by the release of neuropeptides from the nerve endings. This may eventually lead to central sensitization of dorsal horn neurons manifested as prolonged neuronal discharges, increased responses to defined noxious stimuli, response to non-noxious stimuli, and expansion of the receptive field. Extensive animal experiments have supported this notion by showing that the sensitization of dorsal horn neurons may be a possible cause of muscular hyperalgesia and referred pain [3]. The brain response to standardized painful stimuli in musculoskeletal pain conditions has not been studied extensively, although the techniques are available and preliminary results suggest abnormal processing of the nociceptive input (refer to

Bradley *et al.* [4] for a review). A hypothesized central sensitization in spinal or brain stem neurons is depicted as an abnormal brain response.

Induction and Assessment of Muscle Pain and Hyperalgesia in Humans

The ultimate goal of advanced human experimental pain research is to obtain a better understanding of the mechanisms involved in pain transduction, transmission, and perception under normal and pathophysiologic conditions.

Experimental muscle pain research involves two separate topics. One topic is standardized activation of the muscle nociceptive system, and the other measurements of the evoked responses. Experimental approaches can be applied in the laboratory for basic studies (*eg,* central sensitization or preclinical screening of drug efficacy) and in the clinic to characterize patients with sensory dysfunctions and musculoskeletal pain.

Because pain is a multidimensional perception, the reaction to a single standardized stimulus of a modality can represent only a limited fraction of the entire pain experience. It is neccessary to combine different stimulation and assessment approaches to gain advanced differentiated information about the nociceptive system under normal and pathophysiologic conditions. For musculoskeletal pain research, muscle sensitivity and possible modality-specific somatosensory changes in the referred areas should be assessed. A major advantage of experimental muscle pain models is that isolated aspects of muscle pain mechanisms can be investigated in a standardized setting without confounding factors.

Various methods can be used to induce and assess muscle pain. Usually, the techniques are divided into methods with (exogenous) and without (endogenous) external stimuli [5]. The following is a summary of the available methods based on Arendt-Nielsen [5], Svensson and Graven-Nielsen [6], and Graven-Nielsen *et al.* [7].

Endogenous models

The endogenous methods are characterized by a high response rate and are suitable to study general muscle pain states. However, they have the disadvantage of involving several or all muscle groups within the region investigated. Pain from other somatic tissues often cannot be excluded.

Ischemic muscle pain is a classic experimental pain model and has been used for many years as an unspecified pain stimulus. The method is found to be reliable and has been used for human analgesic assay. This is an efficient model to induce pain in muscles, but skin, periosteum, and other tissues will contribute to the overall pain perception. The model is applicable in experimental studies requiring a general tonic pain stimulus.

Various forms of heavy and unaccustomed exercise can evoke exercise-induced pain in specific muscles. Together with overloading and insufficient resting periods, concentric dynamic and isometric contractions can elicit muscle pain, which may share the same physiopathogenetic mechanisms as ischemic pain.

In contrast, eccentric contractions induce a delayed onset of muscle pain or soreness. The mechanisms underlying this kind of muscle pain after excercise seem to be different from those of ischemic muscle pain and are probably related to ultrastructural damage resulting in the release of algesic substances. This may produce an inflammatory reaction because nonsteroidal anti-inflammatory drugs (NSAIDs) appear to have an effect on this type of muscle soreness.

Exogenous models

Mechanical stimulation is another method for excitation of muscle nociceptors. Pressure algometry is the most generally applied technique for quantification of tenderness, which in clinical practice is assessed by palpation. Using this technique, it can be difficult to distinguish between peripheral and central sensitization unless the sensitization is restricted to a single muscle or joint. Therefore, control determinations from unaffected, extrasegmental areas are important. The pain and tolerance thresholds can be measured easily; the stimulus-response functions can provide important information on muscle hyperalgesia. Normally, hand-held algometers are used [8], with which the rate of pressure increase and absolute values can be monitored. It has been difficult to compare thresholds from various clinical pressure pain studies because different instrumentation, different probe diameters and shapes, and different force increase rates have been used. The diameter is most important because there is not always a simple relationship between diameter and threshold; spatial summation plays an important role for pain. The shape and contour of the probe are important because sharp edges may excite more cutaneous receptors as a result of high shear forces compared with blunt probes. Attempts have been made to standardize the technique. In addition, normal values for various muscles have been published [8]. Hopefully, quantitative techniques will be more applicable and standardized for clinical applications in the future. Recently, we developed a new pressure algometry technique based on stimulus-response recording of the pain response to increasing pressure in a cuff placed around a limb [9]. This technique is fully automated, which increases the reliability. The sensitivity seems to be less influenced by minor site variations.

Intraneural stimulation of muscle afferents is a laboratory model that selectively elicits muscle pain accompanied by referred pain, which increases for increasing pain intensity. Intramuscular (IM) electrical stimulation can evoke deep pain, but the sensation is confounded by concurrent activated muscle twitches. This method is adequate for studies in which muscle pain and referred pain should be induced in a phasic manner, because the pain is present only during the stimulation (*eg,* in contrast with referred

pain after saline-induced pain, which will last several minutes). This provides the possibility to observe a given intervention over time (*ie,* what happens before and after a referred area is anesthetized). However, electrical stimulation is not nociceptive specific.

Chemical stimulation (*ie,* by IM infusion of hypertonic saline) causes local and referred pain. Recent animal studies have shown that the method does not cause any muscle toxicity; therefore, the method is adequate for human experimentation. A major advantage of the hypertonic saline model is that a detailed description of sensory and motor effects can be obtained because the pain lasts for minutes. Furthermore, the model is reliable for studying referred pain from musculoskeletal structures as a result of the longer-lasting pain. In most of the earlier studies, manual bolus infusions of hypertonic saline were used. However, standardization of the infusion of small volumes is easier to accomplish by computer-controlled infusion pumps.

Intramuscular injections of algesic substances (such as capsaicin, bradykinin [BK], serotonin [5-HT], potassium chloride, glutamate, levo-ascorbic acid, and acid phosphate buffer) have been used experimentally to induce muscle pain in humans. These methods elicit mild to moderately intense levels of pain.

Deep Tissue Hyperalgesia

Many clinical studies report increased sensitivity to painful stimuli of deep tissues within and outside muscle pain areas in patients compared with controls. Peripheral mechanisms (sensitization of receptors) may explain deep tissue hyperalgesia, whereas modulation of somatosensory sensitivity at referred sites without obvious tissue pathologies is mediated by central mechanisms.

Experimental findings

Sensitization of muscle nociceptors may explain deep tissue hyperalgesia because this phenomenon decreases the mechanical excitation threshold and increases responses to noxious stimuli [10]. Experimentally, this has been seen as decreased pressure pain thresholds after IM injections of capsaicin [11]. Intra-arterial injections of serotonin, BK, and postaglandin E_2 have been effective in sensitizing nociceptors in animals [3]. In humans, deep tissue hyperalgesia is reflected in an increase in sensitivity to pressure after combined IM injections of 5-HT and BK [12•] (Fig. 1). Hyperalgesia to pressure from the combined injection of 5-HT and BK is detected at the injection site and 10 cm away from the injection site [13]. Recently, Ernberg *et al.* [14] found that co-injection of 5-HT and the 5-HT3 receptor antagonist granisetron into the masseter muscle reduced the spontaneous pain evoked by injection of 5-HT and prevented allodynia/hyperalgesia to mechanical pressure stimuli. Therefore, peripheral serotonergic receptors could be involved in the regulation of musculoskeletal pain disorders.

The ionotropic and metabotropic glutamate receptors are other receptor types, which are found on peripheral unmyelinated sensory afferents in the skin [15] and presumably on sensory muscle afferents. Intramuscular injections of glutamate produce hyperalgesia to pressure stimuli in humans [16••] and sensitize rat muscle afferents [17]. Therefore, it is likely that the glutamate receptors can contribute to deep tissue hyperalgesia through peripheral sensitization. The glutamate-evoked muscle pain in humans and afferent responses in rats were higher in females compared with males [16••]. Considering the high prevalence rate of chronic musculoskeletal pain conditions in women, such sex-related differences are important as possible peripheral neurobiologic mechanisms involved in chronic musculoskeletal pain.

Based on the results of many clinical studies, one would expect to observe muscle hyperalgesia in the presence of experimental muscle pain. Svensson *et al.* [18] performed an experimental study in which increased tenderness assessed by pressure algometry was observed after the jaw muscle had been exposed to experimental muscle pain (hypertonic saline). Moreover, pain thresholds to IM electrical stimulation are significantly lower in muscles 24 hours after they have been exposed to hypertonic saline [19]. Such findings on pressure and IM electrical pain thresholds are also seen after infusion of isotonic saline in the leg muscles [20]. Therefore, the findings on muscle sensitivity in saline-induced muscle pain areas are unclear. Muscular hyperalgesia has been detected mainly on the masticatory muscles or brachioradialis muscle, whereas hypoalgesia or unchanged sensitivity is found in studies on the larger tibialis anterior muscle. This could suggest that the development of muscular hyperalgesia depends on the size of the muscle and possibly the level of afferent barrage. This is supported by the pressure pain thresholds being higher for a large muscle such as the tibialis anterior compared with a smaller muscle such as the brachioradialis.

For the superficial tissue overlying the saline-induced muscle pain area, increased sensitivity to electrical [19] and pinprick stimulation [21] is found. In contrast, decreased responses to pinprick stimuli [22] and unchanged pain thresholds to pinch stimulation [20] have been reported. These findings may be related to central mechanisms discussed in a later section on referred hyperalgesia.

Another model on deep tissue hyperalgesia is the soreness developed after eccentric muscle work (delayed onset muscle soreness), with peak soreness after 24 to 48 hours. A feature of delayed onset muscle soreness is that there is no pain at rest, but pain is evoked by muscle function and during palpation (*ie,* allodynia/hyperalgesia). An example of delayed onset muscle soreness from a model of deep tissue pain in wrist extensors with characteristics similar to lateral epicondylalgia [23] is shown in Figure 2. Peripheral sensitization is probably the main mechanism responsible

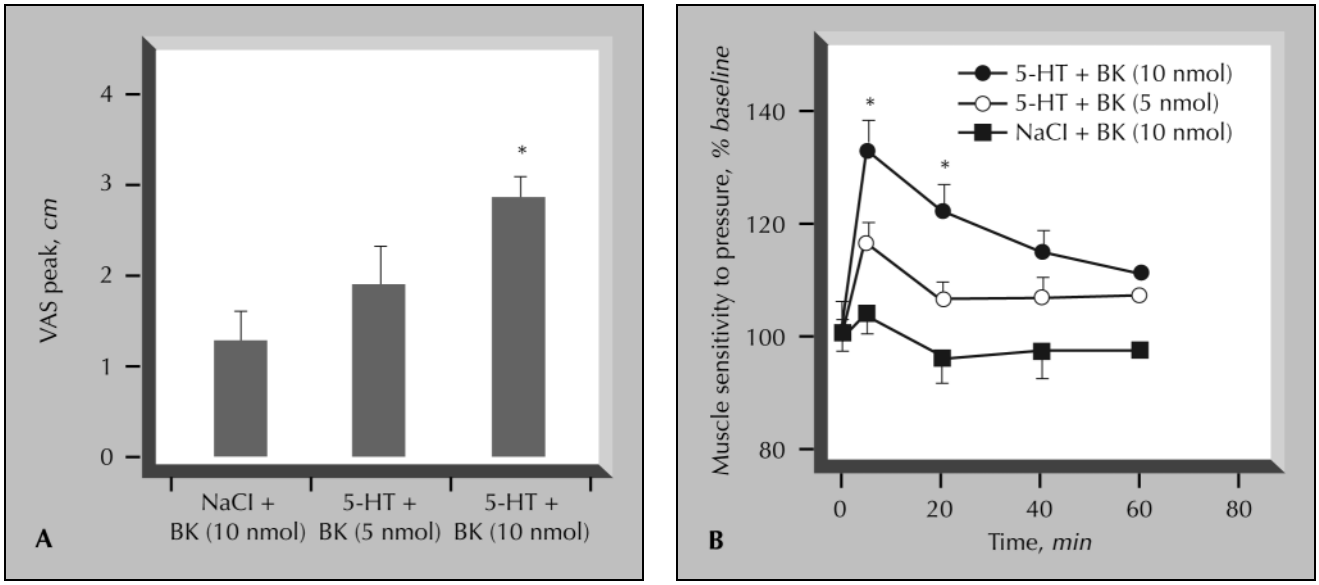

Figure 1. A, Peripheral sensitization in humans leads to an increase in maximal pain intensity (Visual Analogue Scale [VAS] peak) when intramuscular injections of serotonin (5-HT) combined with bradykinin (BK) are administered, compared with isotonic saline (NaCl) combined with BK (mean ± standard error; $n = 10$; $^*P < 0.05$ compared with BK plus isotonic saline). **B**, The area infiltrated with 5-HT and BK shows increased muscle sensitivity to pressure (*ie,* decreased pressure pain thresholds). The muscle sensitivity is normalized to the muscle sensitivity before injection (mean ± standard error; $n = 10$; $^*P < 0.05$ compared with pre-injection). (*Adapted from* Babenko *et al.* [12•].)

for hyperalgesia to pressure. The allodynic component in delayed onset muscle soreness is suggested to be mediated by the thick myelinated afferents and not exclusively by the thin unmyelinated nociceptive afferents [24]. Nonetheless, the central mechanism responsible for temporal summation of nociceptive input (*ie,* progressive increase in pain perception during repetitive stimuli) is also facilitated in the course of muscle soreness after exercise [25].

The phenomenon of neurogenic inflammation (axon reflex) caused by a noxious stimulus is well-known and studied as the flare reaction in human skin but is also important for muscles. Neurogenic inflammation in a muscle may cause the release of peptides that can increase the blood flow locally. Edema and plasma extravasation may follow. This phenomenon plays a role in the development of localized muscle hyperalgesia.

Clinical findings

Pressure pain sensitivity is the most common technique to assess painful musculoskeletal conditions (such as tender points, fibromyalgia, work-related myalgia, myofacial pain, strain injuries, myositis, chronic fatigue syndrome, arthritis/arthroses, and other muscle/tendon/joint inflammatory conditions) [8]. The technique is adequate to quantify and follow the development of certain diseases. It is also adequate for documenting treatment outcome, such as local/systemic administration of NSAIDs. An example is the recording of the joint pain threshold before and weeks after topical application of an NSAID to patients suffering from unilateral finger joint inflammation and pain. Stimulus response functions can provide more information than a threshold because sensitization to low and high intensities can be assessed. A shift in parallel toward the left, together with an increased slope, has been found in patients with myofacial pain [18]. After anesthetizing the muscle, the curve was shifted toward the right with a reduced slope [18].

Referred Pain

Referred pain has been known and described for more than a century and has been used extensively as a diagnostic tool in the clinic. Originally, the term "referred tenderness and pain" was used. It has since been used to describe pain perceived at a site adjacent to or at a distance from the site of origin. Referred pain and referred hyperalgesia to somatic structures from viscera are important in diagnosis and treatment but is not the scope of this paper. For a review, see the paper by Vecchiet *et al.* [26].

Several neuroanatomic and neurophysiologic theories regarding the appearance of referred pain have been suggested. They state that nociceptive dorsal horn or brain stem neurons receive convergent inputs from various tissues, thus higher centers cannot identify correctly the input source [27,28]. Most recently, the models have included newer theories that state that sensitization of dorsal horn and brain stem neurons plays a central role.

Experimental findings

Referred pain is probably a combination of central processing and peripheral input because it is possible to induce referred pain to limbs with complete sensory loss as a result of an anesthetic block [29•]. However, the involvement of peripheral input from the referred pain area is unclear because anesthetizing this area shows inhibitory or

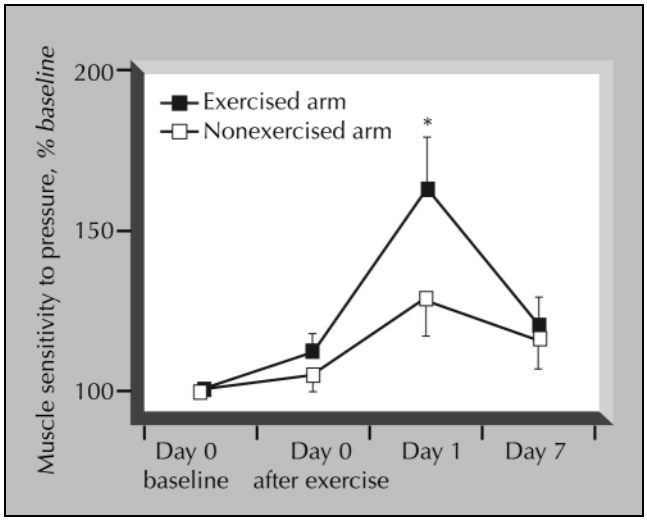

Figure 2. An example of muscle soreness after exercise as a model of deep tissue hyperalgesia. Muscle sensitivity to pressure of the extensor carpi radialis brevis muscle before and after eccentric work with the wrist (mean ± standard error; $n = 12$). The muscle sensitivity rates are normalized to day 0 (baseline); increased muscle sensitivity rates equal decreased pressure pain thresholds. Significantly decreased thresholds compared with the unexercised arm (*$P < 0.05$). (*Based on data from* Slater *et al.* [23].)

no effect on the referred pain intensity. Central sensitization may be involved in the generation of referred pain. Animal studies show a development of new and expanded receptive fields by a noxious muscle stimulus [3,30]. Recordings from a dorsal horn neuron with a receptive field located in the biceps femoris muscle show new receptive fields in the tibialis anterior muscle and in the foot after IM injection of BK into the tibialis anterior muscle [30]. In the context of referred pain, the unmasking of new receptive fields as a result of central sensitization could mediate referred pain [3]. This has been suggested to be the phenomenon of secondary hyperalgesia in deep tissue. Several studies have found that the area of the referred pain correlated with the intensity of the muscle pain, which parallels the observations for cutaneous secondary hyperalgesia in which the hyperalgesic area is related to the capsaicin-induced pain intensity. This type of plasticity of the central nervous system may also alter somatosensory sensitivity and account for deep tissue hyperalgesia.

Clinical findings

Substantial clinical knowledge exists concerning the patterns of referred muscle pain from various skeletal muscles and after activation of trigger/tender points [31]. However, few clinical studies have aimed to study central sensitization in combination with chronic musculoskeletal pain.

Recent studies have provided the first evidence of central sensitization in chronic musculoskeletal pain. In the first study [32], it was found that patients with fibromyalgia experienced stronger pain and larger referred areas after IM injection of hypertonic saline. The most interesting aspect was that these manifestations were present in lower limb muscles where the patients normally do not experience ongoing pain. The subjective pain ratings may be a result of hypervigilance, but the patients had no clue of the normal referred pain area to injection of hypertonic saline in the tibialis anterior muscle. Normally, pain from the tibialis anterior is projected distally to the ankle, rarely proximally. In these patients, there was substantial proximal spread of the referred areas. This corresponds to basic neurophysiologic experiments in rats, in which dorsal horn neuron recordings from various spinal segments were investigated before and after muscle nociception [30]. In these experiments, the muscle nociception caused a proximal spread of sensitization, which explains the clinical findings. Moreover, in patients with fibromyalgia, IM electrical stimulation was used to assess the efficacy of temporal summation of painful muscle stimuli; temporal summation was found more potent in the patients compared with control subjects [32]. Recently, the increased efficacy of temporal summation in patients with fibromyalgia has been reproduced with cutaneous heat stimulation [33]. Facilitated temporal summation is most likely a reflection of central sensitization and an important parameter to assess in chronic musculoskeletal pain conditions. Temporal summation of pain stimuli applied to skin, joint, and muscle was most pronounced for muscle tissue [34], illustrating the importance of testing the temporal summation from deep tissue because this may be affected by central sensitization in musculoskeletal pain conditions. Increased referred pain areas and facilitated temporal summation in patients with pain suggest that the efficacy of central processing is increased (central sensitization) in these patients. Moreover, in patients with fibromyalgia, the expanded referred pain areas and exaggerated temporal summation were partly inhibited by ketamine (an *N*-methyl-D-aspartate antagonist) targeting central sensitization [35••].

Similar findings on extended referred pain areas from the tibialis anterior muscle have been shown in patients suffering from chronic whiplash pain [36•]. The extended areas of referred pain were found in the neck and shoulder region and in distant areas where the patient does not normally experience pain (*ie,* lower leg). This finding could be a manifestation of central sensitization and may support the hypothesis that central pathogenic mechanisms are involved in the whiplash syndrome. Central sensitization in patients with whiplash is suggested based on increased sensitivity to IM electrical stimulation of the tibialis anterior muscle compared with healthy patients [37]. In patients suffering from knee osteoarthritis [38•], extended areas of saline-induced referred pain have been found. This shows that noxious joint input to the central nervous system may facilitate the referred pain mechanisms, possibly as a result of central sensitization. Similarly, in patients with temporomandibular pain disorders, enlarged pain areas were found when injecting the masseter muscle [39•].

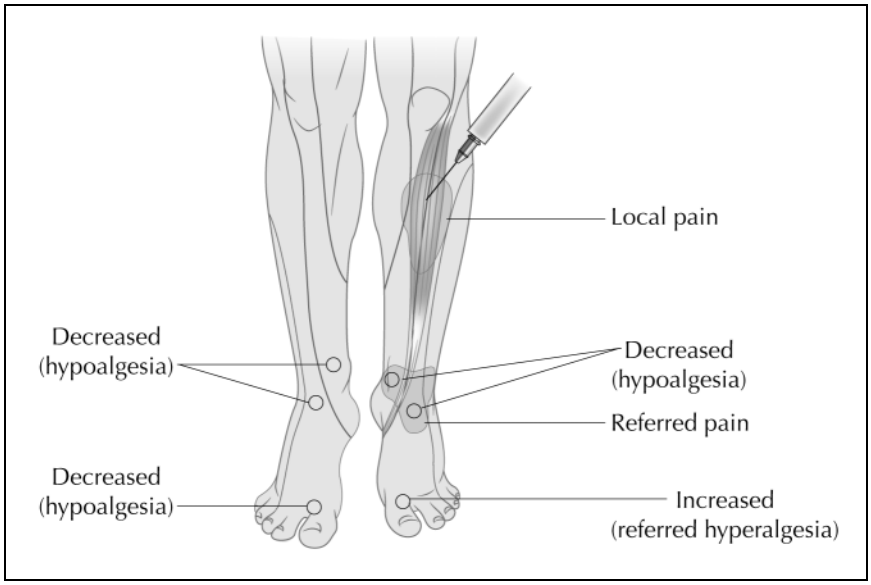

Figure 3. An illustration of deep tissue sensitivity to pressure segmentally and extrasegmentally after induction of muscle pain in a lower limb muscle. Hypoalgesia is found in most areas, most likely caused by muscle pain-induced pain inhibitory mechanisms. In areas with a common nerve supply, referred hyperalgesia are seen as a result of central summation. (*Based on data from* Graven-Nielsen *et al.* [42].)

Referred and Widespread Hyperalgesia

Central sensitization may facilitate the mechanism for referred pain. Likewise, central sensitization may be involved in hyperalgesia at sites distant from the pain locus as referred or widespread hyperalgesia. Moreover, referred hyperalgesia can be present in areas with or without referred pain.

Experimental findings

In referred areas of experimental induced muscle pain, Kellgren [2] found tenderness to pressure, but not all the later studies have been able to reproduce this finding. Similarly, skin sensitivity in the referred pain area has been reported to depend on the stimulus modality tested [22,40,41]. Increased pain response to electrical cutaneous stimulation and decreased sensitivity to radiant heat or pinprick stimulation have been reported in referred pain areas [22,40]. This modality-specific somatosensory change found in the referred pain area is similar to findings in secondary hyperalgesic areas of the skin after injury.

Infiltration of the muscle tissue with anesthetics 30 minutes after injection of hypertonic saline (*ie,* no ongoing pain) completely reverses cutaneous and muscular hyperalgesia [19]. This effect of a peripheral block on the muscle hyperalgesia may suggest peripheral sensitization. Alternatively, the mechanisms responsible for deep and cutaneous hyperalgesia after muscle pain may be caused by a central mechanism in which peripheral input is needed, which is also a necessary condition for referred pain [40]. Recently, we found hyperalgesia to pressure distal to the referred pain area produced by experimental pain induced in the tibialis anterior muscle [42] (Fig. 3). The referred hyperalgesic area was innervated by the deep peroneous nerve, which also innervates the tibialis anterior muscle. This suggests involvement of summation between muscle afferents and the somatosensory afferents from the hyperalgesic area eventually facilitated by central sensitization.

Central sensitization of dorsal horn or brain stem neurons initiated by nociceptive activity from muscles may explain the expansion of pain with referral to other areas and probably hyperalgesia in these areas. However, facilitated neurons cannot account for the decreased sensation to certain sensory stimuli in the referred area. Descending inhibitory control of the dorsal horn neurons may explain the decreased response to additional noxious stimuli in the referred pain area and at the contralateral limb (Fig. 3). Recently, it was found that saline-induced muscle pain resulted in deep tissue hypoalgesia in extrasegmental areas distant from the pain focus [21,43,44]. Similar findings have been reported for the cutaneous touch perception [45]. In addition, segmental inhibition at the spinal cord or brain stem level may contribute to the decreased sensitivity. In animals, IM capsaicin injections have been shown to produce inhibition of C-fiber activity from the contralateral leg. This inhibition was blocked by cooling of the spinal cord [46] and by the application of naloxone and phentolamine to the spinal cord [47]. Descending inhibitory mechanisms may mask any eventual increase in somatosensory sensitivity caused by experimental pain.

Clinical findings

There are only a few studies on referred hyperalgesia. Recently, Leffler [48] assessed the somatosensory function in the referred pain area in patients with long-term trapezius myalgia. Hyperalgesia to pressure and hypoalgesia to light mechanical stimulation were found in the referred pain area, suggesting a modality or tissue-specific change of the somatosensory function similar to previous experimental findings [40]. However, in patients with lateral epicondylalgia, only hypoalgesia to light mechanical stimulation was found in the referred pain area produced

by muscle contractions [49]. A factor that may influence the somatosensory changes is the duration of habitual pain. The patients in whom referred hyperalgesia was found on average had experienced pain for 6 years [48], whereas in the study in which hyperalgesia was not detected, the patients on average had pain for 6 months [49]. Similarly, increased sensitivity to pressure in a nonpainful area was found in patients with rheumatoid arthritis suffering for more than 5 years in contrast to patients with pain for less than 1 year [50•]. This fits well with the concept of central sensitization because a certain period of nociceptive input is needed to induce central sensitization. Widespread pain in musculoskeletal pain disorders is frequently initiated by localized deep pain, indicating the development of central sensitization over time.

Another manifestation of central sensitization may be the number of palpable trigger points. Recently, we found a significantly higher number of these points in the lower limb muscles in patients suffering from knee osteoarthritis compared with controls [51]. The presence of central sensitization may facilitate low intensity input (possibly muscle allodynia) and may result in pain when a possible latent trigger point is activated. This may also be one of the reasons why a localized painful condition can spread and become generalized.

A dysfunction of the descending inhibitory control systems may have similar effects as central sensitization. In healthy subjects, generalized hypoalgesia to pressure is found during strong experimentally induced pain (Fig. 3). In contrast, patients with fibromyalgia do not show such modulation, indicating a dysfunction of the descending inhibitory control [52]. The efficacy of descending inhibition is similar in patients with short- and long-term rheumatoid arthritis compared with controls [50•]. Before surgery (*ie,* hip replacement), patients with osteoarthritis lacked the generalized hypoalgesic effect to pressure during a strong experimental pain in contrast with the normalized descending inhibition after hip surgery [53•]. This may indicate that the descending system is maximally involved in the condition with continuous pain before surgery and that, after surgery, the dynamics of the system is reestablished and effectively modulate the sensitivity to pressure. Therefore, a dysfunction of the descending inhibitory control system may be involved in chronic musculoskeletal pain conditions, although it has not been a systematic finding in different groups of patients.

Conclusions

An important part of the pain manifestations related to chronic musculoskeletal disorders may be caused by peripheral and central sensitization. Better knowledge and evaluation possibilities of the mechanisms involved in chronic musculoskeletal pain may provide better clues to revise and optimize diagnosis and treatment. Some manifestations of central sensitization, such as expanded referred pain areas and referred hyperalgesia in patients with chronic musculoskeletal pain, have been explained with animal experiments by extrasegmental spread of sensitization.

Acknowledgments

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