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Referred Muscle Pain: Basic and Clinical Findings

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Acute pain and long-term pain originating from deep somatic structures represent a major part of pain complaints in many patients. Deep pain is a diagnostic and therapeutic problem, and further insights into the peripheral and central neurophysiologic mechanisms are necessary to improve diagnosis and therapy. Systematic studies of referred pain from muscles may help to reveal such mechanisms. The focus of this paper is discussion of the possible mechanisms behind pain referred from muscles.

Paradoxically, a large amount of experimental pain research has been obtained from studies of cutaneous pain. Cutaneous pain varies from deep pain in many ways. Typically, it is described as a localized sharp or burning pain and is rarely (if ever) referred to other somatic structures. Conversely, deep pain often is described as a diffuse, dull pain, with frequent referral to distant sites.[1]

Referred pain has been known and described for more than a century, and it has been used extensively as a diagnostic tool in the clinical setting. Head[2] initially used the term "referred tenderness and pain" in 1893. However, other clinicians had reported the phenomenon previously (for a review, see Bonica[1]). Since then, it has been used to describe pain perceived at a site adjacent to or at a distance from the site of origin. The taxonomy committee of the International Association for the Study of Pain has not defined the term; however, several authors have defined it in different ways. In this paper, we will use the definition "pain felt at a site remote from the site of origin/stimulation."

Several neuroanatomic and physiologic theories regarding the appearance of referred pain have been suggested, and they state that nociceptive dorsal horn and brain stem neurons receive convergent inputs from various tissues; therefore, higher centres cannot identify correctly the actual input source. Most recently, the models have included newer theories in which plasticity of dorsal horn and brainstem neurons plays a central role. During the past decades, a systematic attempt to chart referred musculoskeletal pain areas in humans has been made.[3] Some of these findings have been reproduced in experimental muscle pain studies in humans.[4–15]

BASIC ASPECTS

Clinical versus experimental studies regarding referred pain

Further basic research of all aspects of referred pain is needed to obtain a better understanding of pain pathologies related to deep somatic structures. Clinical research and, in particular, research of pain, often are confounded by many factors that make it difficult to look at specific aspects of the disease. Experimental models seem to be good alternatives.

Human experimental pain research classically involves two separate topics: (1) standardized activation of the nociceptive system and (2) measurements of the evoked responses (for a review, see Arendt-Nielsen[16]). The ultimate goal of advanced human experimental pain research is to obtain a better understanding of mechanisms involved in pain transduction, transmission, and

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perception under normal and pathophysiologic conditions. Hopefully, this can give more insight regarding the mechanisms underlying referred pain and provide better characterization, prevention, and management of pain. Experimental studies are useful in basic research because they can be standardized by using healthy individuals, allow a study with few confounding factors, and studies can be performed during very standardized conditions.[16]

Studies of clinical pain are limited by bias because of cognitive, emotional, and social aspects of the disease. Pain is a multidimensional and highly individualized perception that is difficult to quantify and to validate in the clinical setting. In experimental pain, the researchers have the possibility to control stimulus intensity, duration, and modality. Furthermore, the psychophysical-evoked responses can be assessed quantitatively (using, for example, visual analog scores) or qualitatively (using, for example, the McGill Pain Questionnaire). Stimulus-response relations, being of great value in, for example, pharmacologic research, can also be investigated. Disadvantages of experimental models are the short-lasting acute stimuli, which may not parallel long-term clinical pain. The psychological involvement may also be limited in experimental models; therefore, the stimuli may not mimic clinical pain sufficiently. Therefore, multimodality experimental pain stimuli may be recommended for assessment of pharmacologic interventions.[16–18] A multimodal sensory test regime also should be used when hyper-/hypoalgesia is assessed in referred pain areas.

Muscle pain

Various methods can be used to induce experimental muscle pain. Usually, the methods are classified in two groups: (1) endogenous (without external stimuli); and (2) exogenous (external stimuli) methods.[17]

Human endogenous methods (e.g., ischemia and exercise) are characterized by high response rate and are suitable for studying general pain states. However, they have the disadvantage of involving several or all muscle groups within the region investigated, and often pain from other somatic tissues cannot be excluded.[17,19] Finally, endogenous methods are not suitable to induce referred pain. Therefore, we will concentrate on exogenous models in this paper.

Referred muscle pain using algogenic substances

A number of exogenous methods have been used to induce experimental human muscle pain. The most commonly used method is intramuscular infusion of hypertonic saline (6%). Kellgren and Lewis introduced the method in 1938,[20,21] and intramuscular infusion of hypertonic saline subsequently has been used extensively.[4–6,11–15,22–31] A variety of parameters have been shown to correlate with the infusion of hypertonic saline (e.g., saline concentration, infusion rate and pressure, and amount of saline infused).[4,29,32] Nevertheless, the mechanisms responsible for the excitation of nociceptive activity shortly after the infusion are still unknown. A direct excitation of afferents because of osmotic difference has been proposed, although other mechanisms can not be excluded.[32] Referred pain is felt in structures at a distance from the infusion site, and it appears with a delay of approximately 20 seconds in comparison with local pain[5] (Fig. 1). This referred pain is characterized as being diffuse and unpleasant.[4]

Infusion of hypertonic saline has several advantages. It is easy and safe to use, and it induces local and referred muscle pain in most individuals (40–85%), depending on the actual muscle of injection.[4–6,11,12,14] The disadvantage of this muscle pain model is the relatively long-lasting pain (several minutes) after a bolus infusion.[4,5,6,10,17,31]

In recent years, more potent algogenic substances have been tested as muscle pain models. Bradykinin,[33–37] serotonin,[35–37] capsaicin,[38–40] and substance P[35–37] have been used separately or in combination to induce muscle pain. This model combining different algogenic substances has been a promising model for deep tissue hy-

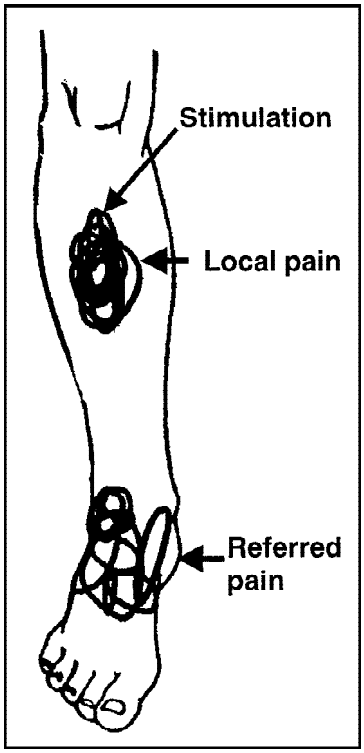

FIG. 1. The distribution of local and referred muscle pain after continuous (10 seconds, 10 Hz) electrical stimulation of the anterior tibialis muscle in 10 healthy individuals.

peralgesia. One study has shown referred pain after subsequent intramuscular injections of serotonin and bradykinin was used.[35]

Referred muscle pain using electrical stimulation

Intramuscular electrical stimulation (IMES) of muscle tissue has been used in various experimental and clinical settings. Intramuscular electrical stimulation offers an advantage in that it can induce referred muscle pain in an on-and-off manner. It is an easy method to use, and a high incidence of local (94%) and referred (78%) pain is induced.[7] In our studies of IMES, we used 10-Hz stimulation for at least 10 seconds to generate referred muscle pain (Fig. 2).

Intramuscular electrical stimulation has been used to assess somatosensory sensibility by determining various thresholds (e.g., of sensation and of pain). Vecchiet et al.[41] found a significantly lower pain threshold in muscle, subcutis, and skin of patients with chronic fatigue syndrome in comparison with healthy controls, which indicated hypersensitivity to painful stimulation in this group of patients. In a recent study, IMES was used to evaluate the effect of ketamine on muscle pain induced using single electrical stimulation in comparison with repeated (temporal summation) electrical stimulation for patients with fibromyalgia. A significant increase in the pain summation threshold to repeated IMES was found during the ketamine infusion.[42]

Referred pain after IMES appears with different delays in the various studies[7–10] that range from immediately after the referred pain occurs to a delay of 43 seconds on average. A difference in stimulus intensities could account for the variances of referred pain onset.[7] A more consistent delay of referred pain onset is characteristic for hypertonic saline experiments.[6] The reason for the difference in time delay between the two models could be due to different excitation mechanisms of the nociceptive afferents and/or because of central mechanisms (temporal summation or hyperexcitability). However, IMES has a shortcoming in comparison with hypertonic saline in that it bypasses the sensory nerve endings, which makes investigations of receptor transduction mechanisms impossible.

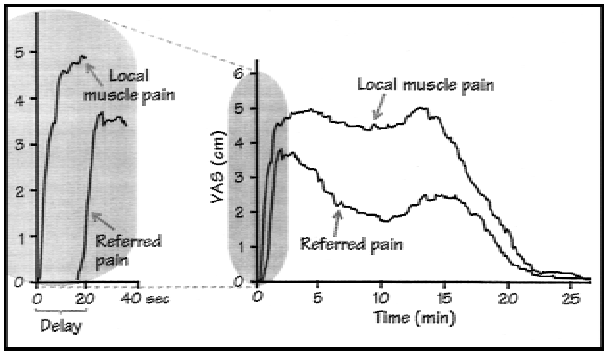

FIG. 2. Schematic illustration of the ongoing local and referred pain after infusion of hypertonic saline into the tibialis anterior muscle. There is a short delay between onset of local and referred pain.

Significantly higher stimulus intensity is necessary to elicit referred pain in comparison with local pain, and a significantly positive correlation has been found among the stimulus intensity and the local pain and referred pain intensity ratings.[7] This is in accordance with previous experimental and clinical studies[5,6,23,43,44] and studies that used direct intraneural electrical stimulation of muscle nociceptive afferents.[38,43,45]

Spatial summation is a well-described feature in many experimental pain models of cutaneous pain,[46] deep pain,[6,38,45] and visceral pain.[47,48] The mechanism responsible for spatial summation observed most likely is an additional recruitment of nociceptor units,[49] which results in an increased barrage to dorsal horn and brainstem neurons and, consequentially, increased local pain and referred pain.

Significant correlations between the size of local pain and referred pain areas and the local sensation/pain and referred sensation/pain intensity ratings have been demonstrated.[7] Similar observations have been detected in studies in which sequential infusions of hypertonic saline into a muscle resulted in an increasing number of individuals experiencing referred pain and increasing areas of referred pain,[5] and in which intraneural electrical stimulation of muscle afferents at a constant frequency and intensity evoked an expansion of the projected pain area over time.[38] Increased nociceptive input to the dorsal horn or brainstem neurons, which generates an expansion of receptive fields,[50,51] may be responsible for the expansion of referred areas detected during increased intramuscular stimulation.[7]

Manifestation of referred muscle pain

Inman and Saunders systematically investigated the distribution of referred pain in relation to the activated muscle groups.[52] Based on their observations, they suggested that referred pain followed the distribution of sclerotomes (muscle, fascia, and bone) more frequently than it followed the classical dermatomes.[53]

Sensory manifestations of clinical and experimental muscle pain are seen as diffuse aching pain in the muscle, pain referred to distant somatic structures, and modifications in superficial and deep tissue sensibility in the painful areas.[1,6,20] These manifestations differ from cutaneous pain, which normally is superficial and localized around the injury and has a sharp and burning quality.[1,4] Referred pain and sensibility changes in the pain-

ful structures have been known for many years,[20,24] but the neural mechanisms responsible for these phenomena are not understood fully.

Referred muscle pain probably involves a central neurobiological mechanism because it is possible to induce referred pain to limbs with complete sensory loss using an anesthetic block.[24] However, the lack of peripheral input from the referred pain area seems to decrease the referred pain intensity,[8] which suggests that the peripheral input from the referred pain area is involved but not a necessary condition for referred pain. Hypothetically, convergence of nociceptive afferents on dorsal horn neurons may mediate referred pain, but studies by Hoheisel and Mense[54] showed a rare convergence of muscle afferents and other deep tissue afferents, such as muscle, although Sessle et al.[55] showed an extensive convergence between both deep and superficial afferents in the craniofacial region. Central hyperexcitability may modulate the manifestation of referred pain. Animal studies have found a development of new receptive fields via noxious muscle stimuli.[56–58] Recordings from a dorsal horn neuron with a receptive field located in the biceps femoris muscle indicated new receptive fields in the tibialis anterior muscle and in the paw after intramuscular injection of bradykinin into the tibialis anterior muscle.[58] In the context of referred pain, revealing new receptive fields could be the mechanism behind referred pain because of central hyperexcitability.[59] Forming of new receptive fields has been suggested to be the phenomenon of secondary hyperalgesia in deep tissue.[59] Similar findings are shown in humans after intradermal injection of capsaicin in which a rapid development of central hyperexcitability (seen as secondary cutaneous hyperalgesia) is found. The time needed for revealing (in the range of seconds) may account for the time delay between local pain and the development of referred pain[4] and for the increased number of individuals developing referred pain during repeated hypertonic saline infusions[5] or tonic infusion.[14]

Several studies have found that the area of the referred pain correlated with the intensity[6,7,52,60] and duration[38] of the muscle pain, which parallels the observations for cutaneous secondary hyperalgesia. Chronic musculoskeletal pain has been shown to respond better to treatment using NMDA-receptor antagonists (ketamine) than to conventional morphine management,[61] which indicates the role of central hyperexcitability in these patients, with the reason being that NMDA-antagonists in animal studies, in experimental studies, and in clinical studies are found to inhibit wind-up and hyperalgesia. Therefore, it is reasonable to propose that muscle pain conditions[59] may evoke central hyperexcitability, which may play an important role in long-term musculoskeletal pain syndromes (e.g., whiplash[62]). The relation between temporal summation and central hyperexcitability may be shown by the progressive spread of pain during tonic intramuscular infusion of hypertonic saline.[14] From studies on cutaneous hyperalgesia,[47] central summation of nociceptive input from muscles and referred pain areas is expected to be exaggerated in musculoskeletal pain conditions if central hyperexcitability is involved. Infusions of hypertonic saline have shown larger referred pain areas in fibromyalgia patients than in controls, and also proximal referral of pain was found in the patients, but not in controls.[61] This may reflect central hyperexcitability in fibromyalgia patients as hypertonic saline is infused into muscles with no clinical muscle pain.[61] Moreover, the gain of temporal summation was increased in fibromyalgia patients as the pain threshold for repeated intramuscular electrical stimulation and not single stimulation was decreased in fibromyalgia patients compared to controls.[61]

In a recent study, a similar manifestation of enlarged referred pain areas to intramuscular injection of hypertonic saline was found in chronic pain patients after whiplash injuries.[62] Preliminary data[63] from temporomandibular pain patients show that such enlarged areas also can be manifested in the orofacial region. Similarly, enlarged referred pain areas also are found after visceral stimulation in patients with chronic visceral pain.

Hyperalgesia related to referred muscle pain

The somatosensory sensibility in the referred pain area may provide additional information about the mechanisms involved in generation of referred pain. It is accepted that muscle pain can result in hyperalgesia in the referred somatic structures.

The somatosensory sensibility is affected by saline-induced muscle pain in cutaneous and deep structures in the area of local and referred pain. During saline-induced pain, the deep tissue sensibility may increase,[12,24,27,64] decrease,[65] or remain unaffected[5] in the local and referred muscle pain area.

Increased VAS response to electrical cutaneous stimulation and decreased sensibility to radiant heat stimulation have been reported in referred pain areas.[5] This modality-specific somatosensory change found in the referred muscle area is similar to findings in secondary hyperalgesic areas of the skin.

The mechanisms of sensibility changes may be of peripheral origin or of central origin. Infiltration of the muscle tissue by anesthetics 30 minutes after injection of hypertonic saline completely reverses the cutaneous and muscular hyperalgesia.[27] The effect of a peripheral block on the hyperalgesia[27] suggests that the hyperalgesia is

caused by maintained peripheral input which is also a necessary condition for referred pain.[5,20] Alternatively, the mechanisms responsible for deep and cutaneous hyperalgesia after muscle pain may be caused by central hyperexcitability.

Central hyperexcitability of dorsal horn and brainstem neurons initiated by nociceptive activity from muscles may explain the expansion of pain with referral to other areas, and it probably also explains hyperalgesia in these areas. However, facilitated neurons do not 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. Recently, we found that saline-induced muscle pain resulted in deep-tissue hypoalgesia in extra segmental areas (including the area of referred pain) distant from the pain focus.[13,66] In addition, segmental inhibition at the spinal cord or brainstem level may contribute to the decreased sensibility.

Modulation of referred pain

During the past century, several theories on the origin of referred pain have been suggested (see later in this paper). To illuminate possible mechanisms of referred pain, a number of case reports and experiments regarding the effect of anesthetizing the referred pain area have been published. Often, when referred visceral pain has been investigated, contradictory results have been shown. Weiss and Davies[67] published the first large study. They found that patients with various diseases (e.g., angina pectoris, pleuritis, stomach ulcer, chronic cholecystitis, salpingitis, and kidney stones) experienced pain at structures (most often the skin) located at a distance from the affected organ(s), which could have been partially and, in some cases, completely abolished by infiltrating the area using a local anesthetic.

Conversely, Wollard et al.[68] found minor or no changes of referred pain intensity in an anesthetized skin area. Furthermore, Kellgren[20] did not see a decrease in referred pain intensity when he anesthetized areas to which saline-induced muscle pain was referred.

Several explanations regarding the divergent results obtained when an area of referred pain is anesthetized have been offered: (1) the variation in the number of structures (skin, subcutis, fascia, muscle, tendons, ligaments, and bone) anesthetized. This is likely a major bias because referred pain areas and, especially visceral referred pain, tend to be located in the deep tissues in which complete anesthesia of a referred pain area is difficult; (2) the duration and level of local pain; (3) the site of the local pain (skin, viscera, and deep structures); (4) whether sensory changes (hypersensitivity) occur at the referred pain site.

The IMES technique recently has been used to investigate systematically the effect of anesthetizing the referred areas. In a placebo-controlled experiment,[8] an eutectic mixture of local anesthetics was applied to the skin lying over the referred pain area. Reduction of the referred pain intensity by 22.7% was shown in the local anesthetic group in comparison with the placebo group.

A similar result has been reported when ethyl chloride was sprayed onto the saline-induced referred pain area, which greatly reduced referred pain.[69] This suggests that referred pain to some degree is dependent on spontaneous input from cutaneous receptors. Although cutaneous nociceptors do not exert resting activity,[70] a reduction of activity from other skin receptors (e.g., thermal receptors and possibly low-threshold mechano-receptors) could explain the finding.

To completely block all afferents from the referred pain area two techniques have been used: (1) differential nerve blocking with an inflated tourniquet between the site of stimulation and the corresponding distal referred area;[9] and (2) intravenous regional analgesia (IVRA).[9]

Interestingly, the referred pain intensity was reduced by 40.2% while myelinated nerve fiber function was impaired, which suggests that referred pain has a peripheral component associated with intact myelinated nerve fiber function. When the nerve fiber function was blocked completely, referred pain still occurred.

Other studies in which the afferent input from the referred area has been completely blocked, have reported similar findings.[24,71] Therefore, evidence seems to suggest that referred pain, to some degree, depends on an intact peripheral nervous system, with some spontaneous input.

Neurophysiological mechanisms for referred pain

The mechanisms responsible for referred pain referral to adjacent anatomical segment are not known in detail. Several theories have been suggested and will be summarized briefly. These theories have been developed for visceral pain, for muscle pain or for both, and, as such, are very general.

The convergent-projection theory

Based on the ideas of Sturge[72] and Ross,[73] Ruch[74] proposed that afferent fibers from different tissues converge onto common spinal neurons (Fig. 3A). The foundation of this suggestion is that the nociceptive activity from the spinal cord is misinterpreted as originating from other structures. This could explain the segmental nature of referred muscle pain and the increased referred pain intensity recorded when local muscle pain was intensi-

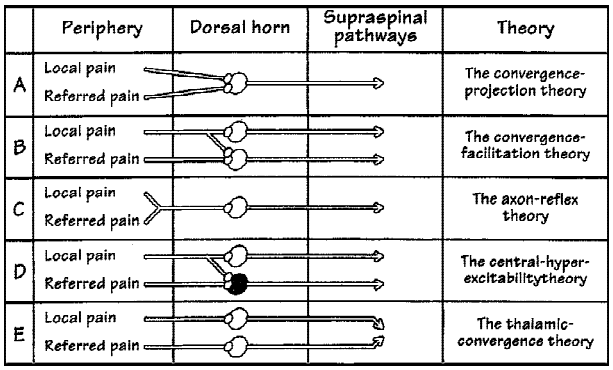

FIG. 3. The different possible mechanisms of referred pain. Dorsal horn neurons are shown as open circles, and the shaded circles indicate connectivity changes in the dorsal horn. The letters A–E refer to the explanation in the text. Part of the figure is modified from Selzer and Spencer.[85]

fied.[6,7,16,48] However, it does not adequately explain the apparent delay in the development of referred pain after local pain.[4,5,7,23] Also, referred pain has not been shown to be a stereotypical bidirectional phenomenon (e.g., muscle pain in the anterior tibial muscle produces pain in the ventral part of the ankle, but the opposite condition has not been shown). However, jaw muscle pain can be referred to the teeth, and tooth pain can be referred to the muscles. Finally, the threshold for eliciting local and referred muscle pain is different.[7,23,43,44,75]

The convergence-facilitation theory

MacKenzie[76] was also inspired by the ideas of Sturge[72] and Ross.[73] He believed that viscera were totally insensitive and that nonnociceptive afferent input to the spinal cord created an irritable focus in the spinal cord (Fig 3B). This focus would make other somatic inputs appear in an abnormal fashion and, in some cases, be perceived to be referred pain. The theory was not recognized, mainly because it did not accept true visceral pain. In recent years, however, MacKenzie's simple idea of an irritable focus has reclaimed awareness under another term–central sensitization. The somatosensory sensibility changes reported in referred pain areas could in part be explained by similar mechanisms in the dorsal horn and brainstem neurons and the delay in appearance of referred pain shown in various studies[6,7] could also be explained because the creation of central sensitization may require time.

The axon-reflex theory

Bifurcation of afferents from two different tissues has been suggested as an explanation of referred pain[75] (Fig. 3C). Although bifurcation of nociceptive afferents from different tissues (muscle and skin[77] and intervertebral discs and skin[78]) exists, generally it is agreed that these types of neurons are rare.[79] Moreover, a time delay in the appearance of referred pain, different thresholds for eliciting local and referred muscle pain, and somatosensory sensibility changes in referred pain area cannot be explained by this theory.

The hyperexcitability theory

Numerous experimental and clinical studies (see previous section) have documented some effects of anesthetizing the referred pain area; therefore, referred pain may likely not be explained solely by a central mechanism, although the central component is assumed to be the most predominant.

The aforementioned theories lack some of the referred pain characteristics previously described in this article. Recently, Mense[59] suggested an interesting theory, especially from a perspective regarding referred muscle pain, that is known as the central-hyperexcitability theory (Fig. 3D).

Recordings from a dorsal horn neuron in animals have revealed that noxious stimuli to a receptive field in a muscle generated within minutes at a distance from the original receptive field.[3,54,58] The appearance of two new receptive fields could indicate that latent convergent afferents on the dorsal horn neuron may be opened by noxious stimuli arising from muscle tissue,[59] and this facilitation of latent convergence connections could appear as referred pain. Recent observations from the same group have shown that substance P released from the terminal ends of primary afferents plays a role in the connectivity in the dorsal horn.[80] Furthermore, an expansion of the receptive fields proximal to the normal receptive field was found in a study in which experimental myositis was induced, and, subsequently, application of antagonists to three different neurokinin receptors is effective in preventing the induced hyperexcitability.[81] The idea of this theory is in line with several of the characteristics of referred muscle pain (dependency on stimulus and a delay in appearance of referred pain in comparison with local pain). The proximal appearance of receptive fields, thought of as referred pain, is in contrast to the reports from a majority of the experimentally referred pain studies, including healthy individuals.[4–10,20,52,65] Clinical studies regarding the spread of experimentally induced referred pain in patients with whiplash syndrome and fibromyalgia have shown proximal and distal referral of pain.[42,62] In only one study have we seen proximal spread of referred muscle pain in a few healthy volunteers after intramuscular injection of capsaicin**.** A possible explanation of the divergence in these observations could be that an already ongoing pain is necessary to have a massive barrage or to induce a state of hyperexcitability in the spinal cord. This results in

proximal and distal referral in comparison with the predominant distal referral in healthy individuals.

The hyperexcitability theory[3,58,59,82] is based on animal studies in which receptive fields appeared within minutes. This does not fit exactly with the development of referred pain in humans, which occurs within seconds. However, we think that the idea of latent connections between dorsal horn neurons is convincing. To explain the referred pain, which could not be anesthetized, supraspinal mechanisms that could mimic the mechanisms seen in the dorsal horn or brainstem regions can not be excluded. If the processing of local and referred muscle pain is not performed in the same supraspinal pathways and centers, neuroimaging techniques (positron emission tomography and functional magnetic resonant imaging) might be possible to visualize the underlying nociceptive processing responsible for referred pain in humans.

The thalamic-convergence theory

Theobald[83] suggested that referred pain appeared as a summation of input from the injured area and the referred pain area within neurons in the brain, and not in the spinal cord (Fig. 3E). A recent study of referred pain in monkeys that applied computer simulations has shown several pathways that converge on different subcortical and cortical neurons.[84]

CONCLUSION

Referred muscle pain has some fundamental features.

1. The size of referred pain is related to the intensity and duration of ongoing/evoked pain.
2. Temporal summation is a potent mechanism for generation of referred muscle pain.
3. Central hyperexcitability is important for the extent of referred pain.
4. Patients with chronic musculoskeletal pains have enlarged referred pain areas to experimental stimuli. Proximal spread of referred muscle pain is seen in patients with chronic musculoskeletal pain and very seldom seen in healthy individuals.
5. Modality specific somatosensory changes occur in referred areas, which emphasizes the importance of using a multimodal sensory test regime for assessment.

Human experimental pain research has provided new possibilities to study referred pain quantitatively in volunteers and patients. Clinical studies and pharmacologic modulation of experimentally induced referred pain may contribute with additional information regarding the underlying mechanisms. Better characterization and understanding of referred pain mechanisms and related hyperalgesia may help to optimize and to rationalize pain management and clinical diagnosis.

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