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This section, edited by Charles B. Berde, MD, PhD, and Michael C. Rowbotham, MD, presents timely topics in pain research and treatment.

Referred Pain and Hyperalgesia Related to Muscle and Visceral Pain

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Human experimental pain research involves two separate topics: standardized activation of the nociceptive system and measurements of the evoked responses. The ultimate goal of advanced human experimental pain research is to better understand mechanisms involved in pain transduction, transmission, and perception under normal and pathophysiological conditions. The hope is to better characterize, prevent, and manage pain (Arendt-Nielsen 1997).

Experimental approaches can be applied in the laboratory for basic studies (e.g., central hyperexcitability or preclinical screening of drug efficacy) and also in the clinic to characterize patients with sensory dysfunctions or pain (e.g., neurogenic pain). A recent Technical Corner (K.L. Petersen, November-December 1997) reviewed experimental pain research on cutaneous hyperalgesia. Hyperalgesia in deep tissues is extremely common and of great clinical importance. This Technical Corner reviews current knowledge of hyperalgesia from muscle and viscera.

Muscle Pain

Several experimental techniques have been used to induce muscle pain in humans, for example, intramuscular (i.m.) injection of algogenic substances, i.m. electrical stimulation, production of ischemia, and exercise. The experimental method that has gained most acceptance is i.m. injection of hypertonic saline because the quality of the induced pain is comparable to clinical muscle pain with localized and referred pain (Kellgren 1938; Feinstein et al. 1954; Stohler and Lund 1995).

Experimental muscle pain is characterized by diffuse, aching pain in the target muscle, pain referred to distant somatic structures, and modifications in superficial and deep tissue sensibility in the painful areas (Kellgren 1938; Graven-Nielsen 1997). These manifestations are different from cutaneous pain, which is normally superficial, localized around the injury, and sharp and burning. Referred pain and sensibility changes in the painful structures have been known for many years (Kellgren 1938; Feinstein et al. 1954), but the mechanisms responsible for these phenomena are not fully understood.

Referred pain and temporal summation in muscle pain. Referred pain involves central mechanisms because it is still possible to induce referred pain to limbs after complete sensory loss from an anesthetic block (Feinstein et al. 1954). However, the lack of peripheral input from the referred pain area decreases the referred pain intensity (Laursen et al. 1998), 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 (1990) show only rare convergence between muscle and other deep tissues or muscle. Central hyperexcitability may be involved in generation of referred pain. Animal studies show a development of new receptive fields following noxious muscle stimuli (Hoheisel et al. 1993). For example, 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 at the foot after i.m. injection of bradykinin into the tibialis anterior muscle (Hoheisel et al. 1993). The unmasking of new receptive fields may be a deep tissue phenomenon equivalent to secondary hyperalgesia in skin. Humans receiving an intradermal injection of capsaicin rapidly develop central hyperexcitability and a zone of cutaneous hyperalgesia. The time needed for unmasking may account for the time delay between local pain and the development of referred pain (Graven-Nielsen et al. 1997b). The increased percentage of subjects developing referred pain during repeated hypertonic saline infusions (Graven-Nielsen et al. 1997a) or tonic infusion (Svensson et al. 1998) suggests that temporal summation plays an important role. Several studies have found that the size of the area of referred pain correlates with the intensity (Stohler and Lund 1995; Graven-Nielsen et al. 1997a) and duration (Marchettini et al. 1996) of the primary muscle pain.

In a recent study of fibromyalgia patients, pain responded better to NMDA-antagonist (ketamine) treatment than to conventional morphine management (Sørensen et al. 1998), which indicates a role for central hyperexcitability in these patients. As illustrated in Fig. 1, infusions of hypertonic saline (even into muscles without clinical muscle pain) produce larger referred pain areas in fibromyalgia patients than in controls; proximal referral of pain also was found in these patients but not in controls (Sørensen et al. 1998). Moreover, in fibromyalgia patients but not in controls temporal summation to repeated intramuscular electrical stimulation was potentiated (Sørensen et al. 1998). Based on results from these studies and others on cutaneous hyperalgesia (Arendt-Nielsen et al. 1996), we can conclude that central summation of nociceptive input from muscles and referred pain areas is exaggerated in musculoskeletal pain conditions, which strongly suggests the involvement of central hyperexcitability.

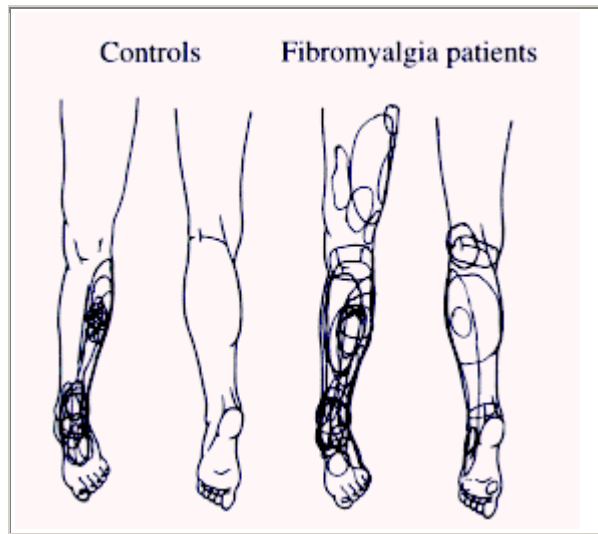


Fig. 1. Illustration of the referred pain pattern from saline-induced muscle pain in the anterior tibial muscle in healthy controls (n=12) and in fibromyalgia patients (n=12). The fibromyalgia patients showed increased areas of referred pain and atypical locations for referred pain (proximal referred pain). No continuing pain was experienced in the anterior tibial muscle before induction of muscle pain (modified from Sørensen et al. 1997).

Hyperalgesia related to muscle pain. Somatosensory sensibility is variably affected by saline-induced muscle pain in cutaneous and deep structures in the area of local and referred pain. During saline-induced pain, muscular sensibility has been reported as increased (Feinstein et al. 1954; Vecchiet et al. 1988; Svensson et al. 1995), decreased (Arendt-Nielsen et al. 1997a), or unaffected (Graven-Nielsen et al. 1997a) in the muscle pain area. Increased muscular sensibility has mainly been detected on the temporalis or brachioradialis muscle, whereas the decreased or unchanged sensibility is found in studies on the tibialis anterior muscle. These findings suggest that the development of muscular hyperalgesia is dependent on the size of muscles. Increased sensibility to electrical stimulation and pinprick is found in the superficial tissue overlying the saline-induced muscle pain area (Vecchiet et al. 1988; Svensson et al. 1998). However, decreased responses to pinprick stimuli (Graven-Nielsen et al. 1997a) and unchanged pain thresholds to skin-fold stimulation (Graven-Nielsen et al. 1998b) have also been reported.

The somatosensory sensibility in the referred pain area is also variably affected. Although the recent findings of decreased visual analog scale (VAS) responses to pressure stimulation in the referred pain area (Graven-Nielsen et al. 1997b) contradict older studies showing referred tenderness (Kellgren 1938; Feinstein et al. 1954), the study of Steinbrocker et al. (1953) did not uniformly report referred tenderness. In the referred pain area, the VAS response to electrical cutaneous stimulation increased and sensibility to radiant heat stimulation decreased compared to pre-infusion tests (Graven-Nielsen et al. 1997b). After extensive studies, including findings from many infusions, it has not been possible to detect cutaneous sensibility changes in the referred pain area (Kellgren 1938), and Feinstein et al. (1954) could not determine whether the i.m. injection of

hypertonic saline produced cutaneous hypoesthesia rather than increased sensibility to pricking stimuli.

The mechanisms behind sensibility changes may be of peripheral or central origin. Infiltration of the muscle tissue with anesthetics 30 minutes after injection of hypertonic saline completely reverses the cutaneous and muscular hyperalgesia (Vecchiet et al. 1988). The effect of a peripheral block on the hyperalgesia (Vecchiet et al. 1988) suggests that the hyperalgesia is caused by maintained peripheral input, which is also a necessary condition for referred pain (Kellgren 1938; Graven-Nielsen 1997a). Alternatively, the mechanisms responsible for deep and cutaneous hyperalgesia after muscle pain may be caused by central hyper-excitability.

Central hyperexcitability of dorsal horn neurons caused by the muscle pain may explain the expansion of pain with referral to other areas and probably also hyperalgesia in these areas. However, facilitated neurons do not readily account for the decreased sensation to certain sensory stimuli in the referred area. Descending inhibitory control of the dorsal horn neurons and segmentally organized inhibitory mechanisms may explain the decreased response to additional noxious stimuli in the referred pain area. Recently, we found that saline-induced muscle pain gave rise to deep tissue hypoalgesia in extra segmental areas (including the area of referred pain) distant from the pain focus (Graven-Nielsen et al. 1998a).

Summary on muscle pain. At least two mechanisms may be operating during local and referred muscle pain: (1) central hyperexcitability generates referred pain and increased modality-specific responses, and (2) descending or segmental inhibition modulates the sensory neurons in the dorsal horn. These mechanisms may be competitive, thus resulting in the complex sensory findings involved in muscle pain.

Visceral Pain

In chronic diseases of the gut, nonpainful stimuli (e.g., gas, stool) may be perceived as painful and lead to referred pain. It is believed that visceral referred pain and hyperalgesia contribute significantly to the painfulness of these conditions.

Referred pain and temporal summation in visceral pain. Referred pain from visceral stimulation has been suggested as a manifestation of central hyperexcitability related to nociceptive visceral input (Mayer et al. 1995). As with referred muscle pain, this central hyperexcitability might share some features with secondary hyperalgesia after cutaneous C-fiber stimulation. In recent animal studies, NMDA-antagonists have inhibited visceral nociceptive mechanisms (Cervero 1995). In addition, the degree and spread of hyperalgesia depend on the duration and intensity of stimulation. In healthy subjects, Ness and Gebhart (1990) performed a series of ten colonic distensions of 30 seconds duration separated by four minutes and observed that both the pain intensity and the referred pain area increased during the sequential stimulations. Repeated electrical stimuli in different areas of the esophagus (Frøbert et al. 1995) and the gut (Arendt-Nielsen et al. 1997b; Drewes et al. 1997a) also produced temporal summation. We found

(Arendt-Nielsen et al. 1997b) that continuous electrical stimulation of the gut caused a progressive increase in the referred pain area as the stimulus time was increased from 30 to 120 seconds, which indicates the dynamic character of the referred area. Although subjects may hardly perceive a single stimulus, repeated stimuli are much more potent in generating pain from viscera. Central hyperexcitability and alterations in supraspinal descending modulation, evoked by repeated stimulation of afferent fibers, may increase the visceral sensation of stimuli that are normally not perceived as pain (Mayer et al. 1995; Kolhekar and Gebhart 1996).

Although sustained central hyperexcitability could explain many aspects of chronic pain in inflammatory and functional visceral disorders, only limited evidence is available in human visceral pain (Gebhart 1995). Swarbrick and colleagues (1980) reported increased and atypical areas of referred pain to visceral stimulation in patients with irritable bowel syndrome compared to controls. Recently, Munakata et al. (1997) demonstrated that repetitive rectal balloon distension in patients with irritable bowel syndrome results in hyperalgesia and increased viscerosomatic referral compared to controls. Mertz and colleagues (1995) found increased responses to distension and electrical stimulation. Therefore, a central hyperexcitability may affect the processing of sensory input from the rectum in these patients. Increased responses to electrical stimulations and distension have also been demonstrated in patients with nonulcer dyspepsia (Klatt et al. 1997).

Hyperalgesia related to visceral pain. Visceral hyperalgesia probably includes both peripheral and central components. Afferent fibers innervating the gut can be sensitized by endogenous chemicals that are released or synthesized after tissue injury (Mayer and Gebhart 1994; Gebhart 1995). This process results in the development of hyperalgesia with decreased excitation thresholds of both low-threshold and high-threshold visceral afferents. In addition, recruitment of "silent" nociceptors may occur (Cervero and Jänig 1992).

In visceral pain, hyperalgesia in referred pain areas has been described in human (Ness and Gebhart 1990) and animal (Ness and Gebhart 1990; Giamberardino et al. 1994) studies. In systematic clinical studies of patients with calculosis of the upper urinary tract, hyperalgesia in cutaneous and muscular tissue was seen in the referred pain area, with normalization after stone elimination (Giamberardino et al. 1994). In another model, electrical stimulation of the stomach and duodenum during gastroscopy made it possible to stimulate a well-defined area of the mucosa under visual inspection. In a study of healthy subjects, Drewes et al. (1997b) administered painful continuous electrical stimulation in the prepyloric area of the stomach to assess the sensitivity in the referred pain area to electrical and mechanical stimuli and heat. They reported hyperalgesia to heat but no change in the sensitivity to other stimuli.

Summary on visceral pain. Sensitization of visceral afferents, recruitment of "silent" nociceptors, central summation of noxious input, and central hyperexcitability may explain aspects of the pain associated with inflammatory and functional disorders of the gut. These mechanisms are usually reversible, and the nervous system normalizes when the inflammation subsides. The mechanisms underlying painful chronic "functional"

disorders of the gut, such as irritable bowel syndrome, remain unclear, although heightened local and referred responses to visceral stimulation have been demonstrated.

Conclusion

Hyperalgesia is most likely related to pain in deep tissue and, evidently, it is an important clinical phenomenon. There are common features in relation to referred pain, temporal summation, and hyperalgesia from muscle and viscera. Hyperalgesia from deep tissue can be detected as increased pain responses to normally nonpainful stimuli or increased pain to a normally painful stimulation. The extent of referred pain is related to the degree and duration of continuing pain and, most likely, to the degree of central hyperexcitability. Temporal summation is a potent mechanism and may be strongly facilitated by hyperexcitability. However, inhibitory mechanisms may also be involved in the somato-sensory sensibility changes in muscle and visceral pain.

In recent years, human experimental pain research has provided some quantitative methods to study this phenomenon. Only a few clinical studies have been performed, but we hope that future studies will apply the available experimental techniques to investigate the important mechanism of deep tissue hyperalgesia. Better characterization of referred pain and hyperalgesia involved in deep pain may also help to optimize and rationalize pain management.

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