

## REFERRED MUSCLE PAIN/HYPERALGESIA AND CENTRAL SENSITISATION

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**Referred muscle pain, resulting from algogenic conditions in viscera or other deep somatic structures (another muscle, a joint), is most often accompanied by secondary hyperalgesia and trophic changes (hypotrophy). Referred pain/hyperalgesia from viscera is partly due to central sensitisation of viscerosomatic convergent neurons (triggered by the massive afferent visceral barrage) but also probably results from a reflex arc activation (the visceral input triggers reflex muscle contraction in turn responsible for sensitisation of muscle nociceptors). Referred pain/hyperalgesia from deep somatic structures is not explained by the mechanism of central sensitisation of convergent neurons in its original form, since there is little convergence from deep tissues in the dorsal horn neurons. It has been proposed that these connections, not present from the beginning, are opened by nociceptive input from skeletal muscle, and that referral to myotomes outside the lesion results from the spread of central sensitisation to adjacent spinal segments.**

*Key words:* referred pain, secondary hyperalgesia, muscle, central sensitisation

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### INTRODUCTION

Pain at the muscle level not only derives from pathologies primarily involving the tissue but can also result from algogenic conditions occurring in distant structures, either visceral or deep somatic (another muscle, a joint) (*referred muscle pain from viscera and deep somatic structures*). In the referred area, the symptom is frequently accompanied by secondary hyperalgesia and trophic changes (1).

In the following sections the characteristics of referred muscle pain/hyperalgesia in various clinical conditions will be briefly examined and the pathophysiological role of central neuroplastic changes versus the role of possible peripheral mechanisms will then be discussed, based on the results of experimental studies on animal models of the condition.

### REFERRED MUSCLE PAIN FROM VISCERA

#### *Clinical aspects*

The process of pain referral occurs constantly in visceral nociception. After a transitory phase in which visceral pain is in fact perceived as a direct symptom (the so-called 'true visceral pain', always felt along the midline, accompanied by marked neurovegetative signs and emotional reactions), the sensation is 'transferred' to somatic areas of the body wall which are generally located within the metameric field (homologous segments) of the affected internal organ (2, 3). In these areas, secondary hyperalgesia may arise (referred pain without and with hyperalgesia). The hyperalgesia most frequently involves the muscle layer, where it is often accompanied by a state of sustained contraction, but can also often extend upwards to involve the subcutaneous tissue and the skin, in the case of repeated and/or long-lasting algogenic processes (1).

The muscle hyperalgesia has been documented in the areas of referred pain from viscera in terms of a significant decrease in pain thresholds to both mechanical and electrical muscle stimuli in a number of clinical studies in patients affected with various visceral pathologies (e.g. renal colics, biliary colics, primary dysmenorrhea) (4–11). This hyperalgesia appeared to be an early process, as it tended to manifest as early as the first visceral episodes, was accentuated in extent by the repetition of the visceral pains and lasted for a long time, i.e. it not only outlasted the spontaneous pain from the internal organ, but sometimes also the presence itself of the primary focus in the viscus. In patients affected with urinary calculosis, in fact, it was often detectable even a long time after the stone had been expelled. In addition to the hyperalgesia, the muscle in the areas of referred pain from viscera is also often the site of trophic changes, mostly in terms of decreased thickness and section area (tendency to muscle atrophy) (5). This phenomenon has been documented via clinical procedures but also precisely quantified through ultrasound evaluation in patients (see 12).

Referred muscle hyperalgesia/trophic changes in a specific body area can also be the result of concurrent algogenic processes in two different visceral domains which share part of their central sensory projection, e.g. female reproductive organs and urinary tract (T10–L1) or heart and gallbladder (T5) (phenomena of viscerovisceral hyperalgesia). In this case, the extent of the referred hyperalgesia is notably enhanced, as happens, for instance, in the oblique musculature of female calculosis patients who also suffer from dysmenorrhea (8).

*Pathophysiological aspects*

Mechanisms underlying referred muscle pain from viscera are still incompletely known, in spite of an exponential rise in the number of studies in the field in recent years (5, 13). Interpretation problems particularly concern the form of referred muscle pain with hyperalgesia.

Simple referred pain (without hyperalgesia) is in fact relatively easy to account for, given the extensively documented phenomenon of viscerosomatic convergence in the central nervous system (at both spinal and supraspinal levels). At the spinal level, in particular, neurons receiving convergent input from deep somatic structures (including muscles) and visceral structures appear located in the deep layers of the dorsal horn (14). The pain would be directly referred to muscle instead of to the viscera because of a misinterpretation on behalf of higher brain centres (see 2, 3).

Regarding referred muscle pain with hyperalgesia, the most credited hypothesis attributes the phenomenon to a process of central sensitisation taking place in the CNS, triggered by the massive afferent visceral barrage. This process, involving hyperactivity and hyperexcitability of viscerosomatic convergent neurons, would facilitate the central effect of the normal input coming from the muscle (14–16). Signs of central sensitisation have, indeed, been found in electrophysiological studies on animal models of referred muscle hyperalgesia from viscera, such as the rat model of artificial ureteric calculosis, in which the animals display hypersensitivity of the oblique musculature ipsilateral to the implanted ureter (17).

Changes in the excitability and response properties of dorsal horn neurons which receive input from the hyperalgesic muscle have been found in rats with artificial calculi as compared to control animals. A significantly increased percentage of dorsal horn neurons displayed a receptive field in the hyperalgesic muscle; a significantly higher percentage of these neurons also showed ongoing activity. Neurons with muscle input also presented a decreased threshold of activation via mechanical stimuli. These changes were more marked in animals that had presented more behavioural episodes indicative of visceral pain and more muscle hyperalgesia (18, 19). Similar results were obtained by Roza et al. (20), employing this same model, in electrophysiological experiments in which they examined the characteristics of neurons processing information from the ureter (in calculosis rats versus rats with intact ureters). These authors concluded that the presence of a ureteric stone evokes excitability changes of spinal neurons (enhanced background activity, greater number of ureter-driven cells, decreased threshold of convergent somatic receptive fields) which probably account for the referred muscle hyperalgesia seen in rats with calculosis.

When muscle hyperalgesia results from algogenic processes involving two different visceral districts with partially overlapping sensory projection, it is probably contributed to by phenomena of central sensitisation involving visceroviscerosomatic convergent neurons (21). Viscerovisceral convergences have in fact

been shown to exist among different internal organs, in addition to viscerosomatic convergence (13, 21).

It has been suggested that N-methyl-D-aspartate acid (NMDA) receptors play an important role in the generation of central hyperexcitability changes mediating referred hyperalgesia from viscera (14, 16).

The persistence of hyperalgesia often beyond the presence of the 'macroscopic' peripheral visceral focus in the clinical setting has been interpreted by some authors as the indicator that central plastic changes, once established, may persist, becoming relatively independent of the primary triggering event (see 7). However, the results of studies on ureter motility in rats with artificial ureteral calculosis (abnormal hypermotility persisting long after stone elimination) suggest that a number of 'clinically inapparent' peripheral visceral changes are likely to outlive the presence of the primary focus and thus maintain the state of central hyperexcitability via persistence of the peripheral drive (22).

Central changes, however, are probably not the sole mechanism involved in referred muscle phenomena, as suggested by the presence of trophic changes in the muscle.

The afferent barrage from the internal organ is likely to activate a number of viscerosomatic reflexes towards the periphery responsible for both the increased sensitivity and the modification of thickness and consistency of deep body wall tissues (2, 3, 23). Regarding the muscle, in particular, the 'reflex arc activation' would promote reflex muscle contraction, in turn possibly responsible for sensitisation of nociceptors locally, which would account for the hyperalgesia (1).

This theory had originally been put forward on the basis of the clinical observation of the sustained muscle contraction that so often accompanies the states of prolonged visceral pain in the area of referral (3). Recent studies by our group have provided some experimental evidence for this as yet theoretical mechanism, by employing the previously mentioned animal model of artificial ureteric calculosis. In the hyperalgesic muscle of stone rats, we found a number of morphofunctional changes indicative of skeletal muscle contraction [decreased I band length/sarcomere length ratio, increased muscle cell membrane fluidity, increased Ca<sup>++</sup> uptake capacity by the sarcoplasmic reticulum (SR) and decreased Ca<sup>++</sup> release capacity by the SR] which were proportional to the number of ureteral 'crises' displayed by the animals, in turn proportional to the degree of the muscle hyperalgesia itself (see 5). These results suggest a contribution by peripheral mechanisms to the generation of secondary muscle hyperalgesia.

## REFERRED MUSCLE PAIN FROM DEEP SOMATIC STRUCTURES

*Clinical aspects*

*Referred pain from muscles.* A typical clinical example of referred pain from one muscle to another is represented by myofascial

pain syndromes sustained by trigger points, defined as: 'spots of exquisite tenderness in muscles or their fascia, localised in taut, palpable bands, which mediate a local twitch response of muscular fibres under a specific type of palpation (snapping) and give rise to pain, tenderness and autonomic phenomena as well as dysfunction in areas usually remote from their site, called targets'. In the target zone, muscle hyperalgesia accompanies the spontaneous pain, as documented by a significant decrease in the pain threshold to electrical and pressure stimulation (24–27).

*Referred pain from joints.* A typical example of referred muscle pain from a joint is the painful symptomatology in osteoarthritis of the knee (28). The skeletal muscles connected to the joint are tender and tense. In patients with unilateral osteoarthritis of the knee, pain thresholds to pressure stimulation (Fischer's algometer) (refs. in 1) in the periarticular area are significantly lower on the affected than on the nonaffected side at the level of the vastus lateralis muscle, but more so of the vastus medialis, which proves to be the most involved muscle structure. Pain thresholds to electrical stimulation of the vastus medialis, evaluated in the same area as that tested with the pressure algometer, also reveal significantly lowered values on the affected side as compared to the opposite side. The section area of this same muscle, examined by echographic scans, is smaller on the affected than on the non-affected side. In the standing position, intense electromyographic activity of the vastus medialis is seen in the patients, which increases on straightening the trunk (28), in contrast to a total absence of activity in healthy subjects in the same conditions.

#### *Pathophysiological aspects*

Similarly to what has been described for visceral nociception, referred muscle pain from somatic structures (which is so often accompanied by referred hyperalgesia) has been attributed to phenomena of central hyperexcitability triggered by the primary algogenic focus. Animal studies have indeed provided good evidence that dorsal horn neurons become hyperexcitable in response to noxious stimulation of deep tissues (and that NMDA receptors and neurokinin receptors are most likely involved in this mechanism) (29–31).

To account for the phenomenon of referral, however, central hyperexcitability should involve neurons receiving convergent input from the site of injury and the referred zone, while it is known that in dorsal horn neurons there is little convergence from deep tissues (whether between different muscles or between muscles and joints) (32). Thus, referred pain from somatic structures is not easily explained on the basis of the 'convergence-facilitation' theory in its original form.

Mense (32) suggested an interesting theory, especially to account for referred pain from one muscle to another, in the light of the results of experimental studies in animals. Recordings from dorsal horn neurons revealed that noxious stimuli to a specific receptive field in a muscle generated within minutes new muscle receptive fields at a distance from the original one (29, 33). Based

on these data, the explanation proposed is that convergent connections from deep tissues to dorsal horn neurons are not present from the beginning but are opened by nociceptive input from skeletal muscle, and referral to myotomes outside the lesion is due to the spread of central sensitisation to adjacent spinal segments (32). Many features of referred pain (intensity, time duration, and distribution) can be explained by this theory.

As for visceral nociception, however, central mechanisms alone do not seem sufficient to account for all the phenomena present in the area of referral, especially the trophic changes accompanying hyperalgesia. Thus, in line with the hypothesis put forward for internal organs, it has been suggested that the afferent barrage from the deep focus (in muscle or joint) triggers the activation of a reflex arc towards the periphery (area of referral) via somatic efferent fibres towards the muscle. These reflex mechanisms would be responsible for the frequent finding of sustained contraction of muscles in the areas of referral (leading in time to a dystrophic state of the tissue) (see 28).

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