doi:10.1111/j.1468-2982.2007.01295.x

REVIEW

Myofascial trigger points and sensitization: an updated pain model for tension-type headache

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Cephalalgia

Fernández-de-las-Peñas C, Cuadrado ML, Arendt-Nielsen L, Simons DG & Pareja JA. Myofascial trigger points and sensitization: an updated pain model for tension-type headache. Cephalalgia 2007; 27:383–393. London. ISSN 0333-1024

Present pain models for tension-type headache suggest that nociceptive inputs from peripheral tender muscles can lead to central sensitization and chronic tension-type headache (CTTH) conditions. Such models support that possible peripheral mechanisms leading to pericranial tenderness include activation or sensitization of nociceptive nerve endings by liberation of chemical mediators (bradikinin, serotonin, substance P). However, a study has found that non-specific tender points in CTTH subjects were not responsible for liberation of algogenic substances in the periphery. Assuming that liberation of algogenic substances is important, the question arising is: if tender muscle points are not the primary sites of on-going neurogenic inflammation, which structure can be responsible for liberation of chemical mediators in the periphery? A recent study has found higher levels of algogenic substances, and lower pH levels, in active myofascial trigger point (TrPs) compared with control tender points. Clinical studies have demonstrated that referred pain elicited by head and neck muscles contribute to head pain patterns in CTTH. Based on available data, an updated pain model for CTTH is proposed in which headache can at least partly be explained by referred pain from TrPs in the posterior cervical, head and shoulder muscles. In this updated pain model, TrPs would be the primary hyperalgesic zones responsible for the development of central sensitization in CTTH. □*Algogenic substances, central sensitization, myofascial trigger points, peripheral nociception, tension-type headache*

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Introduction

Headache is one of the most common problems seen in medical practice. Among the many types of headache disorders, tension-type headache (TTH) is one of the most prevalent in adults. Population-based studies suggest 1-year prevalence rates of 38.3% for episodic TTH and 2.2% for chronic TTH (1). In addition, the prevalence of TTH has increased in recent years (2).

Despite some advances, the pathogenesis of TTH is not clearly understood. It has been demonstrated that the most prominent clinical finding in both adults and children suffering from TTH is an increased tenderness to palpation of pericranial tissues (3–7). The increased tenderness seems to be

uniformly increased throughout the pericranial region and both the muscles and tendon insertions have been found to be excessively tender (6, 7). In addition, it has also been reported that pressure pain threshold (PPT) levels are lower in patients with chronic tension-type headache (CTTH) compared with control healthy subjects (8–10).

It has been postulated that increased pericranial tenderness and decreased PPT levels in CTTH subjects may be due to an increased sensitivity (hyperexcitability) in the central nervous system or in the periphery. However, the demonstration of a relation between pericranial tenderness and central sensitization does not reveal the cause–effect relationship between these factors. Bendtsen et al. (11) established a pain model in which the main problem in CTTH is the sensitization of central pathways due to prolonged nociceptive inputs, possibly provoked by the liberation of algogenic substances at the periphery, from pericranial myofascial tender tissues. The presence of prolonged peripheral inputs can be a mechanism of major importance for the conversion of episodic into chronic TTH (11). The proposed model explains the sensitization at the level of the spinal dorsal horn/trigeminal nucleus, the slightly increased supraspinal hypersensitivity, the slightly increased muscle activity, the increased muscle hardness, the chronic pain and the absence of objective signs of peripheral pathology in patients with CTTH with increased pericranial tenderness. However, the model does not account for the mechanisms that initiate the central sensitization, i.e. the structures responsible for the nociceptive input from the periphery (11).

The aims of the present paper were: (i) to review the fundamental neurophysiology of central sensitization in CTTH; and (ii) to update the pain model for CTTH based on recent histochemical and clinical studies on referred muscle pain in TTH patients.

Central sensitization in CTTH

Sensitization of peripheral muscle nociceptors by liberation of algogenic substances

Spinal dorsal horn neurons that receive inputs from myofascial tissues can be classified as high-threshold mechano-sensitive (HTM) neurons, which require noxious intensities of stimulation for activation, or as low-threshold mechano-sensitive (LTM) neurons, which are activated by innocuous stimuli (12). It has been demonstrated that HTM dorsal horn neurons have a positively accelerating stimulus–response function, whereas LTM neurons have a linear stimulus–response function (13). This finding suggests that the linear stimulus–response function in human muscles may be caused by activity in LTM afferents, although at first this seems unlikely. Furthermore, several studies have demonstrated that prolonged noxious input from the periphery is capable of sensitizing spinal dorsal horn neurons, showing that LTM afferents can mediate pain (12, 14–16).

It is known that chemical mediators may sensitize the nociceptive nerve endings. Particularly effective stimulants for skeletal muscle nociceptors are endogenous substances such as bradykinin or serotonin (12). Several studies have found that sensitization of nociceptive nerve endings is greater with the combination of both substances rather than with each substance alone (17, 18). Therefore, muscle pain is produced mainly by noxious stimuli that lead to increased synthesis and release of endogenous algogenic substances such as serotonin, bradykinin, histamine or prostaglandins. Such stimuli may cause the antidromic release of neuropeptides from the nerve endings of C fibres which contain neuropeptides such as calcitonin gene-related peptide, substance P or neurokinin A (19, 20). The liberation of algogenic substances would lower tissue pH and then activate the arachidonic acid cascade that produces a number of unsaturated lipid products. Sensitization of nociceptors would cause spontaneous neuronal discharge, a lowered threshold to stimuli that normally provoke pain and an increased firing to stimuli that are not ordinarily perceived as painful. Previous studies have confirmed the presence of sensitization of peripheral muscle nociceptors in both chronic (11) and episodic TTH (21, 22). Finally, other inflammatory chemicals believed to be involved include bradykinin from plasma, serotonin (5HT) from platelets and glutamate, which are known to affect the membranes of polymodal nociceptors to produce sensitization (23).

In addition, activation of silent peripheral nociceptors might result in a qualitatively changed stimulus–response function, explaining the abnormal stimulus–response function seen in patients with chronic myofascial pain (24). Further, it has been recently found that the displacement of the stimulus–response function is closely associated with frequency of headache in CTTH sufferers (25).

Sensitization of second-order neurons in the dorsal horn and in the trigeminal nucleus caudalis

Central sensitization can be generated by prolonged nociceptive inputs from the periphery (26). This mechanism is particularly important in patients with chronic myofascial pain, since inputs from muscle nociceptors are more effective in inducing prolonged changes in the behaviour of dorsal horn neurons than inputs from cutaneous nociceptors (27).

Increased excitability of the dorsal horn neurons would alter pain perception significantly. In this sensitized state, previously ineffective low-threshold Aβ fibre inputs to nociceptive dorsal horn neurons may become effective (28. 29). In such a way, pain could be generated by low-threshold Aβ fibres, which clinically will manifest as allodynia. It has been suggested that the major cause of increased pain sensitivity in chronic pain is an abnormal response to inputs from low-threshold Aβ fibres (30). In addition, the response to activation of high-threshold afferents would be exaggerated, which clinically will manifest itself as hyperalgesia. Decreased PPT levels, i.e. local hyperalgesia, has been found in both cephalic (9, 10) and extracephalic (8, 31) sites in CTTH, and other chronic musculoskeletal conditions such as whiplash (32).

Further, in the sensitized state, the afferent Aβ fibres, which normally inhibit Aδ and C fibres by presynaptic mechanisms in the dorsal horn, will, on the contrary, stimulate the nociceptive second-order neurons. Therefore, the effect of Aδ and C fibre stimulation of the nociceptive dorsal horn neurons will be promoted and the receptive fields of the dorsal horn neurons will be expanded (33). The nociceptive input to supraspinal structures will be considerably increased and, if more spatial input exists, may result in increased excitability of supraspinal neurons (34) and decreased inhibition or increased facilitation of nociceptive transmission in the spinal dorsal horn (35), which will manifest clinically as generalized pain hypersensitivity. Generalized hyperalgesia has been recently demonstrated in CTTH patients (36), and other chronic musculoskeletal conditions, i.e. osteoarthritis (37) and fibromyalgia (38).

Which peripheral structure is responsible for the liberation of algogenic substances?

Actual pain models for TTH establish that prolonged nociceptive inputs from myofascial tender tissues, i.e. peripheral sensitization of muscle nociceptors provoked by the liberation of algogenic substances, could lead to central sensitization in CTTH (11). The question arising is: which structures and mechanisms are responsible for initiating the liberation of algogenic substances in the periphery?

Bendtsen et al. have suggested that pericranial tender points could lead to central sensitization in CTTH (11). However, Ashina et al. found no difference in change in interstitial concentration of adenosine 5′-triphospate (ATP), glutamate, bradikinin, prostaglandin E_2, glucose, pyruvate and urea from baseline to exercise and post-exercise periods between non-specific tender points of CTTH subjects and controls (39). Authors of that study concluded that tender points in CTTH subjects are not responsible for liberation of algogenic substances in the periphery (39). On the other hand, significantly higher levels of algogenic substances, i.e. bradykinin, calcitonin gene-related peptide, substance P, tumour necrosis factor-α, interleukin-1β, serotonin and norepinephrine, and lower pH levels, have been found in active but not in latent myofascial trigger points (TrPs) (40). Since tender points (increased tenderness, local but not referred pain) and myofascial TrPs (hypersensitive spot, taut band in a skeletal muscle, both local and referred pain pattern) are different disorders, we can update the pain model for TTH based on peripheral sensitization of muscle nociceptors provoked by myofascial TrPs.

In conclusion, intense afferent nociceptive input from peripheral muscle sensitization may alter the dorsal horn circuitry by unmasking, or activating, previously ineffective synapses to form novel synaptic contacts between low-threshold afferents and high-threshold mechanosensitive dorsal horn neurons (41). Therefore, in these patients the prolonged nociceptive input from muscle TrPs may lead to sensitization of nociceptive second-order neurons at the level of the spinal dorsal/trigeminal nucleus.

Muscle referred pain and myofascial trigger points

Convergence of nociceptive inputs on the trigeminal nucleus caudalis explaining muscle referred pain to the head

Small diameter group III and IV fibres from neck and shoulder muscles terminate mainly on neurons located in the superficial and intermediate dorsal horn (laminae I and V) of the spinal cord (42, 43).

Myofascial afferents from several different areas converge onto the same second-order nociceptive relay neurons in the spinal cord and the trigeminal nucleus caudalis. Animal (44) and human (45, 46) studies have clearly shown the convergence of cervical and trigeminal afferents in the trigeminal nerve nucleus caudalis, constituting the anatomical basis for the referred head pain from neck and shoulder muscles. Since nociceptive somatic afferents from muscles of the upper cervical roots, particularly C1 to C3, and the trigeminal nerve, particularly V1 (oftalmic) and V3 (mandible) nerves, converge on the same relay neurons, it is assumed that the message to supraspinal structures can be misinterpreted and localized as pain in other structures distant from the site of painful stimulus (muscle referred pain).

In addition, dorsal horn neurons that receive afferents from muscles frequently receive input from other structures (47, 48). This extensive convergent input to dorsal horn neurons may account for the often diffuse and poorly localized nature of deep pain sensation in humans, particularly when pain is intense. In addition, animal studies have demonstrated spinal level spread of the pain message from one dorsal horn cell to another that is initiated by strong input from muscle nociceptors (29, 49) and can be interpreted as a likely contributing cause of muscle referred pain (50).

Different experimental pain models have been proposed in order to elicit referred pain from pericranial muscles. Hypertonic saline injections induce firing in a large proportion of Aδ and C fibres and cause deep, aching, referred pain in humans, similarly to clinical muscle pain (51). Schmidt-Hansen et al. have recently demonstrated that referred pain elicited by the infusion of hypertonic saline into the anterior or posterior temporalis muscles is perceived as head pain (trigeminal or cervical dermatomes) in healthy subjects (52). Further, Ge et al. have demonstrated that injection of hypertonic saline into the upper trapezius muscle elicited a referred pain to the neck and to the head in asymptomatic subjects (53, 54).

Clinical and physiological presentation of myofascial trigger points

Simons et al. define a TrP as a hyperirritable spot associated within a taut band of a skeletal muscle that is painful on compression, and usually responds with a referred pain pattern distant from the spot (a TrP) (55). From a clinical viewpoint, active TrPs cause pain symptoms, and their local and referred pain is responsible for patients' complaints. In patients, the referred pain elicited by active TrP reproduces at least part of their clinical pain pattern. Latent TrPs also evoke referred pain with mechanical stimulation or muscle contraction, but this pain is not a usual or familiar pain for the patient. Both active and latent TrPs can provoke motor dysfunctions, e.g. muscle weakness or imbalance, altered motor recruitment (56), in either the affected muscle or in functionally related muscles (55).

The formation of TrPs may result from a variety of factors (e.g. muscle overuse, mechanical overload or psychological stress). Under normal conditions, pain from TrPs is mediated by thin myelinated (Aδ) fibres and unmyelinated (C) fibres (57). Various noxious and innocuous events, such as mechanical stimuli or chemical mediators, may excite and sensitize Aδ fibres and C fibres and thereby play a role in the development of TrPs (58). Recent studies have hypothesized that the pathogenesis of TrPs could result from injured or overloaded muscle fibres (59). This could lead to endogenous (involuntary) shortening, loss of oxygen supply, loss of nutrient supply and increased metabolic demand on local tissues (60). However, these events have not been completely proven and more research is needed.

The most credible aetiological suggestion of TrPs is the integrated hypothesis, which hypothesizes that abnormal depolarization of motor endplates and sustained muscular contraction give rise to a localized 'ATP energy crisis' associated with sensory and autonomic reflex arcs that are sustained by central sensitization (61). A recent study found higher levels of pain when a noxious stimulus was applied to the motor endplate region compared with silent muscle sites (62). In addition, pain evoked from motor endplate regions was described as throbbing, sharp or aching; similar descriptions to TrP referred pain sensations (55). It has been suggested that a higher density of muscle nociceptors in the vicinity of the motor endplate region may account for the observed differences in pain (62), but this has not been confirmed in other studies. Furthermore, endplate noise and endplate spikes [electromyographic (EMG) signal from dysfunctional motor endplate regions] has been identified and significantly associated with TrPs (63, 64). Findings from these studies support the theory that TrPs could be dysfunctional motor endplates (65); however, further studies are required.

Further, it has been previously assumed that contraction of head, neck or shoulder muscles could

play a relevant role in the development of TTH. However, numerous surface EMG studies have reported normal or, more often, only slightly increased muscle activity in TTH (66–72). A pioneer study analysing EMG activity with needle electrodes found an increased EMG activity in TrPs compared with an adjacent non-tender point (73). Furthermore, spontaneous EMG activity (endplate noise) in the TrPs was significantly higher in patients with CTTH than in healthy controls (73). Since the endplate region of a muscle fibre is only 0.1 mm at the most in diameter, the increased EMG activity (motor endplate noise and spikes) could be detected only with needle electrodes precisely placed within the TrP. A histopathological cause of taut bands in human trPs has not been convincingly demonstrated. Many findings confirm the presence of excessive muscle-fibre tension, but fail to identify adequately what causes the tension. Also, there is scientific evidence showing that increased autonomic activity increases endplate noise and clinical symptoms caused by TrPs, but the specific mediator of this link is conjectural; norepinephrin is a likely candidate. Finally, although there is evidence to support the integrated hypothesis of an aetiological origin of TrPs, the above-mentioned studies have several shortcomings which should be addressed in future studies in order to confirm definitively this etiological hypothesis as the genesis of TrPs.

Finally, it has been recently demonstrated that active TrPs may cause peripheral sensitization of muscle nociceptors, since higher levels of algogenic substances and lower pH levels have been found in active TrPs compared with both latent TrP and tender points (40).

Myofascial trigger points referred pain in TTH

In their comprehensive text, Simons et al. have described the referred pain patterns from different TrPs in several head and neck muscles which have the potential to refer pain to the head: upper trapezius, temporalis, sternocleidomastoid, spleniis capitis, suboccipital muscles, etc. (Fig. 1) (55). Since TTH is characterized by bilateral, pressing or tightening pain; pressure or band-like tightness; and/or increased tenderness on palpation of neck and shoulder muscles (74), these pain features resemble the descriptions of referred pain originating in TrPs (55).

Recent studies have demonstrated clinical evidence of the presence of TrPs in certain neck and shoulder muscles in CTTH. Marcus et al. found, in a non-blinded study, that TTH subjects had a greater number of either active or latent TrPs than healthy subjects (75). However, these authors did not specify in which muscles TrPs were observed more frequently. Similar findings have been reported for osteoarthritis patients (37). We recently demonstrated, in blinded controlled studies, that CTTH is associated with active TrPs in the suboccipital muscles (76), and in the upper trapezius, sternocleidomastoid and temporalis muscles (77). All CTTH patients had active TrPs which, when pressed, elicited referred pain that reproduced the same head pain as during their headache attacks (Fig. 2). We also found that those CTTH patients with active TrPs had greater headache intensity and frequency than those with latent TrPs, which can be considered as temporal integration of the nociceptive barrage from TrPs (76, 77). In addition, in another study we also found that patients with CTTH with bilateral TrPs in the upper trapezius muscle had greater headache pain, longer headache duration and lowered pressure pain thresholds compared with those with unilateral TrPs, which can be considered as spatial integration of nociceptive inputs from muscle TrPs (78). In these studies active TrPs, which referred a pain pattern that reproduced the patients' pain, were bilaterally located in CTTH (75–78). In a recent study, we found that patients with strictly unilateral migraine showed a unilateral distribution of active TrPs which were mostly located ipsilateral to migraine headaches compared with the non-symptomatic side (79). These findings support that, in patients with bilateral TTH, referred pain from active TrPs could be contributing to their headache perception, since TrPs were located on both sides in most of them (75–78).

Although there is scientific evidence for a close relationship between TrPs in certain head and neck muscles and CTTH (75–78), the type of research data reported to date does not establish a cause-and-effect relationship between TrPs and CTTH. It is known that central sensitization may also be involved in the generation of muscle referred pain from TrPs (80). Different studies have found that the area of the referred pain correlated with the intensity of the muscle pain in patients with sensitization of central pathways (81). It has been suggested that referred pain in deep somatic secondary hyperalgesia areas resembles that found in secondary hyperalgesic areas at the skin following, for example, capsaicin application (82). In that way, muscle referred pain may also correlate with the phenomena of secondary hyperalgesia and tenderness seen

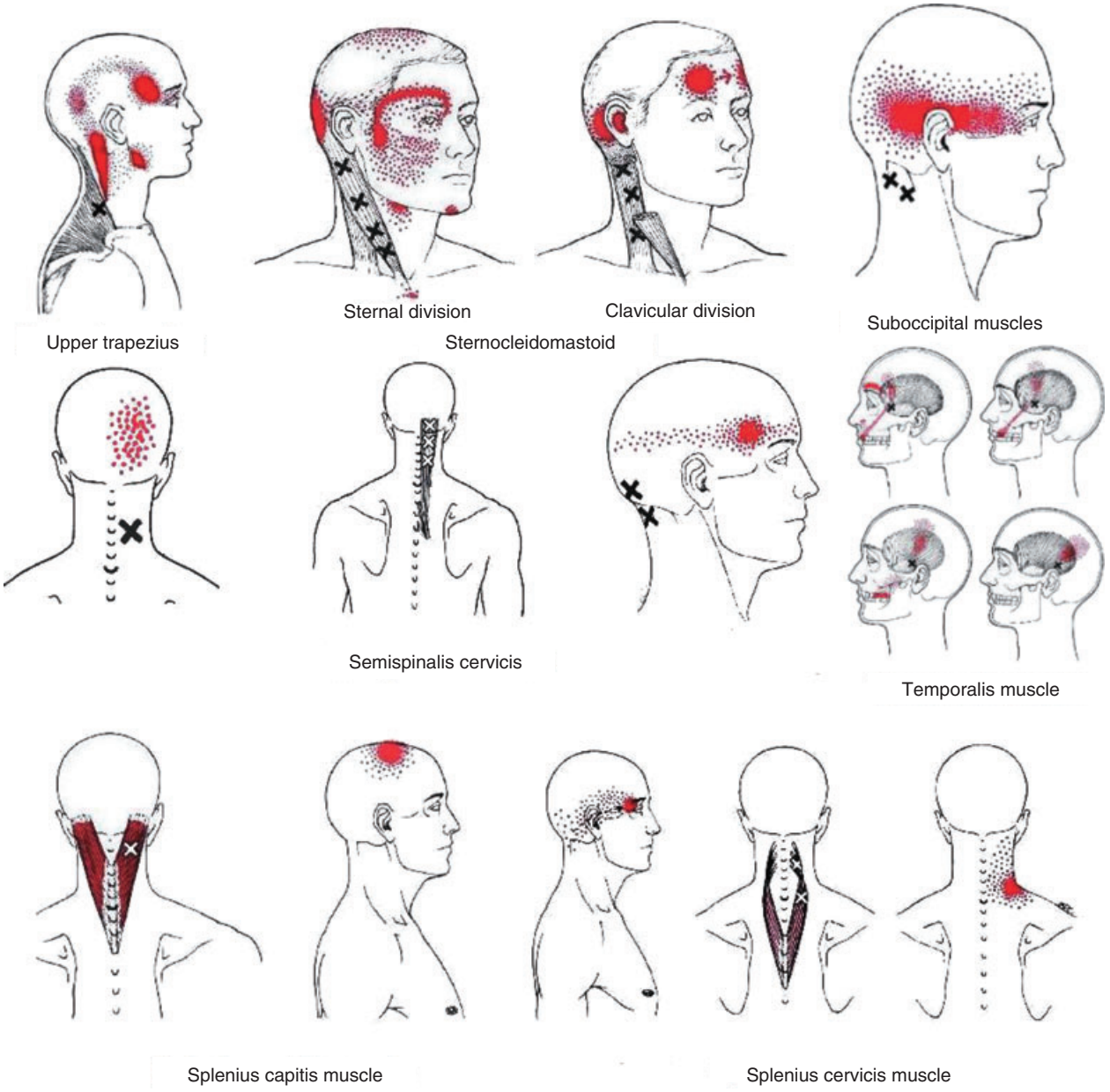

Figure 1 Referred pain patterns from upper trapezius, sternocleidomastoid, suboccipital, splenius capitis, splenius cervicis, semispinalis capitis and temporalis muscle trigger points as described by Simons et al. Reprinted with permission from Simons D, Travell J, Simons L. Travell & Simons' myofascial pain and dysfunction: the trigger point manual, Vol. 1, 2nd edn. Baltimore: Williams & Wilkins, 1999.

in CTTH patients (81). In addition, peripheral and central sensitization, and decreased descending inhibition induced by long-term nociceptive stimuli from TrPs, may also be involved in referred pain (83). Larger referred pain areas have been found in chronic musculoskeletal conditions, e.g. fibromyalgia (84), whiplash (85) and myofascial temporomadibular pain patients (86). These studies have demonstrated that patients with central sensitization showed larger referred pain areas in both symptomatic areas and distant, not usually symptomatic areas (e.g. tibialis anterior muscle), which indicates that nociceptive inputs to the central nervous system may facilitate the referred pain mechanisms possibly resulting from central sensitization (38). In addition, we have found larger referred pain areas from upper trapezius muscle TrPs in CTTH patients compared with healthy

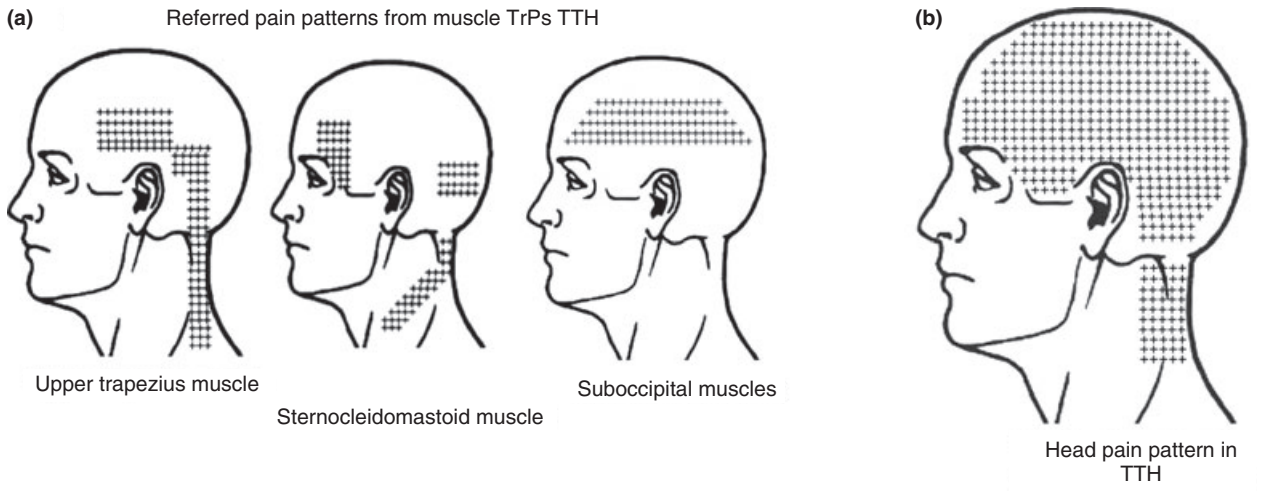

Figure 2 Similarities between the elicited referred pain from manual examination of upper trapezius, sternocleidomastoid and suboccipital muscle trigger point (TrP) in tension-type headache (TTH) patients (a) and the head pain pattern described by patients themselves (b).

subjects (78). These studies support the hypothesis that the area of muscle referred pain provoked by TrPs in neck and shoulder muscles could be enlarged in CTTH patients, contributing to sensitization of central pathways.

Since active TrPs are related to several chronic conditions accounting for sensitization of central pathways, the question arising should be: are active TrPs the consequence of central sensitization? If the central sensitization were causing active TrPs, they would not be expected in patients suffering from episodic TTH (ETTH), in which central sensitization has not been demonstrated (11). Since there is a lesser degree of central senzitisation in ETTH, because of the intermittent nature of the condition, one would expect fewer active and more latent TrPs in ETTH than in CTTH. We have demonstrated that active TrPs in the suboccipital, upper trapezius, sternocleidomastoid and temporalis muscles are also present in ETTH (87, 88), to a similar degree as in CTTH (76, 77). However, active TrPs were not related to headache clinical parameters in ETTH, supporting the hypothesis that there was no temporal summation of peripheral nociceptive inputs in patients with ETTH, due the intermittent nature of the condition. These findings indicate that active TrPs are not the consequence of central sensitization, since they are also present in ETTH.

Based on available data, we can make two assumptions: (i) myogenic referred pain elicited by active TrPs in head, neck and shoulder muscles contribute to headache pain patterns in TTH patients (75–78, 87, 88); and (ii) persistent peripheral sensitization provoked by algogenic substances elicited by active TrPs (40), could lead to sensitization of nociceptive second-order neurons at the level of the spinal dorsal/trigeminal nucleus.

Updated pain model for TTH

Olesen (89) has suggested that perceived headache intensity might be due to the sum of nociceptive inputs from cranial and extracranial tissues converging on the neurons of the trigeminal nucleus caudalis. Bendtsen (11) has suggested that the barrage of peripheral nociceptive inputs is responsible for the development of central sensitization. Our updated model suggests that TrPs located in head and neck muscles innervated by C1–C3 (e.g. upper trapezius, sternocleidomastoid, suboccipital muscles) or by the trigeminal nerve (e.g. temporalis, masseter) are responsible for the peripheral nociceptive input and could produce a continuous afferent barrage into the trigeminal nerve nucleus caudalis. Connections between afferents innervating deep structures and second-order neurons could be altered by these nociceptive afferent inputs from muscle TrPs. Convergent synaptic connections on dorsal horn neurons, which are not usually functional, could be activated if intense nociceptive input reaches the dorsal horn. Changes in size and shape of peripheral receptive fields, and the formation of new receptive fields, would occur if nociceptive barrage from muscle TrPs is maintained during time. This would result in temporal and spatial integration of neuron signals and might be one of the reasons for the central sensitization in CTTH.

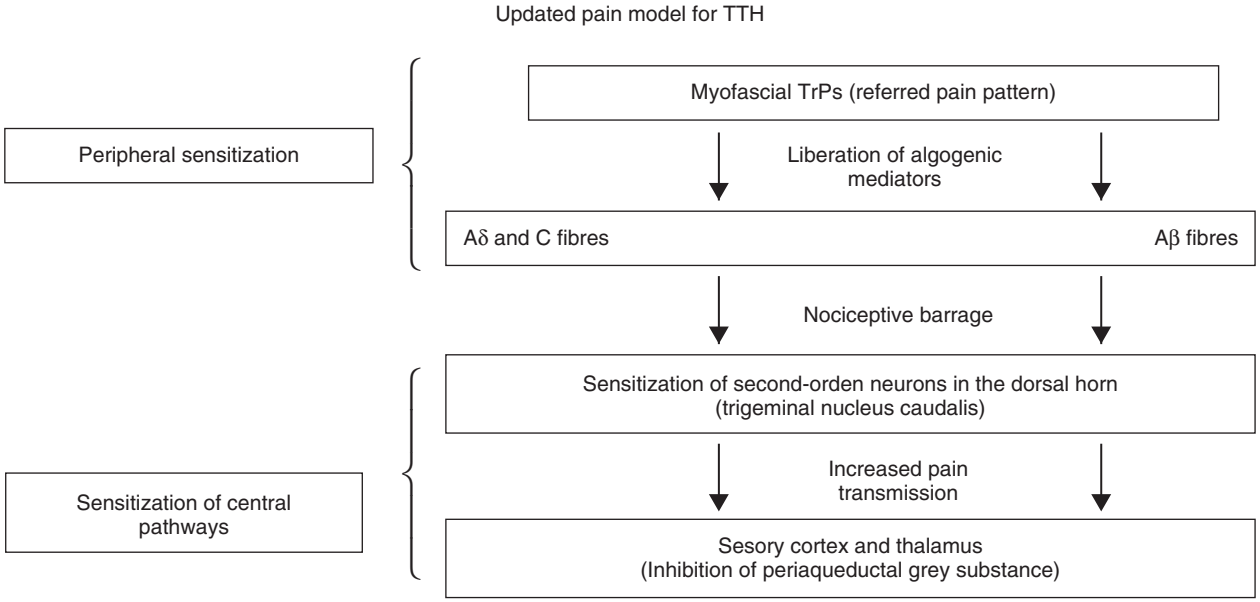

Figure 3 Updated pain model for tension-type headache (TTH) in which peripheral sensitization provoked by muscle trigger points (TrPs) can lead to sensitization of dorsal-horn neurons.

Based on new available data, an updated pain model for TTH could be hypothesized as follows: TTH can at least partly be explained by referred pain from TrPs in the posterior cervical, head (including extraocular muscles) and shoulder muscles, mediated through the spinal cord and the brainstem trigeminal nucleus caudalis, rather than only tenderness of the pericranial muscles themselves. In this updated pain model, we could consider TrPs as primary hyperalgesic zones in which referred pain areas to the head exhibit increased tenderness and decreased pressure pain thresholds (secondary hyperalgesic zones). Figure 3 illustrates the updated pain model for TTH.

Finally, a TrP role in headache does not negate the importance of other physical (e.g. malalignment of upper cervical vertebrae (90) or forward head posture (91)) or psychological (e.g. anxiety or depression) factors in exacerbating and sustaining CTTH. It is of great clinical interest to note that these same factors are known to aggravate and promote TrP activity. Many elements traditionally deemed important in the genesis of CTTH may result from inadequate strategies devised to cope with TrP-induced head pain.

In conclusion, an updated pain model for CTTH has been proposed in which headache can be at least partly caused by referred pain from active TrPs in the posterior cervical, head and shoulder muscles mediated through the spinal cord and the brainstem trigeminal nucleus caudalis. In this updated pain model, TrPs would be the primary hyperalgesic zones responsible for the development of central sensitization in CTTH. If this model is valid, every patient seen for TTH needs to be examined for TrPs, which are often apparently contributing significantly to their symptoms.

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