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REVIEW

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Pain and tension-type headache: a review of the possible pathophysiological mechanisms

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Abstract Tension-type headache represents a considerable health problem and is one of the most costly diseases in the modern society. However, the knowledge about the pathophysiological mechanisms leading to this disorder is limited. The review presents a summary of available research and experimental data on the pathophysiological mechanisms and the recent pathophysiological models. Although the pain in tension-type headache clinically resembles pain from myofascial tissues, both peripheral and central mechanisms are believed to be involved. It is likely that myofascial nociception is important in episodic tension-type headache and that central mechanisms are involved in the pathophysiology of the chronic form. Neurophysiological investigations are introduced to be the most suitable to confirm an involvement of trigeminal pathways, to substantiate recent theories on sensitization phenomena, and to disclose the exact pain-control mechanisms. More studies are needed to elucidate the mechanisms leading to central sensitization and to develop new therapeutic strategies.

Key words Central sensitization • Pathophysiology • Tension-type headache

Introduction

Tension-type headache represents a considerable health problem and is one of the most costly diseases in modern society [1]. It leads to impairment in work and social activities, and to poorer emotional and physical functioning while performing everyday roles [2]. Almost every person in the world has suffered at least once from episodic tension-type headache. A Danish population-based study found that 59% of the persons experiencing tension-type headache had it one day per month or less and 37% had it several times a month [3]. Chronic tension-type headache, i.e. headache ≥180 days per year, was found to affect 3% of the total population [3]. So as far as the socio-economic impact is concerned, this is the most important type of headache [4].

In the 1988 classification of the International Headache Society [5] and in its recently available second edition [6], tension-type headache was precisely classified and defined by means of operational criteria. The subdivision into episodic and chronic forms and into types with and without a muscular factor (i.e. disorder of the pericranial muscles) was developed mainly on the basis of clinical experience and not on scientific evidence [1]. This headache may be stress-related or associated with functional or structural cervical or cranial musculoskeletal abnormalities [7].

Tension-type headache is a separate nosological entity although it coexists with migraine in many patients [1, 8]. Many migraine attacks are accompanied by tension headache-like symptoms, particularly muscle tension and associated neck pain [8]. Moreover, migraine can be a precipitating factor in genetically predisposed individuals [9]. A genetic predisposition to a chronic tension-type headache is reflected by the 3.18-fold increased risk in first-degree relatives compared with the general population [10, 11], but the mode of transmission seems to be complex.

This type of headache typically causes pain that radiates in a band-like fashion bilaterally from the forehead to the occiput [12]. It is rarely severe but often radiates to the neck muscles and is described as tightness, pressure, or dull ache [12]. However, the knowledge about the pathophysiological mechanisms leading to this disorder is limited.

Pathophysiological hypotheses

Reviewing the existing data, Jensen [1] concluded that the underlying pain mechanisms in tension-type headache are highly dynamic, as it represents a wide variety of frequency and intensity between and within individual subjects over time. Mental or motor stress, a local myofascial release of irritants, or a combination of these may initiate the process [1]. Secondary to the peripheral stimuli, the supraspinal pain-perception structures may become activated, and because of the central modulation of the incoming stimuli, a self-limiting process results in most individuals [1].

An interesting pathophysiological model presented by Bendtsen [4] proposes that the main problem in chronic tension-type headache is central sensitization at the level of the spinal dorsal horn-trigeminal nucleus due to prolonged nociceptive inputs from the pericranial myofascial tissues. The increased nociceptive input to the supraspinal structures may in turn result in supraspinal sensitization. The central neuroplastic changes may affect the regulation of peripheral mechanisms and thereby lead to increased pericranial muscle activity or release of neurotransmitters in the myofascial tissues. Thus, central sensitization may be maintained even after the initial eliciting factors have been normalized, resulting in the conversion of episodic to chronic tension-type headache [4]. In migraine, the pain of the headache phase is mediated by the trigeminal vascular system and its central projections to the caudal brainstem nucleus caudalis and to the dorsal horn of the cervical spinal cord [13]. Thus, the trigeminocervical nucleus, in which descending sensory fibers of the trigeminal nerve are colocalized with sensory fibers from the upper cervical roots [14], is the site for an overlapping pathophysiology of migraine and tension-type headache [8]. Moreover, central sensitization has been advocated to explain chronic daily headache (including tension-type headache, chronic or transformed migraine and other chronic headaches) and this concept is now widely accepted [15]. In addition to providing a substrate for referral of neck pain to areas of the face, this convergence of trigeminal and cervical fibers provides a substrate for cervically initiated neurogenic inflammation [14].

Recent studies suggested that central sensitization, i.e. increased excitability of neurons in the central nervous system generated by prolonged nociceptive input from the pericranial myofascial tissues, plays an important role in the pathophysiology of tension-type headache [16]. Sensitivity to the various stimulus modalities (pressure, thermal and electrical) is increased at both cephalic and extracephalic locations [4, 17–20]. This indicates that pain sensitivity in the central nervous system is increased in patients with chronic tension-type headache. This unspecific hypersensitivity pointed that the general pain sensitivity is affected at the supraspinal level rather than at the segmental level of the spinal dorsal horn-trigeminal nucleus [4]. It was assumed that the general pain sensitivity in the central nervous system is increased in patients with chronic tension-type headache, while the central pain processing seems to be normal in patients with episodic tension-type headache [4].

Langemark and Olesen were the first to describe the clinical characteristics and the pronounced tenderness to manual palpation in the pericranial muscles in patients with tension-type headache [21]. It was demonstrated to be the most pronounced and consistent finding in these patients and probably represented the activation of peripheral nociceptors [1].

Human experimental models of peripheral muscle pain are actually few but they have demonstrated that myofascial tenderness can precede the headache and is therefore likely to be involved in the underlying mechanism [22]. Nevertheless, local experimental pain models in which different algogenic substances are injected into the trapezius muscles demonstrate that patients with a history of episodic tension-type headache develop significantly more local pain than healthy controls but that none of the groups develop headache [23]. Intramuscular infusion of a combination of the endogenous substances bradykinin, serotonin, histamine and prostaglandin E_2 produced a reversible, local, prolonged and moderate tenderness in episodic tension-type headache patients and healthy controls. An increased excitability of the peripheral muscle afferents was suggested [24]. The

underlying pain mechanisms for tension-type headache may therefore be an effect of either temporal or spatial summation of the peripheral stimuli or both in predisposed individuals [4].

Increased pericranial muscle tenderness has been found in patients with both episodic and chronic tension-type headache. It is positively associated with both the intensity and the frequency of tension-type headache [1, 25]. The evaluation of tenderness by manual palpation is the most specific and sensitive test for the subdivision [5] of tension-type headache patients into those with and those without a muscular disorder [4].

Pericranial muscles are significantly harder, i.e. they have a higher consistency, in patients with chronic tension-type headache than in healthy controls; muscle hardness does not fluctuate with actual pain. The pericranial muscles are significantly more tender in patients with tension-type headache than in healthy controls during as well as outside an actual headache episode [16]. These findings have previously only been detected by manual palpation, but a newly invented and validated instrument, a hardness meter, has confirmed this observation [16, 26].

The mechanisms leading to these phenomena are largely unknown. It is possible that sustained tonic contraction of muscle due to permanent dysfunction in the central nervous system contributes to the muscle hardness and the increased tenderness [27]. In particular, it would be interesting if there is any correlation between tension-type headache with a muscular contraction and the central nervous system diseases characterized by increased muscle tone. Studies of the therapeutic effect of pericranial botulinum toxin type A injections, which reduce muscle tone, yielded different results [28]. Schmitt et al. [29] demonstrated some improvement in affective variables, but the pain intensity, the number of pain-free days, and the consumption of analgesics, were not statistically different between the groups of patients who received botulinum toxin and placebo. Rollnik et al. [30, 31] did not find any beneficial effect of botulinum toxin compared with placebo despite some objectively recorded reduction in resting muscle activity. They hypothesized that the increased muscle tone plays a minor role in the genesis of chronic tension-type headache [30, 31]. Recently, it was assumed that nociceptive impulses from the pericranial muscles may be referred to the head and perceived as headache, and that myofascial tissues therefore do play an important role in tension-type headache [4]. Other factors such as tissue edema, metabolic alterations or hyperexcitability of muscle fibers may also participate [16]. The study of Ashina et al. [32] provided in vivo evidence of altered blood flow regulation in tender skeletal muscle during static work in patients with chronic tension-type headache. The results indicated that the increased excitability of neurons in the central nervous system might affect the regulation of peripheral mechanisms and thereby lead to increased tenderness and chronic headache. The alteration of the central interpretation and response to normal sensory input was suggested in patients with chronic tension-type headache [32]. In other study Ashina et al. [33] provided normal interstitial levels of inflammatory mediators and metabolites in tender trapezius muscle and assumed that the tender points in patients with chronic tension-type headache are not sites of ongoing inflammation. It is not known for certain whether the increased tenderness in tension-type headache is a primary or a secondary phenomenon to the headache.

In the current model of Bendtsen [4], some mechanisms leading to myofascial pain and tenderness are proposed: (1) sensitization of peripheral myofascial nociceptors; (2) sensitization of second-order neurons at the level of the spinal dorsal horn-trigeminal nucleus; (3) sensitization of supraspinal neurons; and (4) decreased antinociceptive activity from supraspinal structures.

Various noxious and innocuous events such as ischemia, mechanical stimuli and chemical mediators may excite and sensitize Aδ fibers and C fibers [34] and thereby play a role in the increased tenderness in tension-type headache [4]. Particularly effective stimulants for skeletal muscle nociceptors are endogenous substances such as serotonin, bradykinin and potassium ions. The peripheral sensitization induced by a given mediator may be a rather specific process affecting only some aspects of receptor function, e.g. the sensitivity to local pressure [34], and the various mediators may interact and potentiate each other's effects [4].

Central mechanisms have only been sparsely investigated in tension-type headache, although it is increasingly evident that central factors are involved in the pathophysiology of this disorder [1, 4, 17, 18]. Probably, the central mechanisms are more important for the pathophysiology of tension-type headache than previously anticipated [4]. Stress and mental tension are the most conspicuous precipitating factors in tension-type headache [25] and in migraine [9], but the exact mechanisms by which psychological stress plays a role in tension-type headache remain unclear [4]. Central factors, such as involuntary contractions of cephalic muscles, a decrease in supraspinal descending pain-inhibitory activity and supraspinal hypersensitivity to nociceptive stimuli, may be involved [4]. As in other chronic pain disorders, psychological abnormalities in tension-type headache may rather be viewed as a secondary disorder rather than a primary disease [35], and anxiety and depression are probably comorbid with chronic tension-type headache [4].

Neurophysiological evidence

Brainstem structures play a crucial role in modulating and conveying nociceptive impulses [36]. Neurophysiological approach seems to be the most suitable to confirm an involvement of trigeminal pathways and the recent theories on sensitization phenomena in primary headaches [36], although there are some doubts [37]. Controversial results have been reported regarding the different brainstem inhibitory and excitatory responses in patients with headache.

Several articles regarding the blink reflex in different types of headache have been published. Some have reported normal values of R1, R2, and R2' latency, amplitude, and size in patients with tension-type headache and in patients with migraine without aura [38–40]. In contrast, other authors found increased R1 latency in tension-type headache associated with increased headache duration and diminished recovery curve of R2 component [41]. Serotonin and noradrenaline are known to modulate pain transmission in the brain stem, so the diminished recovery curve of R2 in patients with both tension headache types may be related to a relative depletion of these neurotransmitters [41]. Puca and de Tommaso [42] found an early appearance of the R3 component at almost the perceptive threshold and increased amplitude in patients with migraine and tension-type headache. A possible primary dysfunction of central inhibitory pathways was proposed [42].

Schoenen et al. [38, 43–45] postulated that electrostimulation of the infraorbital and mental nerves elicited an early (ES1) and a late (ES2) suppression period of voluntary temporalis muscle activity, ES1 via an oligosynaptic, ES2 via polysynaptic neural net. They described shortened ES2 in patients with tension-type headache [38]. The main advantage of this method was the ability to evaluate certain antinociceptive (trigemino-trigeminal) brainstem mechanisms. The results suggested that in tension-type headache there is a deficient activation or excessive inhibition of the brainstem inhibitory interneurones [38, 44, 45]. It is likely that in tension-type headache, peripheral stimuli reduce ES2 via activation of the periaqueductal grey matter or raphe magnus nucleus. These brainstem structures are thought to inhibit the medullary inhibitory interneurons, mediating ES2 [38, 45, 46]. According to Bendsten et al. [47], ES2 is modulated by serotonergic as well as by noradrenergic neuronal pathways, and thus it is related to pain control. Some authors [48–50] reported normal ES2 in chronic tension-type headache and suggested that it may not be related to the pathophysiology of headache. However, the mean ES2 duration was found to be similar in patients with different chronic pain syndromes - tension-type headache, migraine, symptomatic headache of different etiologies, post-lumbar puncture headache and drug abuse headache [47, 51, 52]. Thus, this antinociceptive reflex may reflect a deficit in the endogenous pain control mechanisms in different types of headache.

Another investigation tool used in patients with chronic pain conditions is the antinociceptive trigeminocervical reflex. In humans it was first investigated in 1986 by Sartucci et al. [53]. The exteroceptive and nociceptive inputs of the trigeminocervical reflex are probably transmitted through a polysynaptic route, including the spinal trigeminal nuclei and reaching the cervical motoneurones [53]. It is easily obtained by stimulation of the supraorbital nerve and recorded by surface electrodes over the resting sternocleidomastoid muscle. Because of the bilateral nature of the responses and the similarities of the latency and duration of the parameters, it is comparable with R2 of the blink reflex [53, 54]. The trigeminocervical reflex had a shortened latency on the painful side in patients with chronic tension-type headache and with migraine, compared to the latency on the normal side after bilateral stimulation and to healthy controls [54]. The results suggested again decreased activity of brainstem inhibitory interneurons. The reflex pattern was the same and independent of the type of headache. It may be supposed that some abnormalities in the endogenous pain control mechanisms are similar in both types of headache - tension-type and migraine [54]. Using another technique with recording in tonically active sternocleidomastoid muscle and stimulation of the infraorbital nerve, Nardone and Tezzon [55] confirmed the abnormality of the trigeminocervical reflex in patients with chronic tension-type headache. Thus, although the ES2 and trigeminocervical reflexes are probably not closely related to the pathophysiology of tension-type headache, they may be of great interest for disclosing the basic pain control mechanisms. That is why future studies of brainstem reflexes in patients with chronic daily headache and possibly for evaluation of drug effects are clearly worthwhile.

Interesting for exploring pain mechanisms in headache are the nociceptive flexor reflexes, which are mediated through interneuronal networks at a segmental level, excitability of which is controlled by spinal as well as supraspinal pain controlling systems [56]. A major advantage of these reflexes is their close correlation with subjective pain perception thresholds. In patients with chronic tension-type headache, a decreased nociceptive flexor reflex threshold and lower pain-tolerance thresholds were reported [19]. A disorder of an endogenous antinociceptive system with disturbed balance between nociceptive and antinociceptive systems was suggested [19]. We assume that the combination of nociceptive flexor reflexes with the brainstem reflexes would be a good scientific perspective in the future headache research.

Although the pain in tension-type headache clinically resembles pain from myofascial tissues, modern pain physiology indicates that both peripheral and central mechanisms are involved [1, 4]. The decreased pain, thermal and electrical thresholds that have been reported in chronic tension-type headache patients [17, 18] probably represent a central misinterpretation of the incoming signals. A study of the stimulus-response function to mechanical pressure [27] demonstrated for the first time that chronic tension-type headache has a physiological basis and is caused at least partly by qualitative changes in the central processing of sensory information, i.e. by a central sensitization, as with other chronic pain conditions.

The pressure pain detection threshold, i.e. the lowest pressure stimulus that is perceived as painful, is normal in patients with episodic tension-type headache [57] and in groups of mixed episodic and chronic tension-type headache patients [58, 59]. In contrast, pressure pain detection thresholds were decreased in patients with chronic tension-type headache in two studies [18, 20].

The general lowering of pressure pain detection and tolerance thresholds indicates that both allodynia (pain elicited by stimuli which are normally not perceived as painful and are generated by low threshold Aβ) and hyperalgesia (increased sensitivity to painful stimuli with activation of high-threshold afferents) are present in patients with chronic tension-type headache [4, 28].

Pain detection and pain tolerance, as well as pain perception in different parts of the body, are decreased in parallel in chronic tension-type headache patients compared with controls and are modulated by a common, probably supraspinal, factor in these patients [4, 20]. Pressure pain threshold studies demonstrated a relationship between central hypersensitivity and increased pericranial myofascial tenderness in patients with chronic, but not in patients with episodic tension-type headache [4, 14, 20]. It is therefore likely that factors other than general hypersensitivity contribute to the increased pericranial muscle tenderness [4].

It has been hypothesized that the central nervous system may be sensitized at the level of the spinal dorsal horn-trigeminal nucleus in patients with chronic myofascial pain and that this central sensitization probably accounts for a large part of the increased tenderness in patients with chronic myofascial pain [4]. Bendsten [4] proposed that this central sensitization might be a prerequisite for the development of alterations at the level of spinal dorsal horn-trigeminal nucleus. Investigating this phenomenon, De Tommaso et al. [60] suggested that the pericranial tenderness might be a primary phenomenon that precedes headache and is mediated by a greater pain-specific hypervigilance at the cortical level.

Since patients with episodic tension-type headache have increased pericranial tenderness but normal central pain sensitivity, and since chronic tension type-headache usually evolves from the episodic form [1, 4, 14, 61], it is most likely that the central sensitization in patients with chronic tension-type headache is induced by prolonged nociceptive inputs from myofascial tissues, as previously suggested [20, 27]. The central sensitization could theoretically also be secondary to the chronic pain condition itself, but this is most unlikely, because the central nervous system is not sensitized in patients with chronic tension-type headache who are not tender to palpation [4]. Thus, the peripheral mechanisms in episodic tension-type headache lead to a central mechanism in chronic tension-type headache [1, 4, 28].

Biochemical evidence

It is likely that an impaired supraspinal modulation of the repeated peripheral stimulation may play a part in these chronic pain disorders, but a precise molecular identification is lacking and the cause-effect relationship to pain continuous for decades is yet unclear. Biochemical defects either in the opioid system or in the production of neurotransmitters have been suspected [19], but no recent studies have confirmed these findings. Normal plasma levels of substance P, neuropeptide Y, vasoactive intestinal polypeptide [62] and calcitonin gene-related peptide [63] in patients with chronic tension-type headache, unrelated to headache state, have been demonstrated. Among the studies of neuropeptides and endorphins only one study [64] indicated activation of the enkephalinergic antinociceptive system at the spinal-trigeminal level, whereas the beta-endorphinergic system appears normal. This enkephalinergic activation may be caused by increased activity in the primary nociceptive afferents, or may be compensatory to decreased activity in endogenous antinociceptive systems other than the opioid one [64]. Various abnormalities may result in or be a function of the disturbed balance between peripheral input and central modulation, but the primary eliciting cause and the evolution of pain are, however, still unknown [1].

Nitric oxide (NO) plays an important role in the pathophysiology of primary headaches including chronic tension-type headache [1, 4, 14, 65]. Gallai et al. [15] reported a significant increase in glutamate and nitrite levels in the cerebrospinal fluid of patients with chronic daily headache. Sarchielli et al. [65] showed increased NO synthase activity and glutamate content in platelets of patients with chronic tension-type headache. This may reflect an analogous central up-regulation in the spinal

horn-trigeminal nucleus and supraspinal structures involved in the modulation of nociceptive input from myofascial cranial structures [65]. A NO synthase inhibitor reduced headache and muscle hardness, whereas the NO donor glyceryl trinitrate caused more pain in patients with chronic tension-type headache than in healthy controls [66]. A direct effect of NO on perivascular sensory afferents or NO-induced arterial dilatation may be responsible for the immediate headache, and central sensitization at the spinal and trigeminal levels may be responsible for the delayed headache [67]. NO diffusing from the post-synaptic production site to the presynaptic glutamatergic fibers increases glutamate release that, acting on NMDA (*N*-methyl-D-aspartate) and non-NMDA receptors, further activates the nitric oxide synthase enzyme via Ca^{2+} increase, with a mechanism which can be defined as "long-term potentiation" [14]. The NMDA receptor antagonist ketamine inhibits central temporal summation in humans and has a marked hypoalgesic effect on high intensity nociceptive stimuli [68]. The central sensitization was experimentally demonstrated to be both prevented, and reversed, by NMDA receptor antagonism [69]. It was concluded that NMDA antagonists are potentially useful in treating pain hypersensitivity [69]. The nitric oxide synthase inhibitor N^G-monomethyl-L-arginine has an effect on human experimental pain [70]. With the development of more specific drugs with higher efficacy and fewer side effects, it is likely that compounds such as NMDA receptor antagonists and inhibitors may become of value in the treatment of chronic daily headache [4, 64]. These findings point out that NO-related central sensitization may be an important factor in the underlying pathophysiology [1, 65, 71].

Serotonin (5-HT) has an important role in pain modulation but its exact role is far from understood [5]. Previous studies measured peripheral serotonin metabolism in tension-type headache and provided inconsistent results: plasma and platelet 5-HT concentrations have been reported to be reduced, normal, or increased [72–74]. The number of platelet 5-HT transporters was reported to be normal in patients with chronic tension-type headache [70]. A decreased number of binding sites of $5\text{-}HT_{2A}$ receptors was found in patients with tension-type headache, suggesting post-synaptic serotonergic dysfunction in that group [75]. Using sumatriptan as a pharmacological probe, it was concluded that cerebral serotonergic functions mediated by $5\text{-}HT_{1D}$ receptors are altered in patients with chronic tension-type headache and that these patients have a dysfunction of cerebral $5\text{-}HT_{1D}$ receptors [72]. Additional studies are needed to investigate the involvement of serotonergic systems in the pathophysiology of the disease.

Conclusions

The impact of different therapeutic strategies on the pathophysiological mechanisms in tension-type headache is still open for debate. Combined first-line drug and behavioral treatments, chiefly relaxation, biofeedback and cognitive-behavioral therapy, are more beneficial in chronic tension-type headache than if administered alone [76]. It is likely that the efficacy of amitriptyline, used as first-line therapy in chronic tension-type headache, could be only partly explained by the blockade of 5-HT reuptake. Central (NMDA antagonism, e.g. reduction of central sensitization) and peripheral anti-nociceptive actions are also involved [4, 22].

Finally, sensitization of nociceptors (peripheral sensitization) and central nociceptive neurons (central sensitization) are common mechanisms contributing to the development of chronic pain. From experimental research and clinical studies, it appears that myofascial nociception is important in episodic tension-type headache and the central mechanisms are involved in the pathophysiology of the chronic form. Future research into the mechanisms leading to central sensitization may lead to a better understanding of its nature and could allow for development of new treatment strategies. The effective prevention of the evolution from a peripheral mechanism in episodic to a central mechanism in chronic tension-type headache would be a major advance.

More investigations are needed to detect the relative importance of peripheral, spinal and supraspinal central pain mechanisms and the interactions among them. The neurophysiological approach is recommended as a valuable and perspective tool for investigations into the pathophysiology of tension-type headache.

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