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 extracranial locations [4, 17–20]. This indicates that pain sensitivity in the central nervous system is increased in patients with chronic tension-type headache. This unspecified 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 E₂ 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 hyper-sensitivity 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 interneurons [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
receptors was 2+. 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.

References

1. Jensen R (2001) Peripheral and central mechanisms in tension-type headache: an update. Cephalalgia 23(Suppl):49–52
2. Waldie K, Poulton R (2002) The burden of illness associated with headache disorders among young adults in a representative cohort study. Headache 42(7):612–619
3. Rasmussen BK, Jensen R, Schroll M, Olesen J (1991) Epidemiology of headache in a general population - a prevalence study. J Clin Epidemiol 44:1147–1157
4. Bendtsen L (2000) Central sensitization in tension-type headache - possible pathophysiological mechanisms. Cephalalgia 20:486–508
5. – (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society. Cephalalgia 8(Suppl 7):1–96
6. – (2003) The international classification of headache disorders, 2nd edn. Headache Classification Subcommittee of the International Headache Society. Cephalalgia 24(Suppl 1):1–136
7. Steiner TJ, Lange R, Voelker M (2003) Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. Cephalalgia 23(1):59–66
8. Kaniecki RG (2002) Migraine and tension-type headache: an assessment of challenges in diagnosis. Neurology 58(Suppl 6):S15–S20
9. Ulrich V, Russel MB, Jensen R, Olesen J (1996) A comparison of tension-type headache in migraineurs and in non-migraineurs: a population-based study. Pain 67:501–506
10. Østergaard S, Russell MB, Bendtsen L, Olesen J (1997) Increased familial risk of chronic tension-type headache. BMJ 314:1092–1093
11. Russell MB, Østergaard S, Bendtsen L, Olesen J (1999) Familial occurrence of chronic tension-type headache. Cephalalgia 19:207–210
12. Millea PJ, Broadie JJ (2002) Tension-type headache. Am Fam Physician 66(5):797–804
13. Welch KM, Cutrer FM, Goadsby PJ (2003) Migraine pathogenesis: neural and vascular mechanisms. Neurology 60(Suppl 2):S9–S14
14. Biondi DM (2001) Cervicogenic headache: diagnostic evaluation and treatment strategies. Curr Pain Headache Rep 5:361–368
15. Gallai V, Alberti A, Coppola F, Floridi A, Sarchielli P (2003) Glutamate and nitric oxide pathway in chronic daily headache: evidence from cerebrospinal fluid. Cephalalgia 23:166–174
16. Ashina M, Bendtsen L, Jensen R, Sakai F, Olesen J (1999) Muscle hardness in patients with chronic tension-type headache: relation to actual headache state. Pain 79:201–205
17. Langemark M, Jensen K, Jensen TS, Olesen J (1989) Pressure pain thresholds and thermal nociceptive thresholds in chronic tension-type headache. Pain 38:203–210
18. Schoenen J, Bottin D, Hardy F, Gerard P (1991) Cephalic and extracephalic pressure pain thresholds in chronic tension-type headache. Pain 47:145–149
19. Langemark M, Bach FW, Jensen TS, Olesen J (1993) Decreased nociceptive flexion reflex threshold in chronic tension-type headache. Arch Neurol 50:1061–1064
20. Bendtsen L, Jensen R, Olesen J (1996) Decreased pain detection and tolerance thresholds in chronic tension-type headache. Arch Neurol 53:373–376
21. Langemark M, Olesen J (1987) Pericranial tenderness in tension-type headache. Cephalalgia 7:249–255
22. Jensen R, Olesen J (2000) Tension-type headache: an update on mechanisms and treatment. Curr Opin Neurol 13:285–289
23. Mørk H, Ashina M, Bendtsen L, Olesen J, Jensen R (2003) Experimental muscle pain and tenderness following infusion of endogenous substances in humans. Eur J Pain 7(2):145–153
24. Mørk H, Ashina M, Bendtsen L, Olesen J, Jensen R (2003) Induction of prolonged tenderness in patients with tension-type headache by means of a new experimental model of myofascial pain. Eur J Neurol 10(3):249–256
25. Rasmussen BK (1993) Migraine and tension-type headache in a general population: precipitating factors, female hormones, sleep pattern and relation to lifestyle. Pain 53:65–72
26. Sakai F, Ebihara S, Akiyama M, Horikawa M (1995) Pericranial muscle hardness in tension-type headache. A non-invasive measurement method and its clinical application. Brain 118:523–531
27. Bendtsen L, Jensen R, Olesen J (1996) Qualitatively altered nociception in chronic myofascial pain. Pain 65:259–264
28. Vandenheede M, Schoenen J (2002) Central mechanisms in tension-type headaches. Curr Pain Headache Rep 6(5):392–400
29. Schmitt W, Slowey E, Fravi N, Weber S, Burgunder J (2001) Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. Headache 41(7):658–664
30. Rollnik JD, Dengler R (2002) Botulinum toxin (DYSPORT) in tension-type headaches. Acta Neurochir Suppl 79:123–126
31. Rollnik JD, Karst M, Fink M, Dengler R (2001) Botulinum toxin type A and EMG: a key to the understanding of chronic tension-type headaches? Headache 41(10):985–989
32. Ashina M, Stallknecht B, Bendtsen L, Pedersen J, Galbo H, Dalgaard P, Olesen J (2002) In vivo evidence of altered skeletal muscle blood flow in chronic tension-type headache. Brain 125:320–326
33. Ashina M, Stallknecht B, Bendtsen L, Pedersen JF, Schifter S, Galbo H, Olesen J (2003) Tender points are not sites of ongoing inflammation - in vivo evidence in patients with chronic tension-type headache. Cephalalgia 23(2):109–116
34. Mense S (1993) Nociception from skeletal muscle in relation to clinical muscle pain. Pain 54(3):241–289
35. Holroyd KA, France JL, Nash JM, Hursey KG (1993) Pain state as artefact in the psychological assessment of recurrent headache sufferers. Pain 53:229–235
36. Cecchini A Proietti, Sandrini G, Fokin IV, Moglia A, Nappi G (2003) Trigeminofacial reflexes in primary headaches. Cephalalgia 23(s1):33–41
37. Sandrini G, Friborg L, Schoenen J, Nappi G (2003) Preface. Cephalalgia 23(Suppl 1):IV
38. Schoenen J, Jamart B, Gerard P, Lenarduzzi P, Delwaide PJ (1987) Exteroceptive suppression of temporalis muscle activity in chronic headache. Neurology 37:1834–1836
39. Avramidis TG, Podkogolou DG, Anastasopoulos IE, Kourotumanidis MA, Papadimitriou AL (1998) Blink reflex in migraine and tension-type headache. Headache 38:691–696
40. Aktekin B, Yalkaya K, Ozkayak S, Oguz Y (2001) Recovery curve of the blink reflex and exteroceptive suppression of temporalis muscle activity in migraine and tension-type headache. Headache 41:142–149
41. Sand T, Zwart JA (1994) The blink reflex in chronic tension-type headache. Migraine, and cervicogenic headache. Cephalalgia 14:447–450
42. Puca F, de Tommaso M (1999) Clinical neurophysiology in childhood headache. Cephalalgia 19(3):137–146
43. Schoenen J, Gerard P, De Pascua V, Sianard-Gainko J (1991) Multiple clinical and paraclinical analyses of chronic tension-type headache associated or unassociated with disorder of pericranial muscles. Cephalalgia 11:135–139
44. Schoenen J (1993) Exteroceptive suppression of temporals muscle activity: methodological and physiological aspects. Cephalalgia 13:3–10
45. Schoenen J (1993) Exteroceptive suppression of the temporal muscle activity in patients with chronic headache and in normal volunteers: methodological, clinical and pathophysiological relevance. Headache 33:3–17
46. Schoenen J, Wang W, Gerard P (1994) Modulation of temporals muscle exteroceptive suppression by limb stimuli in normal man. Brain Res 657:214–220
47. Bendsten L, Jensen R, Olesen J (1996) Amitriptyline, a combined serotonin and noradrenaline re-uptake inhibitor, reduces exteroceptive suppression of the temporal muscle activity in patients with chronic tension-type headache. Electroencephalogr Clin Neurophysiol 101:418–422
48. Bendtsen L, Jensen R, Brennum J, Arendt-Nielsen L, Olesen J (1996) Exteroceptive suppression of temporal muscle activity is normal in chronic tension-type headache and not related to actual headache state. Cephalalgia 16:251–256
49. Lipchik GL, Holroyd K, Talbot F, Green M (1997) Pericranial muscle tenderness and exteroceptive suppression of tension-type headache. Headache 37:368–376
50. Zwart JA, Sand T (1995) Exteroceptive suppression of temporals muscle activity: a blind study of tension-type headache, migraine and cervicogenic headache. Headache 35:338–343
51. Nakashima K, Takahashi K (1991) Exteroceptive suppression of the maseter, temporals and trapezius muscles produced by mental nerve stimulation in patients with chronic headaches. Cephalalgia 11(1):23–28
52. Paulus W, Raunbochl O, Straube A, Schoenen J (1992) Exteroceptive suppression of the temporal muscle activity in various types of headache. Headache 32:41–44
53. Sartucci F, Rossi A, Rossi B (1986) Trigemino cavernous reflex in man. Electromyogr Clin Neurophysiol 26(2):123–129
54. Milanov I, Bogdanova D (2003) Trigemino-cervical reflex in patients with headache. Cephalalgia 23(1):35–38
55. Nardone R, Tezzon F (2003) The trigemino-cervical reflex in tension-type headache. Eur J Neurol 10(3):307–312
56. Sandrini G, Arrigo A, Bono G, Nappi G (1993) The nociceptive flexion reflex as a tool for exploring pain control systems in headache and other pathologies. Cephalalgia 13(1):21–27
57. Jensen R, Rasmussen BK, Pedersen B, Olesen J (1993) Muscle tenderness and pressure pain thresholds in headache. A population study. Pain 52:193–199
58. Jensen R (1996) Mechanisms of spontaneous tension-type headaches: an analysis of tenderness, pain thresholds and EMG. Pain 64:251–256
59. Bovim G (1992) Cervicogenic headache, migraine, and tension-type headache. Pressure-pain threshold measurements. Pain 51:169–173
60. De Tommaso M, Libro G, Giudo M, Sciriuchio V, Losito L., Puca F (2003) Heat threshold and cerebral event-related potentials following painful CO2 laser stimulation in chronic tension-type headache. Pain 104:111–119
62. Ashina M, Bendtsen L, Jensen R, Ekman R, Olesen J (1999) Plasma levels of substance P, neuropeptide Y and vasoactive intestinal polypeptide in patients with chronic tension-type headache. Curr Pain Headache Rep 5:454–462.
63. Ashina M, Bendtsen L, Jensen R, Ekman R, Olesen J (1999) Plasma levels of substance P, neuropeptide Y and vasoactive intestinal polypeptide in patients with chronic tension-type headache. Pain 83:541–547
64. Ashina M, Bendtsen L, Jensen R, Schifer S, Jansen-Olesen I, Olesen J (2000) Plasma levels of calcitonin gene-related peptide in chronic tension-type headache. Neurology 55:1335–1340
65. Langemark M, Bach FW, Ekman R, Olesen J (1995) Increased cerebrospinal fluid met-enkephalin immunoreactivity in patients with chronic tension-type headache. Pain 63:103–107
66. Ashina M, Lassen LH, Bendtsen L, Jensen R, Olesen J (1999) Possible mechanisms of action of nitric oxide synthase inhibitors in chronic tension-type headache. Brain 122:1629–1635
67. Ashina M, Bendtsen L, Jensen R, Olesen J (2000) Nitric oxide-induced headache in patients with chronic tension-type headache. Brain 123:1830–1837
68. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM (1995) The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. Anesth Analg 81(1):638–642
69. Ma QP, Woolf CJ (1995) Nociceptive stimuli induce an N-methyl-D-aspartate receptor-dependent hypersensitivity of the flexion withdrawal reflex to touch: implications for the treatment of mechanical allodynia. Pain 61(3):383–390
70. Kinden-Milles D, Arndt JO (1996) Nitric oxide as a chemical link in the generation of pain from veins in humans. Pain 64:139–142
71. Thomsen L, Olesen J (2001) Nitric oxide in primary headache. Curr Opin Neurol 14:315–321
72. Rainero I, Valfre W, Savi L, Ferrero M, Del Rizzo P, Limone P, Isia GC, Gianotti L, Pollo A, Verde R, Benedetti F, Pinassi L (2002) Decreased sensitivity of 5-HT1D receptors in chronic tension-type headache. Headache 42(8):709–714
73. Bendtsen L, Mellerup ET (1998) The platelet serotonin transporter in primary headache. Eur J Neurol 5:227–282
74. Jensen R, Hindberg I (1994) Plasma serotonin increase during episodes of tension-type headache. Cephalalgia 14:219–222
75. Shukla R, Husain M, Tandon R, Khanna VK, Nag D, Dikshit M, Srima RC, Seth PK (2003) Platelet 5-HT1B receptor binding in tension-type headache. Headache 43(2):103–108
76. Lipchik GL, Nash JM (2002) Cognitive-behavioral issues in the treatment and management of chronic daily headache. Curr Pain Headache Rep 6(6):473–479