Pathophysiological mechanisms of tension-type headache: a review of epidemiological and experimental studies

R. Jensen
Department of Neurology NO1, Glostrup Hospital University of Copenhagen, Glostrup, Denmark

1. Introduction

Despite the fact that tension-type headache is by far the most common type of headache (1, 2), the knowledge about key pathophysiological issues, such as the nature and the site of the noxious stimulus, is surprisingly limited. Several factors may have contributed to this lack of knowledge. One main reason is the previous lack of a proper classification. Before 1988 no precise definition of tension-type headache was available, and terms such as muscle contraction headache, tension headache, psychogenic headache, psychomyogenic, or stress headache were used. Furthermore, since mental stress and tension are the most frequently reported precipitants of tension-type headache (2-4), many scientists equalized this with causative factors and have not tried to describe the pathophysiology and mechanisms behind the disorder.

Tension-type headache is also a graded phenomenon in which pain severity increases with headache frequency. At one extreme are rare episodes of slight pain and discomfort in the head; at the other are daily, disabling headaches with considerable social and personal impact (5). Due to this, and also to the very high prevalence, tension-type headache may be regarded as the most important type of headache.

In the International Headache Classification (IHS) from 1988 (6) tension-type headache has been precisely classified and defined by means of operational criteria (Table 1). The first digit defines tension-type headache according to its clinical features. The second digit subdivides the headache according to its frequency into an episodic and a chronic form. The third digit in the classification characterizes the presence or absence of disorders of pericranial muscle, while the fourth digit concerns possible causative factors. This subdivision was developed mainly on the basis of the experience of a group of experts and not on the basis of scientific evidence, which at that time was very limited.

On this background, a method study of electromyographic (EMG) recordings (7) and a large-scale epidemiological study including a number of paraclinical tests (8-12) were performed. Further data concerning the pathogenic importance of muscular disorders in tension-type headache was obtained from two studies of spontaneous and induced headaches (13, 14). The aim of the present review was to relate the obtained results from the epidemiological and clinical studies to other relevant studies, and to discuss possible pathophysiological mechanisms of tension-type headache.

2. Epidemiology

2.1 Sampling and examination

One thousand subjects aged 25–64 years from 11 municipalities around the Copenhagen County Hospital were randomly selected from the central person registry and invited to attend a general health examination with emphasis on headache disorders (1). A total of 740 subjects was clinically interviewed and 735 of those were examined with both pressure pain thresholds and manual palpation of the pericranial muscles (8, 9, 12) (Fig. 1). Due to initial technical problems, only 547 subjects were examined with EMG (10, 11). The examined population was widely representative of the total sample population and of the general Danish population (1, 10). The headache disorders were classified according to a structured diagnostic headache interview and a neurological examination performed by the physician using the operational diagnostic criteria of the IHS (6). The paraclinical tests were performed in different independent stations (Fig. 1) by means of standardized, blinded procedures (7–11).

2.2 Prevalence

The life-time prevalence of tension-type headache in the general population was 78%, while the 1-year-period prevalence was 74% (1). Thirty percent (223/735) had tension-type headache more than 14 days in the previous year, which in the following is defined as frequent tension-type head-
Table 1. The subgrouping of migraine and tension-type headache (first digit) according to the International Headache Classification and the diagnostic criteria for episodic and chronic tension-type headache (second digit).

<table>
<thead>
<tr>
<th>1.</th>
<th>2.</th>
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<tbody>
<tr>
<td>Migraine</td>
<td>Tension-type headache</td>
</tr>
<tr>
<td>1.1 Migraine without aura</td>
<td>2.1 Episodic tension-type headache</td>
</tr>
<tr>
<td>1.2 Migraine with aura</td>
<td>2.2 Chronic tension-type headache</td>
</tr>
<tr>
<td>1.3-1.7 Other migrainous disorders</td>
<td>2.3 Tension-type like headache</td>
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2.1 Episodic tension-type headache
- A. At least 10 previous headache episodes fulfilling criteria B–D listed below:
  - No. of days with such headache <180/year (<15/month)
  - Headache lasting from 30 min to 7 days
  - At least two of the following pain characteristics:
    1. Pressing/tightening quality
    2. Mild or moderate intensity
    3. Bilateral location
    4. No aggravation by walking stairs or similar physical activity
- Both of the following:
  1. No nausea or vomiting (anorexia may occur)
  2. Photophobia and phonophobia are absent, or one but not the other is present

2.2 Chronic tension-type headache
- A. Average headache frequency ≥ 15 days/month (≥ 180 days/year) for 6 months fulfilling criteria B–D listed below:
- B. At least two of the pain characteristics listed in episodic tension-type headache:
- C. Both of the following:
  1. No vomiting
  2. No more than one of the following: Nausea, photophobia or phonophobia

Tension-type headache with and without association with disorders of pericranial muscles (third digit)

2.x.1 Tension-type headache associated with disorder of pericranial muscles
- A. Fulfils criteria for 2.x.
- B. At least one of the following:
  1. Increased tenderness of pericranial muscles demonstrated by manual palpation or pressure algometer.
  2. Increased EMG level of pericranial muscles at rest or during physiological tests.

2.x.2 Tension-type headache unassociated with disorder of pericranial muscles
- A. Fulfiling criteria for 2.x.
- B. No increased tenderness of pericranial muscles. If studied, EMG of pericranial muscles shows normal levels of activity.

Possible causative factors for tension-type headache (fourth digit)
- 0. No identifiable causative factor
- 1. More than one of the factors 2–9 (list in order of importance)
- 2. Oromandibular dysfunction
- 3. Psychosocial stress
- 4. Anxiety
- 5. Depression
- 6. Headache as a delusion or an idea
- 7. Muscular stress
- 8. Drug overuse for tension-type headaches
- 9. One of the disorders listed in group 5–11 of the IHS classification

*p<0.05; ***p<0.001.

ache. Of these 223 subjects, 22 had chronic tension-type headache and 201 had frequent, episodic tension-type headache (>14 days/year) (12). Few epidemiological studies are comparable, because the majority were carried out before 1988, when the nonuniform diagnostic criteria used were vague (15). Frequently, the overall prevalence of headaches is presented pooling migraine and tension-type headache together, which also may be misleading. The prevalence of chronic tension-type headache is fairly congruent in the few comparable studies (1, 2, 16–18), while the prevalence of the episodic form varies considerably, probably due to methodological variations (1, 2, 17–21).

The point prevalence, which is the prevalence of tension-type headache in a general population on a randomly selected day, was 11% (79/735) in the present study (12). No other studies have dealt with this subject.

2.3 Contact with the healthcare system

One of the explanations for the poor medical attention devoted to tension-type headache is probably that it is usually mild and self-limiting in most cases. Only a minority of headache sufferers are in fact registered in the healthcare system, as only 16% of subjects with tension-type headache
have consulted their general practitioner, only 4% have been examined by a specialist, and less than 1% have been hospitalized because of their tension-type headache (5).

2.4 Variation with sex

In the present population study, there was a female preponderance of tension-type headache sufferers (1, 9). The male:female ratio in the 1-year-period prevalence of tension-type headache was 3:4. When the chronic subform was analysed separately, the male:female ratio was 2:5. These figures correspond widely with the male:female ratio reported in earlier studies (19, 20, 22), from the most recent population studies (2, 18), and from clinical populations where women also have a higher prevalence of tension-type headache than men (23–25).

2.5 Variation with age

Tension-type headache showed decreasing prevalence with increasing age in concordance with other population studies (1, 19, 20, 22). Whether this is due to increasing incidence of tension-type headache in general, or can be explained by a cohort effect where the older age group is more reluctant to confirm that they have or have had tension-type headache, is yet unknown, but hopefully longitudinal studies will answer this question.

3. Pathophysiological background

3.1 Origin of pain

For decades it has been a matter of debate whether the pain in tension-type headache originates from myofascial tissues or from central mechanisms in the brain (26–37). Clinical and laboratory investigations substantiating any of these hypotheses are few, and the pain mechanisms in tension type headache are practically unknown. Although the general knowledge of nociception and pain has improved dramatically in recent decades, the understanding of deep pain processing in visceral and myofascial tissues is still fairly limited. First of all, it is important to consider the following two questions: (i) Is the pain in tension-type headache of myofascial origin? (ii) Is the pain in tension-type headache due to peripheral or to central factors?

As far as the first question is concerned, most previous studies in pain physiology have investigated cutaneous pain, even although cutaneous pain is clinically much less relevant than muscle and visceral pain. However, the following clinical characteristics of myofascial pain have been delineated: (a) Quality of pain: acute muscle lesions and pain elicited from a muscle nerve are described as dull, aching, and cramping in quality (38), while cutaneous pain is characterized by its sharp, pricking, stabbing, and burning nature (39). (b) Localization: Muscle pain is very difficult to localize, in contrast to cutaneous pain which usually is localized with great accuracy (40). (c) Referred pain (defined as pain not only felt at and near the lesion
but also remote from this site: Cutaneous pain is generally very localized, whereas both visceral and muscle pain usually show referral and projection to distant areas (41, 42).

The former headache classification, from 1962 (15), described the quality of pain in tension headache as dull, aching, pressure-like, constricting, or giving a sense of fullness. This has been confirmed in a detailed analysis of 1420 cases by Friedman in 1979 (24). In the IHS classification from 1988 (6) defines pain quality as simply pressing or tightening. This pressing pain quality was confirmed by 83% of chronic tension-type headache sufferers from a general population (1) and in 95 of 100 patients with daily or almost daily headache from a specialized headache clinic (43). Similarly, a typical pattern of pain referral has also been reported (44 - 46), although prospective studies have never been carried out. In conclusion, the pain in tension type headache is similar to myofascial pain elicited from other parts of the body, but whether it is strictly localized to muscle tissues or to other deep tissues is still uncertain. In addition, although the pain clinically resembles pain from the myofascial tissues, components of both peripheral and central origin may contribute.

This leads to the second question, i.e., whether the pain in tension-type headache is due to peripheral or to central factors, and no clear answer has been given. The increased tenderness most likely represents peripheral activation of nociceptors, whereas the decreased pain thresholds which have been reported in most chronic headache patients (32, 35, 47) are probably a central misinterpretation of the incoming signals. On the basis of reduced duration of the late exteroceptive silent period (ES2) of temporalis muscle activity in patients with chronic tension-type headache, it was suggested that the limbic pathways to the brainstem were disturbed, and that studies of ES2 may provide important information about the central mechanisms (31, 48). However, the applied methodology has later been challenged, and negative studies have recently been published (49, 50).

The nociceptive flexor reflex, a spinoally organized reflex, was reported to be decreased in patients with chronic tension-type headache (36). As this reflex is influenced by the endogenous modulating system, a defect either in the opioid system or in the production of neurotransmitters (37, 51, 52) was suspected. Furthermore, the findings of increased metenkephalin levels in the cerebrospinal fluid from these patients (37) support this, although the β-endorphin concentration was normal (53). These various abnormalities may, however, result in a disturbance of the balance between peripheral input and the central modulation, as discussed by Sandrini et al. (54) and by Langemark et al. (37), but the primary eliciting cause and the evolution of pain are still unknown. As the most frequently reported precipitating factors leading to tension-type headache are stress, mental tension, and tiredness (2 - 4), central supraspinal factors are undoubtedly involved too. A specific analysis of the relation between the peripheral, spinal, and supraspinal contribution to pain in tension-type headache was therefore highly warranted.

3.2 Animal models of myofascial pain

There is growing evidence from animal experiments that sensitization, wind-up, or expansion of receptive fields of CNS neurons plays an important role in pain induction and maintenance (39, 55 - 66). Thin peripheral afferent fibers convey inputs originating in muscles and joints, and within a very short time these messages reach upper levels of the central nervous system, such as the thalamus and the somatosensory cortex after a relay in the dorsal horn of the spinal cord or in the trigeminal ganglion. La Motte et al. reported that articular nociceptive fibers and their corresponding spinal neurons can be sensitized within 2 - 3 h after a chemical inflammation of the joint (58). This sensitization observed at the central level may, however, not only reflect peripheral changes but rather an additional change in CNS activity. It is also known from animal experiments that input from deep myofascial tissue is much more effective in inducing central sensitization than cutaneous input (60, 67, 68). In the studies by Hu et al. (69), deep craniofacial muscle afferents were stimulated and prolonged facilitatory effects in the trigeminal nociceptive brainstem neurons of anesthetized rats were induced, later supported by the findings of experimental myositis inducing functional reorganization of the rat dorsal horn (70). What could be the explanation for this? Treede et al. suggested in 1992 that secondary hyperalgesia was due to sensitization of central neurons, possibly in the dorsal horn, as low threshold mecanoreceptor (LTM) input gains access to pain pathways (59). Subsequently, this has been confirmed by Mense and colleagues reporting that activity in high threshold mecanoreceptor fibers (HTM) was shifted to include LTM fiber activity from sensitized muscles in experimental animal models (38, 64, 71, 72).

Since tension-type headache is a disease in humans and not known in animals, experimental animal models are of limited value when evaluating the underlying pathophysiology. Fortunately, quantitative analyses of mechanical and thermal pain thresholds in humans can be used for this purpose. As the extracranial tissues are readily accessible in humans, previously evaluated psychophysical...
examinations were applied to these regions to gain information about the pain processing in tension-type headache. However, the reproducibility and validity of these diagnostic tests represented a problem, as objective measures of pain intensity and quality were not available. Pain recordings were therefore highly dependent on an intense and reliable cooperation with the patient (73). The applied methodology and the results of these psychophysical tests and the EMG recordings from the epidemiological (8–12) and two subsequent clinical studies (13, 14) are summarized and discussed in the following.

4. Synthesis of the applied psychophysical and EMG studies

4.1 Tenderness evaluated by manual palpation

4.1.1 Background and methods. Many patients with tension-type headache relate their complaints to increased muscle stiffness in the neck and shoulders. Increased muscle hardness has recently been demonstrated in patients with chronic tension-type headache (73), and increased tenderness recorded by manual palpation is one of the most consistent findings in these patients (9, 13, 14, 27, 47, 74–78). However, recording of tenderness has been the subject of much debate, as results have been difficult to compare between different observers. A recent methodological study demonstrated that if certain methodological rules are followed manual palpation represents an easy and reliable method of studying myofascial pain sensitivity (79). A standardized, manual palpation of 14 pairs of pericranial muscles and tendon insertions was used in the population study (8, 9). In the following clinical studies, 9 pairs of muscles and tendon insertions were examined (13, 14). In order to minimize interobserver variation, tenderness was recorded by the same examiner throughout each study. The tenderness in each muscle and tendon was scored according to a scale from 0 to 3, and summed to a Total Tenderness Score (TTS) for each subject as described by Langemark and Olesen (27).

4.1.2 Relation to sex. Applying such pain psychophysical procedures as manual palpation, and pressure pain thresholds, is it important to know the possible variation between gender, age, and hand dominance, and it is preferable to examine these parameters in a large sample from the general population, as in the present study (8). Females were considerably more tender in all the pericranial muscles than males (8), confirming prior results from clinical studies (80–82), and indicating that the myofascial pain sensitivity is increased in females compared to males (8).

4.1.3 Relation to age. Pericranial muscle tenderness decreased significantly with increasing age in both sexes (8). The present population study thereby substantiates the former impressions from smaller series in selected age groups (80, 83, 84). Whether these findings from a cross-sectional study represent a real physiological phenomenon or the effect of reluctance in the expression of discomfort and pain in the older age group is still unknown. To my knowledge, no other epidemiological studies have dealt with this subject.

4.1.4 Relation to hand dominance. Previously, it has been debated whether there was a specific relation of psychophysical measurements to hand dominance (27, 85). However, only very few studies have studied this with respect to pericranial tenderness. One study reported muscles on the left side to be more tender than those on the right, and the influence of the observers but not the patients, hand dominance was studied (27). In this study population, no specific side difference was detected among patients with respect to hand dominance (8).

4.1.5 Relation to muscles. In subjects from the general population, the muscles most commonly tender to manual palpation were the lateral pterygoid, the trapezius, and the sternocleidomastoid muscles (8) (Table 2). A similar pattern appeared when the headache subjects from the general population (9) were analyzed in detail, although tenderness was much more pronounced in headache subjects (Table 2, Fig. 2). These findings cor-
Table 2. Tenderness scores in different muscles (m.) and tendon insertions in subjects with frequent tension-type headache (headache >14 days/year and no coexisting migraine) compared to the total study population (mean scores in males and females are shown).

<table>
<thead>
<tr>
<th>Sex (n)</th>
<th>Tension-type headache</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Lat. pterygoid m.</td>
<td>1.2*</td>
<td>1.3*</td>
</tr>
<tr>
<td>Ant. temporal m.</td>
<td>0.1</td>
<td>0.5*</td>
</tr>
<tr>
<td>Post. temporal m.</td>
<td>0.0</td>
<td>0.2**</td>
</tr>
<tr>
<td>Deep masseter</td>
<td>0.4*</td>
<td>0.8***</td>
</tr>
<tr>
<td>Sup. masseter</td>
<td>0.1</td>
<td>0.3***</td>
</tr>
<tr>
<td>Sternocecid.m</td>
<td>1.0</td>
<td>1.4***</td>
</tr>
<tr>
<td>Frontal m.</td>
<td>0.0</td>
<td>0.2***</td>
</tr>
<tr>
<td>Mastoid proc.</td>
<td>0.4</td>
<td>1.0***</td>
</tr>
<tr>
<td>Post. neck m.insert</td>
<td>0.8</td>
<td>1.3***</td>
</tr>
<tr>
<td>Post. rect. cap.m</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Splenius m.</td>
<td>0.3***</td>
<td>0.4</td>
</tr>
<tr>
<td>Trapezius m.</td>
<td>0.8</td>
<td>1.7***</td>
</tr>
<tr>
<td>Coronoid proc.</td>
<td>0.5*</td>
<td>0.8***</td>
</tr>
<tr>
<td>Hamulus pteryg.</td>
<td>0.9</td>
<td>1.6***</td>
</tr>
</tbody>
</table>

T-test: difference between subjects with tension-type headache and the rest of the population. 
*p < 0.05; **p < 0.01; ***p < 0.001.

respond to results from selected clinical populations of chronic headache subjects (27, 47, 74, 80, 86). The comparable distribution of tenderness in patients and in healthy controls indicates a generalized pericranial affection and no specific involvement with regard to the function of the individual muscles.

4.1.6 Relation to headache diagnosis and frequency. Tenderness as recorded by manual palpation was significantly increased in subjects with tension-type headache, both in the episodic and in the chronic form, as compared to the nonheadache population (9) (Fig. 2). These findings were also confirmed in the clinical study where patients with the chronic form were significantly more tender than those with the episodic form (p = 0.03) (14, 87). These findings are in line with previous clinical studies (27, 47, 54, 76, 78). In the general population, subjects with episodic and also subjects with chronic tension-type headache were more tender than migraineurs, who again did not differ significantly from headache-free subjects (9). A strong positive correlation between tenderness and frequency of tension-type headache was found in both sexes (Fig. 3). There was no specific relation between tenderness and migraine frequency (9) confirming previous observations (88, 89) where myofascial tenderness in migraineurs was positively related to the frequency of tension-type headache but not to the frequency of migraine.

4.1.7 Relation to the headache episode. Is the increased tenderness a cause or an effect of the headache? Increased tenderness during migraine attacks compared to the headache-free state has been reported (89, 90), but it was unknown whether this was the case in tension-type headache. Therefore, data from the population study (9) were analyzed with respect to these factors. Seventy-nine subjects had tension-type headache on the day of the examination and their data were compared with those of subjects with a similar frequency of tension-type headache but without actual headache. The TTS was 32% higher in those subjects with actual headache during the examination compared to matched subjects without headache (9). These findings were later con-
firmed in the clinical study, where 28 patients were examined during and outside a spontaneous headache episode (13), where the TTS was 23% increased during the headache episode. The tenderness is therefore highly influenced by the actual headache state, but owing to the fact that patients outside the headache episode also have markedly increased tenderness compared to healthy controls, tenderness of the pericranial muscles is likely to play an important role in the pathophysiology of tension-type headache. To study these relations further, however, it is necessary that the headache state is strictly defined in future studies.

Does the recency of headache also influence tenderness? Soreness of extracephalic muscles usually takes hours or days to develop (91), and the increased tenderness may therefore theoretically reflect a prior event. An analysis of these relations was therefore attempted in the population study and there was in fact a slight positive relation between the tenderness score and the recency of headache (9). However, the relations were weak and may therefore only explain a minor part of the increased tenderness that was seen in these subjects with frequent tension-type headache. Furthermore, no association between tenderness and recency of headache could be detected in the clinical studies of frequent headache sufferers (unpublished results).

In conclusion, the consistent finding of increased tenderness in subjects with tension-type headache indicates that myofascial tenderness plays a key role in the pathophysiology of this type of headache, but it is still uncertain whether it is primary or secondary to the pain.

4.2 Pressure pain threshold

4.2.1 Background and methods. Recordings of Pressure Pain Thresholds (PPT) are recommended as one of the diagnostic criteria for tension-type headache associated with disorders of pericranial muscles (Table 1) (6). However, the applied methodology and the locations that should be examined are not further specified. PPTs can be recorded in two different ways, from a localized tender spot as a quantitative pain measure or from a fixed spot in all subjects disregarding the findings on palpation. Previous findings have demonstrated that the latter method is reliable and reproducible (92–97). Whether the former is more informative with respect to headache is not yet clear. In the present population study, pain thresholds were analyzed at a standardized location, namely the anterior temporal region (8, 9). In the clinical studies, PPTs were recorded from the index finger, and from two cranial locations, one with and one without interposed muscle, namely the temporal and the parietal regions (13, 14). In the latter studies, suprathreshold values were also recorded, i.e. the pressure pain tolerances defined as the maximal pressure pain which could be tolerated (13, 14).

4.2.2 Relation to sex. PPTs from the temporal regions were lower in females than in males (8). These findings contrast with the study by Jensen et al. (92), but correspond with most other clinical studies (93–97), indicating that sensitivity to mechanical pain stimuli is increased in females compared to males. Due to the relative small sample size, these relations were not tested in the clinical studies (13, 14).

4.2.3 Relation to age. PPTs in the temporal regions increased significantly with increasing age (8). Such relations have never been analyzed in general populations before, but the data confirm the clinical impression that pain sensitivity decreases with increasing age.

4.2.4 Relation to hand dominance. As far as pressure pain stimuli and hand dominance are concerned, it was demonstrated that right-handed subjects had a slightly (4%) higher PPT on the right-sided anterior temporal locations than on the left side (8). Similar findings were noted in the study by Haslam (85) and by Petersen et al. (97), whereas no side difference was found by Jensen et al. in their study (92). In the population study, no side differences were detected in the relatively small groups of left-handed and ambidextrous subjects (8).

4.2.5 Relation to headache diagnosis and frequency. The PPTs at the anterior temporal region of 22 subjects with chronic tension-type headache from
the general population did not differ from the rest of the population or from the other headache groups (9) (Fig. 4). Similarly, the pain thresholds and the pain tolerances in the temporal region of 30 patients with chronic tension-type headache were not different from those in 28 patients with episodic tension-type headache or in 30 age- and sex-matched healthy controls in the clinical study (14, unpublished results). These findings contrast with other clinical studies of patients with chronic tension-type headache, where the mechanical pain thresholds were decreased compared to healthy controls (32, 47). Nevertheless, the decrease in PPTs was relatively small in large group comparisons. Thus, Bendtsen et al. were unable to demonstrate any significant difference in PPTs from the temporal regions of 40 chronic tension-type headache patients compared with healthy controls, whereas significantly lower values were demonstrated on the fingers of these patients (47). In 1986, Jensen et al. pointed out that 45 subjects are needed in order to detect a 30% difference in PPT in group comparisons (92) and the negative finding in the present studies may possibly be due to type II statistical errors. This is owing to the fact that only 22 subjects from the population study (9) and 30 patients with chronic, but not daily tension-type, headache from the clinical study (14) were examined. In the latter study, however, subsequent analysis of the mechanical pain thresholds from 18 patients with increased pericranial tenderness was compared to the values from 10 patients without abnormal tenderness (87). The former group had significantly lower thresholds and tolerances in all the examined cephalic and extracephalic locations than the latter group, indicating that there may be a marked difference in the pain processing between these two subgroups of patients (87). The PPTs in patients with episodic tension-type headache were similar to healthy controls (9, 87). Similarly, other groups have reported normal PPTs in patients with frequent episodic tension-type headache compared to healthy controls (98, 99). The variations in previous studies may, however, also reflect the graded phenomenon of chronicity as subjects from the general population (9) and patients with frequent but not daily headache (14, 87) may be less severely affected than patients with daily or almost daily occurrence of headache (32, 35, 47).

Concerning the pressure pain tolerances, no significant differences were found between patients examined outside a headache and healthy controls (14). Bendtsen et al. found significantly decreased pain tolerances on the fingers and a tendency to decreased tolerances in the temple in 40 patients with daily or almost daily headache compared to healthy controls (47). The marked differences between the highly increased tenderness and the normal or slightly abnormal pain thresholds and tolerances are somewhat surprising, but can probably be explained by the fact that the PPT and the pressure pain tolerance represent the two extremes of a stimulus response curve, whereas tenderness recorded by manual palpation represents a graded phenomenon between these two extremes, as discussed by Bendtsen et al. (86). Furthermore, the PPT was recorded from one or two cranial locations, whereas the TTS was a sum of tenderness scores from many different locations, of which the temporal muscles revealed only relatively little tenderness (8, 9). A significant inverse relation between local tenderness and PPT (Table 3) (12, 35, 47, 100), however, indicates that PPT may have a diagnostic value if it is recorded from a tender point. In the present studies, the pain thresholds were recorded from a standardized location and represented fairly low sensitivity and limited diagnostic value (12). The extent to which the sensitivity can be improved by analysing tender locations requires further investigation.

4.2.6 Relation to the headache episode. Neither in the general population (9) nor in the clinical study of headache patients (13) is any relation found between PPTs and headache. Nevertheless, pressure pain tolerances from the parietal region were decreased during the headache episode, whereas tolerances from the hands and the temporal regions remained unaffected by the headache state (13). As decreased pressure pain tolerance represents a hyperalgesic response, these results indicate that the actual headache episode may be associated with a slight, segmental central sensitization and/or a decreased antinociception. Similar modulations of pain thresholds have recently been demonstrated in patients with fibromyalgia during isometric contractions (101). A more generally defective central pain modulation is less likely, as mechanical pain tolerances from extracephalic locations were widely unaffected (for further discussion, see section 7). No specific relation between PPT and recency of an episode of tension-type headache could be detected (9).

4.3 Thermal thresholds

4.3.1. Background and methods. Thermal sensory modalities may provide valuable information about C-fiber mediated cutaneous pain perception and its central processing (102). Thermal pain thresholds were not included in the IHS criteria for tension-type headache associated with disorders of pericranial muscles (third digit, Table 1) and therefore not applied to the population study, but only to the subsequent clinical studies (13,
Several methodological studies and reports on normative data of thermal pain sensitivity with respect to sex, age and side-to-side variation are now available (35, 103–110).

4.3.2 Relation to headache diagnosis. In the clinical study, the heat pain thresholds and tolerances in the hands as well as in the cranial regions of patients with tension-type headache, examined outside a headache episode, were similar to those in healthy controls (14). Warm detection thresholds in the temporal region were slightly higher in patients compared to healthy controls (14). In contrast, Langemark et al. (35) found no differences in the ability to detect temperature changes between 32 subjects with chronic tension-type headache and healthy controls. In the same study (35), heat and cold pain thresholds in the hands and temporal regions were less extreme in patients than in age- and sex-matched controls.

4.3.3 Relation to the headache episode. The thermal pain detection and tolerance thresholds were selectively decreased in the temporal region during a headache episode, indicating that the actual headache episode may be associated with a segmental central sensitization and/or a decreased antinociception (13). A possible segmental disturbance at the spinal/trigeminal level may be transient and reversible in these patients, while a more consistently affected thermal pain perception is more likely in patients with the chronic and almost daily form in the study reported by Langemark et al. (35). However, thermal responses are not uniform in chronic pain conditions. Low back pain patients have reported increased pain thresholds (111, 112) in correspondence with other pain studies where patients had a higher threshold for unpleasantness and judged the suprathreshold stimuli to be less intense and unpleasant than healthy controls (113). With the exception of the Langemark et al. (35) study and the present studies (13, 14), no study has dealt with thermal pain thresholds in patients with tension-type headache and further investigations are needed.

4.4 EMG

4.4.1 Background and methods. For decades it has widely been accepted that excessive muscle activity in the pericranial muscles was of significant importance for the development of tension-type headache, as reflected in the former term muscle contraction headache (45, 114–116). In 1984, Pikoff critically reviewed the existing literature and found that about 50% of the papers reported normal resting values, and that the other half reported higher EMG levels in patients with tension-type headache than in healthy controls (26). Furthermore, the presence of increased muscle activity as reflected by EMG recordings in painful masticatory muscles has also been questioned (117–119). In spite of these divergent results, increased EMG level is included as a diagnostic criterion for the association with disorder of peri-cranial muscles in the IHS classification (third digit) (6), but as for the PPTs no specific methodological requirements are described.

A completely relaxed muscle is silent in the EMG (120). According to this definition, an increased tonus and presence of EMG activity during resting conditions must be considered as neuromuscular activity and insufficient relaxation. The spasm theory was hypothesized by de Vries in 1966 in an attempt to explain the pain of a sore muscle (121). It was based on the assumption that continuously increased activity in motor neurons had an activating influence on the muscle afferents. The slowly conducting muscle afferent units were known to have synaptic connections with flexor alpha motor neurons as well as with flexor and extensor gamma neurons via spinal interneurons, and the increased activity in muscle nociceptors might therefore reflexly cause spasms in the affected muscle. Thus, this has led to the concept that muscle spasm may be due to a vicious circle by the reflexly contracting muscle alpha motor neurons causing ischemia and thus activating muscle nociceptors (121–123). Due to the contrasting results of EMG studies in sore muscles, and to the lack of correlation between changes of EMG activity, soreness and pain, this theory has been questioned (38, 119, 124, 125). Furthermore, the widespread hypothesis of muscle ischemia in tension-type headache could not be supported in the study by Langemark et al. in 1990 (126), and support for the contention that gamma-motor neurons are activated by muscle nociception is also fairly weak, as discussed by Mense (38).

In an attempt to clarify some of these controversies a detailed analysis of the EMG methodology and the relation to headache was performed. In most previous EMG studies in these pain conditions surface electrodes have been used, probably because they are very easy to use, atraumatic, and do not cause pain itself. Are the recordings with surface electrodes reproducible and reliable, however? A detailed analysis of the EMG methodology (7) was therefore performed. EMG levels from the frontal and temporal muscles were recorded during standardized resting conditions and during maximal voluntary contractions (7). Since a completely relaxed muscle is silent in the EMG, and the signal/noise ratio is very small, simultaneous recordings with surface electrodes and needle electrodes were performed initially (7). These recordings indicated...
that the facial muscles were not completely relaxed (7), and that the minimal electrical activity recorded by surface electrodes actually represented activity in motor units. Root mean square (RMS) and mean rectified value (MRV) of the electrical activity from the muscles mentioned above were measured repeatedly in 20 healthy subjects. Power spectrum was calculated and the mean and median frequencies were extracted. The coefficient of intraindividual variation in RMS from the right temporal muscle within the same examination was 14%, between several examinations on the same day 18%, and between measurements on two different days 18% (7). The corresponding coefficients of interindividual variations were 36%, 31%, and 38%. The left temporal and the right frontal muscles showed fairly similar coefficients of variation. At rest, no differences in amplitude levels were found between muscles, but during maximal voluntary contraction (MVC) the frontal muscle revealed a 55% lower RMS value than the temporal muscle. The applied method was found to be reproducible and reliable in measuring quantitative electrical muscle activity in line with a more recent study (127) but due to the high interindividual variation paired studies should be preferred.

This method was used in the population study (10, 11) and later in the clinical studies (13, 14). In the latter studies, the trapezius muscle was investigated instead of the frontal muscle because of much more pronounced tenderness and probably more relevance to tension-type headache than the smaller frontal muscle, which mainly has a mimic function. The inter- and intraindividual variation of EMG recordings from the trapezius muscle was tested in a small pilot study and was found to be similar to the previously tested muscles (unpublished results).

4.4.2 Relation to sex. The EMG findings during resting conditions indicated that the right frontal muscle was less relaxed in females than in males, whereas no other significant sex variation could be detected (10). These results correspond with the few other studies which have analyzed the sex variation in pericranial muscles (128, 129) as well as in extracephalic muscles (130).

Males revealed higher amplitudes in the frontal, but not in the temporal, muscles during maximal voluntary contraction compared to females (10), in support for the structural variations between the frontal and temporal muscles reported by Johnson et al. (131). However, these results partly contrast with those reported by Visser et al. (132), where significantly higher values were found in males when the temporal and masseter muscles were studied with masticatory EMG, emphasizing the need for an extensive EMG analysis during the entire force spectrum and not just during rest and at maximal voluntary contraction, as in the present study.

4.4.3 Relation to age. EMG amplitude levels during the resting condition showed no variation with respect to age in contrast to the single previous study of age relations in pericranial muscles (128) but in line with the results from extracephalic locations (130). During maximal voluntary activity (MVC) both EMG amplitudes and frequency levels from the temporal muscle and partly also the frontal muscle decreased with increasing age in correspondence with previous results. This may be explained by decreased number of motor units and impaired chewing ability with increasing age (132–136).

4.4.4 Relation to hand dominance. De Luca et al. (137) discussed possible relations between side differences in EMG levels and hand dominance. No specific relations between EMG levels and hand dominance were detected in the general population (10), and because of the restricted number of subjects these relations were not further analyzed in the clinical studies. No other studies have dealt with these relations.

4.4.5 Relation to headache diagnosis and frequency. EMG amplitudes during rest were increased in the temporal and frontal muscles of subjects with chronic tension-type headache but not in those with the episodic form from the general population (11) (Fig. 5). These results correspond to the findings in a clinical study of 32 female patients with chronic tension-type headache conducted by Schoenen et al. (34). Similarly, the EMG amplitudes were increased in the trapezius, and partly also in the temporal muscles of frequent headache sufferers from the clinical studies (13, 14), indicat-

Fig. 5. Distribution of EMG amplitudes (µV) in the general population (subjects without experience of headache (Never), migraineurs (Migr), episodic tension-type headache (ETH), chronic tension-type headache (CTH). Mean values from the right and left temporal muscles during rest with standard errors of mean are shown (*indicates p<0.05).
ing insufficient relaxation. In the epidemiological study no variations were detected among those subjects with migraine, episodic tension-type headache, or those without experience of headache (11). Decreased mean and median frequency levels during maximal voluntary contraction were found in the subjects with chronic tension-type headache (11). Mean frequency levels are reported to be positively related to the percentage of type II muscle fibers (130) and median frequency levels are reported to be inversely related to ischemia, cooling, and accumulation of metabolites (139). These results may therefore support the involvement of the pericranial muscles in chronic tension-type headache. The decreased frequency levels during maximal voluntary contraction could not be confirmed in the clinical study, however, where 30 chronic and 28 episodic patients were examined in a similar way (14). Therefore, the relations between EMG level and pain are not simple and the subject needs further investigation before final conclusions about cause/effect relations and pathophysiological relevance can be drawn. In a recent study, neither pain nor subjective muscle tension was found to be related to EMG levels (140), in line with the prior suggestion by Lund et al. that increased EMG levels in pericranial muscles may represent an unspecific mimic reaction without any causal relation to the pain (119).

No significant relation between the amplitude levels during resting conditions and the usual frequency of tension-type headache in the previous year was detected, whereas the frequency levels during MVC decreased significantly with increasing frequency (11), indicating either increased fatigability or changed composition between type I and type II muscle fibers in these muscles. Significant differences in fiber size were found in muscle biopsies from patients with chronic trapezius myalgia compared to healthy controls (141), and it is likely that such changes may also be involved in the mechanism of tension-type headache. No studies have dealt with this subject in headache research.

4.4.6 Relation to the headache episode. The amplitude levels of the temporal muscles recorded during rest were widely unaffected by actual headache state (11, 13), whereas amplitude levels of the frontal muscle showed a minor increase during actual headache in the epidemiological study (11), confirming the finding of Martin and Mathews (142). If increased muscular tension was a mimic reaction to ongoing pain, a more specific relation to the pain state was expected. Schoenen et al. found no relation between EMG activity and headache severity, anxiety, or response to biofeed-

back treatment in their study of CTH patients, and suggested that the increased pericranial EMG activity was produced by central dysfunction (33, 34). These minor EMG differences, however, may contribute to maintain the unspecific tenderness, as discussed previously, and may also explain the increased muscle hardness (73). Similarly, increases in EMG levels from jaw and neck muscles, although shortlasting, have been reported after injections of irritants into the paraspinal tissues or the temporomandibular joint in animal models (60, 143, 144) and in humans after injection of hypertonic saline in muscles (145, 146). A recent study, however, debates this hyperactivity model, which assumes a reinforcing link between pain and muscle hyperactivity (147), and the cause-effect relation in tension-type headache is still unclear.

During maximal voluntary contraction, amplitude levels from both the temporal and the frontal muscles were decreased in subjects with headache compared to those with a similar frequency of headache in the previous year, but without ongoing pain during the examination (11), whereas these results could not be confirmed in the paired study of patients examined during and outside a spontaneous episode of headache (13). A possible submaximal contraction during the pain state of patients with temporomandibular disorders has previously been suggested by Molin et al. (148), and found by van Boxtel et al. in patients with tension headache (149). During pain, the rhythmic jaw movements were highly modified with a decrease in amplitude and velocity (150, 151) similar to extracephalic changes reported in patients with localized myofascial pain or fibromyalgia (152–154). Therefore, it was suggested that motor changes are a reflex response that serves to minimize further damage to injured tissues and should therefore be considered protective rather than pathogenic, the so-called pain-adaption hypothesis (118, 119, 155). The hypothesis was further supported by an experimental animal study (61), and by human studies where hypertonic saline was continuously infused in the masseteric muscles of human volunteers (146, 147, 156, 157). In addition, these pain-induced modifications of the motor patterns seem to be located at a segmental level, since a study where noxious pressure stimuli were applied to the zygoma of decerebrated rabbits showed similar changes in motor pattern (158). In conclusion, a protective reflex response which results in decreased maximal voluntary contraction values during the actual pain is concurrent with the pain-adaption hypothesis, but this hypothesis cannot explain the origin of pain and the slight, but fairly consistent, increase in EMG levels during resting conditions, so other mechanisms must also
be involved. The fact that EMG levels during rest were widely unchanged during an episode of spontaneous headache compared to the headache-free state makes it unlikely that pain elicited activity in pericranial muscles solely can explain the increased tenderness and the headache itself (11). It cannot be excluded, however, that previous microtraumas, unphysiological use, or other muscular stress days or weeks before the tests may contribute to muscle pain, but at least these changes are not reflected in the EMG obtained during the headache episode (13).

4.4.7 EMG evaluation of trigger points. The present analyses indicate that the sensitivity and specificity of EMG amplitudes during rest only were reasonable in chronic tension-type headache and of no informative value in the episodic form (12) (see section 5). Should EMG examinations be directed towards the so-called trigger points? Firstly, it is important to define, describe, and identify what trigger points actually represent, as their existence has been intensively debated and doubted (159, 160, 161). Theoretically, continuous activity in a few motor units over a period is thought to be sufficient for development of myofascial pain. However, several investigators have been unable to find any abnormalities in biopsies or when placing needle electrodes in trigger points (117, 162), whereas others more recently have reported abnormalities (163–166). The slightly increased EMG activity during rest that was recorded in the present study may therefore be explained by either a continuous activity in a few motor units or by slight general activity in several motor units in the muscle. However, whether the recorded EMG activity was derived from activity in the muscle spindles or from the motor endplate zone is not yet clarified (161, 165). If it exists, the trigger point is apparently only a few millimeters in diameter, which may explain why the increased EMG activity may not consistently be detected with surface electrodes (167), or by a needle electrode. In 1993, Hubbard and Berkoff reported increased electrical EMG activity recorded by needles in trigger points compared with adjacent nontender muscle (165), which is in line with the report of continuous motor activity in a small population of motor units from tender trapezius muscles (163, 164). Needle EMG activity was also reported to be markedly increased in subjects with chronic tension-type headache compared to healthy controls, and increased even further during experimental stress (166). Furthermore, as injection of botulinum toxin has been reported to have a beneficial effect in a small controlled study of patients with myofascial pain associated with trigger points (168), this indicates that at least some of the pain is intimately associated with the neuromuscular junction. Until the nature of tension-type headache has been further elucidated the use of EMG remains a controversial matter of debate and cannot be recommended as a diagnostic test.

5. Validation of the diagnostic tests for muscular disorder

5.1. Background for the suggested subdivision of tension-type headache

Is there a pathophysiological difference between the two subforms of tension-type headache (Table 1) (those with and those without association with disorder of pericranial muscles), and is it of relevance to maintain this subdivision? The subdivision was mainly based on the clinical impression that subjects with tension-type headache without disorders of pericranial muscles were very difficult to treat, but it was also based on whether these really represented distinct syndromes or different manifestations of the same disorder. No significant differences were found between the two subgroups when they were analyzed separately with respect to clinical features, such as headache severity, anxiety, and response to biofeedback (33). Likewise, no significant differences were found when a number of clinical parameters were compared between tension-type headache patients with or without increased tenderness (87). These data indicate that the two subgroups of tension-type headache may share several pathophysiological mechanisms, and that further evidence about the fairly rare patients with tension-type headache without association with disorders of pericranial muscles are needed.

5.2. Relation between the diagnostic tests for muscular disorder

Analyses of the relation between the diagnostic tests for association with muscular disorder given in the IHS classification (third digit) were assessed in subjects from the general population (12) (Table 3A, B) and from the clinic studies (13, 14). No significant relation between tenderness and PPTs was found in patients with episodic tension-type headache (87). In patients with chronic tension-type headache, however, the TTS was inversely related to the pain thresholds and tolerances in the temporal region (PPDT: $r = -0.61$, $p < 0.001$, PPTO: $r = -0.65$, $p < 0.001$), and on the fingers (PPDT: $r = -0.36$, $p = 0.06$, PPTO: $r = -0.48$, $p = 0.02$) (87). These data correspond to the study by Bendtzen et al. (47), which confirms that there is a significant relation,
Table 3A. Coefficients of correlation between TTS, LTS, PPTs and EMG from the anterior temporal muscle of subjects with chronic tension-type headache.

<table>
<thead>
<tr>
<th></th>
<th>TTS</th>
<th>LTS</th>
<th>PPT</th>
<th>EMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTS</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LTS</td>
<td>0.81***</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PPT</td>
<td>-0.17</td>
<td>-0.59*</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>EMG</td>
<td>0.56*</td>
<td>0.32</td>
<td>0.02</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*p<0.05; ***p<0.001.

Table 3B. Coefficients of correlation between TTS, LTS, PPT, and EMG from the anterior temporal muscle of subjects with episodic tension type headache.

<table>
<thead>
<tr>
<th></th>
<th>TTS</th>
<th>LTS</th>
<th>PPT</th>
<th>EMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTS</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LTS</td>
<td>0.55***</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PPT</td>
<td>-0.23*</td>
<td>-0.09</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>EMG</td>
<td>-0.01</td>
<td>-0.07</td>
<td>0.03</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*p<0.05; ***p<0.001.

although minor, between tenderness and PPTs at cephalic as well as at extracephalic locations.

In a previous study from a highly specialized headache clinic, an inverse correlation between PPTs and tenderness recorded by manual palpation was found in the episodic form but surprisingly not in the chronic subform, although abnormal values were found in 60% by manual palpation and in 65% by pressure algometry (77). Methodological variations between the studies may explain some of the different results. The Italian group had examined mechanical pain thresholds at 11 different points (169), in contrast to only one standardized location in the population study (8). Tenderness recorded by manual palpation was determined from only two locations (the frontal and the trapezius muscle) in the Italian study, in contrast to 14 locations in the present study (8).

In the population study, 87% of subjects with chronic, and 66% of subjects with episodic, tension-type headache were found to be associated with a disorder of the pericranial muscles (12). Sandrini et al. (77) reported 61% of patients with the episodic, and 66% of patients with the chronic, subform to be associated with a muscular disorder, fairly similar to 72% in a prior study, where only EMG and pressure algometry were assessed (33). However, the specificity appeared to be very low in the Italian study, as the tests also revealed association with a muscular disorder in 60% of the migraineurs (77). A possible coexisting tension-type headache in these migraineurs may have influenced their results but no precise clinical data were given.

When the relations between the diagnostic tests were analyzed in those 66 subjects who were examined with all three diagnostic tests during an ongoing headache episode, the percentage of subjects associated with a muscular disorder increased to 100% in the chronic form, and to 81% in the episodic form of tension-type headache (12). This increase was due to the increased tenderness during the headache phase, whereas the PPTs and the EMG levels were largely unaffected (12). In future studies, it is therefore important to record presence or absence of headache as well as intensity of the ongoing pain.

In conclusion, tenderness recorded by manual palpation was the most specific and sensitive test, whereas EMG and pain thresholds provided only limited diagnostic value. It was therefore suggested that EMG should be omitted from the diagnostic criteria, and that further methodological studies of pressure algometry were needed (12). Finally, it is also important to emphasize that no ideal diagnostic test for tension-type headache exists. The diagnosis of headache, tension-type headache, as well as migraine, is a clinical diagnosis and no diagnostic test can yet replace a clinical interview and an examination of the patient.

6. Human models of tension-type headache

As tension-type headache is a disease in humans, and not known in animals, an ideal human experimental model is much needed, but few attempts have been made to do so (for a review see Bendtsen and Jensen (170)). In contrast, several experimental models for localized myofascial pain have been created (145 - 147, 156, 157, 171-174).

As experimental tooth clenching has previously been reported to induce mild headaches in migraineurs (175) an attempt was made to study the cause–effect relation between such sustained muscle contraction and tension-type headache in predisposed individuals (14). Fifty-eight patients with frequent episodic or chronic tension-type headache and 30 healthy controls were encouraged to clench their molar teeth slightly for 30 min (14). Forty patients (69%) and only 5 (17%) healthy controls developed headache within the 24 h following the clenching procedure. Those patients who later developed headache reported increased tenderness at the recording 90 min after clenching, whereas the patients who did not develop headache reported unchanged tenderness in their pericranial muscles (14) (Fig. 6). This study indicates that tenderness may precede the headache and be an initiating factor. However, the relation is not simple, as only 69% of the patients developed headache after clenching, and as the headache was mild initially in both healthy controls and patients but
Headache development
No headache development

Fig. 6. TTs in 58 patients recorded before and 90 min after experimental tooth clenching with respect to headache development. Median values with quartiles are shown (**p<10⁻³).

increased in intensity within the following hours in headache patients only. This difference may illustrate that headache individuals have an increased sensitivity to incoming stimuli and/or an impaired central antinociception. This central modulation may be disturbed in patients with chronic tension-type headache, as increased concentrations of enkephalines, but not of endorphins, in the spinal fluid have been reported (37, 53). However, the changes are minor and as the reactivity of endogenous opioid systems may be changed by persistent pain it is not yet clear whether these findings are primary or secondary to the chronic pain condition. Furthermore, as chronic use of simple analgesics also influences the central pain modulating system the cause-effect relations are further complicated (176). Further development of an experimental human model of tension-type headache is greatly needed as reproducibility of headache development, response to placebo stimulation, and many other aspects require further investigation.

7. Pathophysiological synthesis

Can the previous and present clinical and experimental findings be combined with results from animal pain models into a coherent hypothesis of the pathophysiological mechanisms of tension-type headache? The consistent findings of increased tenderness (9, 12–14, 27, 47, 74–78) and of slightly decreased cephalic pressure pain tolerances and thermal pain thresholds and tolerances during a headache episode as compared to the headache-free state (13) support the presence of hyperalgesia in chronic tension-type headache. Pain thresholds were normal in patients with episodic tension-type headache (9, 87, 98) and in chronically affected subjects from the population study (9), but rather consistently decreased in other studies of patients with chronic tension-type headache (32, 35, 47). These findings may indicate that, initially, hyperalgesia is reversely linked to the actual pain episode, whereas a more frequent activation may induce a more permanent condition of hyperalgesia. What mechanisms are behind the hyperalgesia? In animal and human experiments, increased nociceptive activity may induce primary and secondary hyperalgesia primarily due to sensitization in the spinal dorsal horn/trigeminal nucleus (38, 69–71, 86, 177, 178). In humans, the sensory consequences of such central changes have been described in studies of experimentally induced cutaneous pain (55, 58, 102) and in myofascial pain induced by hypertonic saline (146, 147, 157, 174). Recently, a qualitatively changed response to mechanical stimuli in human tender muscle was demonstrated for the first time in patients with chronic tension-type headache (86), and in patients with fibromyalgia (179). These findings suggested mediation of pain by low-threshold mechanosensitive afferents projecting to sensitized dorsal horn neurons. Evidence is also accumulating that sensitization is associated with intracellular changes affecting membrane excitability and permeability as well as alteration of gene expression in dorsal horn neurons (64, 178). Thus, perception of pain is not a simple reflection of simultaneous afferent noxious input, but a dynamic process which is highly influenced by the effects of past experiences. In addition, information from muscle and cutaneous nociceptors is processed differently in the spinal cord, as input to dorsal horn neurons from muscle nociceptors is subject to a stronger descending inhibition than the input from cutaneous nociceptors (38, 71).

On this basis, it can be concluded that the underlying pain mechanisms in tension-type headache must be highly dynamic, as tension-type headache represents a wide variety of frequency and intensity, not just between subjects, but also within the individual subject over time. The initiating stimulus may be either a condition of mental stress, unphysiological motor stress, a local irritative process with release of various peptides, or a combination of these. The nociceptors of the deep tissues become activated, resulting in increased afferent input to the spinal dorsal horn or the trigeminal nucleus. Secondary to the peripheral stimuli, the supraspinal pain perception structures may become activated, and, due to central modulation of the incoming stimuli, a self-limiting process will be the result in most subjects. So what maintains the pain and the tenderness? As mental load itself can cause activation of the γ-motor system via the limbic system and elicit muscle activity (163, 180–183), the slightly increased motor activity and insufficient relaxation in pericranial
and shoulder muscles may thereby contribute to maintain the pain (11, 13, 14, 184). The cascade of increased nociceptive activity may induce central sensitization in the spinal dorsal horn or the trigeminal nucleus in predisposed individuals (38, 69, 70, 71, 86, 177, 178, 185). The central nociceptive perception and modulation may then become disturbed, resulting in a prolonged, secondary hyperalgesia. When the central sensitization becomes sufficiently strong and widespread, the pain becomes chronic, due to self-perpetuating disturbances in the pain perception. A vicious circle may be initiated and an abnormal reaction to incoming peripheral stimuli is elicited and probably maintained a long time after the primary eliciting stimuli/stressor has stopped. Such a dynamic condition might be the explanation for the increased tenderness but otherwise normal pain sensitivity in patients with episodic tension-type headache. Similarly, such a mechanism may explain the highly increased tenderness, the slightly increased EMG activity and the impaired pain sensitivity in severely affected patients with chronic tension-type headache. As chronic tension-type headache usually evolves from the episodic form (28), this mechanism may explain the evolution of pain in most patients with tension-type headache, namely those associated with a disorder of the pericranial muscles (87). An effective prevention of this evolution from a peripheral mechanism in the episodic to a central mechanism in chronic tension-type headache will therefore be of major importance in future treatment strategy. Other, yet unknown, mechanisms must be considered in those patients without such muscular disorders, and in the very small subset of patients who have the sudden onset of chronic tension-type headache. Most recently, a report of genetic predisposition for chronic tension-type headache has been published (186), but the transmission seems to be complex. Tension-type headache is in all likelihood a disease where the individual genetic constitution represents only one of several concurrent factors.

8. Future perspectives and concluding remarks

This review has focused mainly on the extracranial factors of relevance to tension-type headache. At present, the most apparent abnormality in these patients is increased pericranial myofascial tenderness. Prolonged nociceptive stimuli from myofascial tissue may sensitize the central nervous system and thereby lead to increased general pain sensitivity. Sensitization, or dysmodulation, of afferent information at the spinal level, impaired supraspinal modulation of incoming stimuli, and reflex motor activity may therefore be of major importance in the evolution from episodic to chronic tension-type headache. The author, however, acknowledges the possibility that extracranial myofascial nociception may be only one of several pathophysiological mechanisms. Studying the extracranial tissues may nevertheless contribute to clarifying some of the mechanisms of tension-type headache and probably also of myofascial pain in general. There are still numerous problems in understanding tension-type headache; of particular importance is the question of initial eliciting factors. This remains unanswered and much more research in the field is required. The present thesis supplements the understanding of the balance between peripheral and central changes in tension-type headache and thereby, hopefully, may assist the development of better prevention and treatment of the most prevalent type of headache.

9. Summary

In this present thesis I have discussed the epidemiology and possible pathophysiological mechanisms of tension-type headache. A population-based study of 1000 subjects randomly selected from a general population, two clinical studies, and a method study of EMG recordings, were conducted. Tension-type headache was the most prevalent form of headache, with a life-time prevalence of 78% in a general adult population. Thirty percent were affected more than 14 days per year and 3% were chronically affected, i.e. had headache at least every other day. Females were more frequently affected than males, and young subjects more frequently affected than older subjects. Females were more sensitive to mechanical pressure pain and revealed more tenderness from pericranial muscles and tendon insertions than males, and young subjects were more pain-sensitive than older subjects. Significantly higher tenderness in pericranial muscles was found in subjects with tension-type headache compared to migraineurs and to subjects without any experience of headache. Tenderness increased significantly with increasing frequency of tension-type headache in both males and females, whereas no such relation was found for mechanical pain thresholds. The applied EMG methodology was fairly reliable and nonpainful, but due to intersubject variability paired studies should be preferred. Subjects with chronic tension-type headache had slightly increased EMG levels during resting conditions and decreased levels during maximal voluntary contraction compared with headache-free subjects, indicating insufficient relaxation at rest and impaired recruitment at maximal activity. In a subsequent clinical, con-
controlled study, the effect of 30 min of sustained tooth clenching was studied. Within 24 h, 69% of patients and 17% of controls developed a tension-type headache. Shortly after clenching, tenderness was increased in the group who subsequently developed headache, whereas tenderness was stable in the group of patients who remained headache-free, indicating that tenderness might be a causative factor of the headache. Likewise, psychophysical and EMG parameters were studied in 28 patients with tension-type headache, both during and outside of a spontaneous episode of tension-type headache. It was concluded that a peripheral mechanism of tension-type headache is most likely in the episodic subgroup, whereas a secondary, segmental central sensitization and/or an impaired supraspinal modulation of incoming stimuli seems to be involved in subjects with chronic tension-type headache. Prolonged nociceptive stimuli from myofascial tissue may be of importance for the conversion of episodic into chronic tension-type headache. The author emphasizes that tension-type headache is a multifactorial disorder with several concurrent pathophysiological mechanisms, and that extracranial myofascial nociception may constitute only one of them. The present thesis supplements the understanding of the balance between peripheral and central components in tension-type headache, and thereby, hopefully, leads us to a better prevention and treatment of the most prevalent type of headache.

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