Central Mechanisms in Tension-type Headaches

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Although tension-type headache is the most frequent primary headache, little is known about its pathophysiology. It is a matter of debate if the pain in tension-type headache originates from myofascial tissues or from central mechanisms in the brain. This article presents a summary of available data on the pathophysiology of tension-type headache and proposes a pathogenic model. From experimental research and clinical studies, it appears that myofascial nociception is important in episodic tension-type headache; however, central mechanisms (*ie*, central sensitization) are preponderant in the pathophysiology of the chronic form. Understanding the mechanisms of this central sensitization could allow for more efficient prophylactic treatments to emerge.

Introduction

Tension-type headache (TTH) is the most frequent primary headache, with a lifetime prevalence of 69% for men and 88% for women [1]. TTH was defined as an ache or sensation of tightness, pressure, or constriction, widely varied in intensity, frequency, and duration; it is long-lasting, commonly occipital, and associated with sustained contraction of skeletal muscles, usually as a part of the patient's reaction during life stress [2]. The International Headache Society (IHS) classification defines this type of headache more precisely and distinguishes between patients with episodic tension-type headache (ETTH) and those with chronic tension-type headache (CTTH). ETTH and CTTH are subclassified based on their association with a disorder of the pericranial muscles (*eg,* presence of tenderness or increased electromyogram activity) [3]. For decades, it has been debated if the pain in TTH originates from myofascial tissues or from central mechanisms in the brain. However, the pain mechanisms in TTH are practically unknown. This article presents a summary of the available data on the pathogenesis of TTH and attempts to propose a pathogenic model.

Tenderness and Pain Thresholds

The results of determining pain detection thresholds with a pressure algometer and of assessing pericranial tenderness by manual palpation are not superposable for several reasons. Pressure pain thresholds (PPT) are usually recorded from one or two cranial locations, mainly from the anterior temporal region to which the algometer can be applied most easily; the tenderness scores on manual palpation are summed up from a number of pericranial locations. Among these locations, the temple, which is the target for pressure algometer studies, is a precise spot with low tenderness on manual palpation in patients with TTH [4]. Nonetheless, it has been demonstrated that there is a significant inverse relationship between local tenderness and PPT [5–9].

Tenderness on manual palpation

Tenderness on manual palpation is usually increased outside of headache in the episodic and the chronic form of TTH [4,10]. Manual palpation is performed bilaterally with small rotating movements of the second and third fingers. The induced tenderness is scored at seven locations on both sides of the cranium to obtain a Total Tenderness Score (TTS) by summation, which has proven to be reliable [11]. It has been demonstrated that tenderness increases during the headache phase [12], indicating peripheral or central sensitization of myofascial nociception. No correlation was found between TTS and levels of pericranial electromyogram activity, nor between the latter and the presence or intensity of headache [5,12]. Levels of TTS are rather low in patients with TTH; they do not exceed 30% of the possible maximum score and are marginally higher than the control values in patients without headache [12]. These findings suggest that peripheral myofascial tenderness may not play a predominant role in TTH and that muscle contraction may be unrelated to the headache.

Bendsten *et al.* [13] showed that the stimulus-response curve for pressure versus pain recorded from normal muscle was well described by a power function, although it was approximately linear (*ie,* qualitatively different from that of normal muscle) when recorded from highly tender muscle in patients with CTTH. The abnormal stimulus-response curve function was related to the degree of tenderness, not to the diagnosis of TTH; it was confirmed in another study of patients with fibromyalgia [14]. This finding of qualitatively altered nociception from tender

muscles indicates that the central nervous system is sensitized at the level of the spinal dorsal horn and trigeminal nucleus in patients with chronic myofascial pain. The largest difference between tender and normal muscles is found at moderate intensities, which may be another reason for the possible discordance between manual palpation (pressures of moderate intensity are exerted) and PPT (pressures are greater and less discriminatory) in patients with CTTH [15]. It has been suggested that this qualitatively altered response may be caused by activity in low-threshold mechanosensitive (LTM) afferents, which do not normally mediate pain [13,16], but have a similar stimulus-response function (linear). However, that strong input from peripheral nociceptors can remodel the circuitry of the dorsal horn by unmasking previously ineffective synapses and by forming novel synaptic contacts between LTM afferents and dorsal horn neurons, which normally receive input from high-threshold mechanoreceptors (HTM) [17,18].

Pressure-pain thresholds

Pressure-pain thresholds (PPT) determined with an algometer were shown to be lower in patients with CTTH compared with patients with migraine without aura and healthy subjects at cephalic sites and at the Achilles tendon [19]. Despite a significant decrease of mean thresholds in CTTH, only 50% of patients had abnormal values (*ie,* values 1.5 SD below the mean of the control group), indicating a low diagnostic usefulness. These results were confirmed by others [7]; however, there are those who did not confirm it, especially when only one site was investigated [4,8,12]. In ETTH, pain-detection thresholds at cephalic sites are usually not different from those determined in healthy subjects [4,8,9,20,21]. These discrepancies could be explained by the frequency of headache in the studied populations, with ETTH and frequent TTH differing from daily or almost daily TTH.

If the findings of decreased extracephalic pain thresholds in patients with TTH can be confirmed [6,13,19], this would support the hypothesis that diffuse disruption of central pain-modulating systems is one of the pathophysiologic hallmarks of CTTH. It would also confirm reports of abnormal sensitivity to pain in paravertebral muscles [22] and a more rapid increase in pain in the fingers [20]. Pain thresholds to pressure are lower in the cranium than in the extremities [21]. This could explain why a general lowering of pain thresholds (increased sensitivity) can result in head pain (with no pain in the rest of the body) [23].

In fibromyalgia, PPT decrease during isometric muscle contraction, which contrasts with a clear increase in healthy subjects and favors an abnormality in central pain [24]. We have obtained similar results at the level of temporalis muscle in patients with CTTH [25].

In most studies, PPT and pain tolerance (cephalic and extracephalic) are not influenced by the presence or absence of headache. This contrasts with the increased palpation tenderness during a headache and may indicate that the factors affecting pain sensitivity in TTH are not limited to the structures normally thought to be involved (*ie,* pericranial and neck muscles). It also indicates that pain sensitivity, if elevated in TTH, may persist in the absence of headache. Thermal pain-detection and tolerance thresholds, although superior to controls interictally, decreased during the headache, suggesting a temporary central change (*ie,* segmental central sensitization or decreased anti-nociception) [12].

Botulinum Toxin A Injections

Studies of the therapeutic effect of botulinum toxin A (BTX-A) in patients with TTH have yielded conflicting results. Two small, placebo-controlled studies [26,27] have found indications for a prophylactic effect of pericranial BTX-A injections in TTH, confirming preliminary results of previous pilot studies. In a randomized, placebo-controlled, double-blind study, Schmitt *et al.* [28] found some improvement in affective variables, although important outcome variables such as pain intensity, analgesics intake, headache-free days, or percentage of responders were not significantly different between the groups. In a double-blind, placebo-controlled study on the effect of BTX-A for the treatment of ETTH and CTTH, and in a pilot study of patients with CTTH, Rollnik *et al.* [29,30] could not find any beneficial effect of BTX-A compared with placebo; however, there was a reduction of temporalis muscle EMG activity after 12 weeks for patients with CTTH. These results suggest that increased cephalic muscle contraction and associated tenderness might play a minor role in the pathogenesis of CTTH [30].

Brain Stem Reflexes

Brain stem reflexes are interesting noninvasive tools to investigate the central processing of sensory information from the cephalic region.

Temporalis exteroceptive silent periods

Motor control of the temporalis muscle, a jaw-closing muscle, can be assessed partly by studying the inhibition of voluntary activity elicited by stimulation of trigeminal territories. Two successive exteroceptive suppressions (ES1 and ES2), also called silent periods, are obtained in this way. They are induced by the activation of the same afferent axons, and mediated in the brainstem by separate oligo- (ES1) and multisynaptic (ES2) neural nets, activating brainstem interneurons that inhibit the motorneurons of jaw-closing muscles [31]. Several studies [32–36] have shown that the second temporalis exteroceptive silent period (ES2) can decrease in patients with CTTH; other studies have demonstrated that silent period remains normal [37–41]. For patients with ETTH, ES2 duration is normal [33,35,36]. On the basis of reduced ES2 duration, it

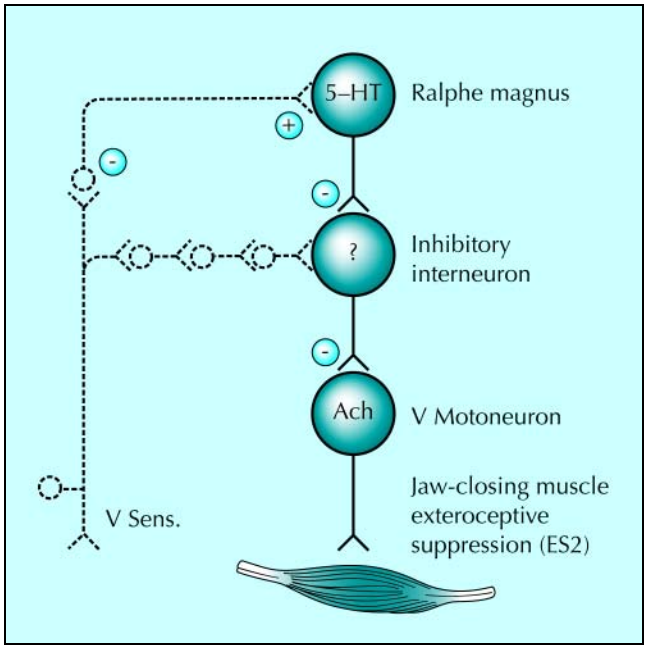

Figure 1. Diagram of the major anatomic relays and neurotransmitters that play a role in exteroceptive jaw-closing muscle suppressions. According to data obtained in animals and pharmacologic results in humans, serotoninergic afferents probably decrease the excitability of inhibitory interneurons through 5-HT receptors. (*From* Schoenen [45]; with permission).

was suggested that there is a deficient activation or excessive inhibition of brainstem inhibitory interneurons [32], which are under the control of limbic structures (periaqueductal grey, amygdala, hypothalamus, and orbitofrontal cortex) (Fig. 1).

Studies of the pharmacologic modulation of ES2 have suggested that inhibitory interneurons mediating ES2 are inhibited by serotoninergic pathways and activated by nicotinic, cholinergic mechanisms [42]. This was confirmed by another study [43] that demonstrated how amitriptyline (a combined serotonin and noradrenalin re-uptake blocker) reduced ES2 in patients with CTTH. However, Göbel *et al.* [44] could not detect any difference in ES2 before or after treatment with amitriptyline in patients with CTTH.

After a single high-intensity (50–75 mA), peripheral-conditioning stimulus (upper and lower limbs) that is perceived as painful, ES2 is reduced in patients with CTTH and in control subjects, with a significantly higher pronounced reduction in patients with CTTH [45]. Although naloxone has no effect on the static ES2, it has been demonstrated that the peripherally induced inhibition of ES2 is transiently (partially, but significantly) reversed after naloxone [46], suggesting that the peripherally-induced inhibition of ES2 is probably produced by the activation of descending opiatergic control systems of the ES2 inhibitory interneurons. The fact that this inhibition is more pronounced in patients with TTH might indicate that opiate receptors in this circuitry are hyperactive.

Aktekin *et al.* [40] did not find any differences in ES2 parameters among patients with ETTH, CTTH, or migraine, and control subjects; the ES2 recovery curve was similar in all of the groups, indicating that the trigeminal nerve and the corresponding brainstem interneurons of the reflex arc could be intact in patients with headache, regardless of the diagnosis.

These discrepancies could be explained by the differences in the methods used for analyzing ES2 [47]. Patient selection is also a critical variable. Patients with daily or almost daily headache or who have a history of experiencing headaches with long durations could be more prone to decreased ES2 than patients with ETTH or frequent headache (> 18 days monthly) [37,48]. Moreover, patients with a moderate form of migraine without aura may be difficult to distinguish from patients with ETTH using the available 1987 IHS criteria. Because of these methodologic difficulties, the diagnostic use of ES2 is limited. Nonetheless, ES2 is reduced in a subgroup of severely affected patients with CTTH and favors a central nervous system dysfunction in these patients.

Blink reflex

Sensory stimulation of the ophthalmic division of the trigeminal nerve evokes reflex responses of the orbicularis oculi muscle. Because the R1 and R2 components are dependent on interneuron activity in the trigeminal nucleus, they may reflect possible brainstem dysfunctions in patients with TTH. Sand and Zwart [49] did not find any differences in R1 and R2 latencies among patients with migraine, CTTH, cervicogenic headache, and control subjects. However, they found a correlation between R1 latency and headache duration in the patients with TTH. This may suggest that hypoactivity of trigeminal neurons or facial motor neurons develops with time in patients with CTTH. Because it has been demonstrated that serotonin may facilitate excitatory input to facial motor neurons [50], brainstem serotoninergic hypoactivity may explain increased blink-reflex latencies. Recovery curves to paired shocks are reported to be a useful method for investigating the excitability of the relevant reflex pathways in patients. From experimental studies, it can be assumed that serotoninergic, noradrenergic, and dopaminergic activity alters the excitability of R2 [51]. It is known that serotonin and noradrenalin modulate pain transmission in the brainstem; therefore, the diminished recovery curve of R2 in patients with ETTH and CTTH may be related to a relative depletion of these neurotransmitters [40].

Puca and de Tommaso [52] found an early appearance of the R3 component at almost the perceptive threshold. They also found increased amplitude in patients with migraine and TTH, compared with age-matched control subjects (not correlated with severity of illness). They proposed a possible primary dysfunction of central inhibitory pathways that could cause pain. However, Ellrich *et al.* [53] demonstrated that the electrical threshold of R3 is mainly

determined by the activation of Aβ fibers. They also showed that there was a contribution of the nociceptive Aδ fibers at higher stimulus intensities [53]. They concluded that the R3 component cannot be assumed to be an adequate model to investigate nociceptive processing. Ellrich *et al.* [53] demonstrated that the nociceptive specificity of the blink reflex is increased using a concentric electrode compared with the conventional electrode [54].

Further studies are needed to determine the usefulness of blink reflex studies in TTH using a specific stimulator to increase its nociceptive specificity.

Nociceptive Flexion Reflex

The nociceptive flexion reflex is considered to be a spinally organized reflex influenced by an endogenous modulating system, which is the threshold that is highly correlated to the pain-perception threshold. The threshold is increased after systemic administration of serotonin re-uptake inhibitors [55] and aspirin; this reflex is subject to supraspinal influences [56]. Langemark *et al.* [57] found a decreased nociceptive flexion-reflex threshold and lower pain-tolerance thresholds in patients with CTTH compared with control subjects. The slope of the stimulus intensity and the Visual Analogue Scale pain-rating response curve was steeper in patients with CTTH. These findings suggest a disorder of an endogenous anti-nociceptive system, with a lowering of tone and recruitment of descending inhibitory systems (disturbed balance between nociceptive and anti-nociceptive systems).

Neurotransmitter Systems

Nitric oxide

Nitric oxide (NO) plays a key role in migraine and cluster headache. This freely diffusible molecule is involved in a variety of biologic functions, including neurotransmission [58]. NO also contributes to sensory transmission in the peripheral and central nervous system [59]. It has been demonstrated that the NO donor glyceryl trinitrate caused more headaches for patients with CTTH than for control subjects, with an immediate headache and a delayed TTH [60]. The authors suggest that a direct effect of NO on perivascular sensory afferents or NO-induced arterial dilatation are responsible for the immediate headache, and central sensitization at the spinal and trigeminal level is responsible for the delayed headache. Because the activation of NO synthase (NOS) is associated with glutamate transmission, and *N*-methyl-D-aspartate *(*NMDA) and α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid glutamatergic excitatory mechanisms are present in the trigeminal nucleus caudalis in experimental animals [61], one can speculate on the possible role of NO generation in central sensitization [62], which may explain part of the CTTH pathophysiology. In situations of tonic and chronic pain in which high-frequency or sustained afferent input produces a prolonged depolarization, the Mg2+ block on the spinal NMDA receptors is removed, allowing for the activation of NMDA receptors, an influx of Ca2+, and a production of NO. These changes in Ca2+ and NO may lead to changes as a result of potentiation of synaptic transmission that would manifest as hyperalgesia, facilitation, an expansion of receptive fields, central sensitization, or wind-up. It has been demonstrated that a NOS inhibitor (NG-monomethyl-L-arginine hydrochloride, [L-NMNA]) is effective at reducing pain and muscle hardness [63••,64]. In animal models of persistent pain, it has been shown that NOS inhibitors reduce central sensitization [62]. The experimental results indicate that the permanently altered muscle hardness, tenderness, and muscle activity may reflect sensitization of second-order neurons at the level of the spinal dorsal horn and trigeminal nucleus; therefore, the effects of L-NMNA observed in the study of Ashina *et al.* [63••] are probably a result of the desensitization of these neurons.

Calcitonin gene-related peptide

Calcitonin gene-related peptide (CGRP) is involved in the pathophysiology of migraine and cluster headache. Ashina *et al.* [65] demonstrated normal plasma levels of CGRP in patients with CTTH; the level was unrelated to the headache state. The interictal plasma level of CGRP was increased in patients with a pulsating pain quality, suggesting that patients who fulfill IHS criteria for TTH may be related pathophysiologically to migraine if their headache has a pulsating quality.

Substance P, neurokinin A, glutamate

There is ample experimental evidence from basic pain research that persistent activity in peripheral nociceptors may lead to increased responsiveness of second-order neurons, and that neurotransmitters released from C-fibers may be responsible for the altered neuronal function [66]. The neurotransmitters involved include the tachykinines substance P (SP) and neurokinin A, and the excitatory amino acid glutamate, which has a prolonged release that may activate post-synaptic receptors that are normally blocked (*ie,* NMDA receptors) [67]. This activation leads to increased influx of calcium, which initiates a cascade of biochemical events that may lead to long-term metabolic changes and increased excitability of the effected cells. In the sensitized state, previously ineffective, low-threshold Aβ-fiber inputs to nociceptive dorsal horn neurons become effective [68], which means that pain can be generated by low-threshold Aβ-fibers that clinically will manifest themselves as allodynia. In addition, the response to activation of high-threshold afferents, which clinically will manifest themselves as hyperalgesia, is exaggerated. Other mechanisms that have increased excitability of second-order neurons have been proposed to be involved in central sensitization [69•]. They include structural reorganiza-

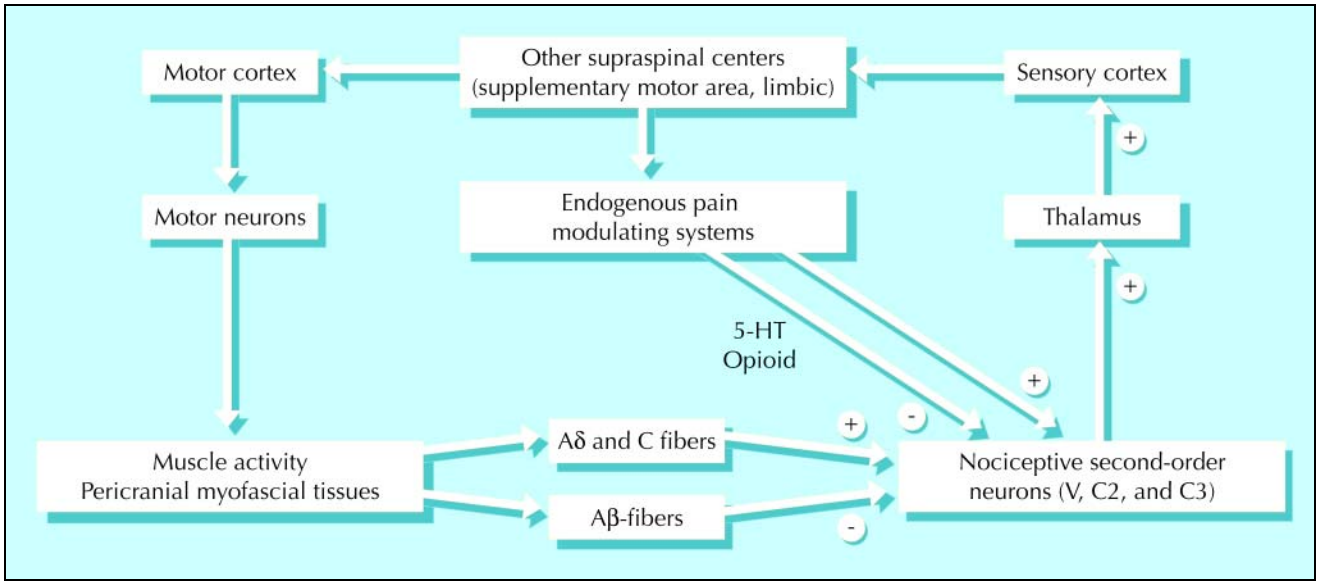

Figure 2. Normal pain processing.

tion through which novel synapses between Aβ-fibers and nociceptive dorsal horn neurons are formed; decreased supraspinal inhibition of Aβ-fiber inputs to nociceptive dorsal horn neurons; and the formation of a presynaptic link between Aβ-fibers and nociceptive dorsal horn neurons as a consequence of C-fiber-induced activation of spinal interneurons. The concentration of platelet SP was found to be significantly higher during headache in patients with TTH than in healthy volunteers [70]; however, lower levels of SP in platelets were found in the headache-free period for patients with ETTH [71]. Taken together, the studies of SP levels in patients with primary headaches or other chronic pain conditions have not led to consistent results. A recent study demonstrates that plasma levels of SP, neuropeptide Y, and vasoactive intestinal polypeptide do not significantly differ between patients with CTTH and healthy volunteers in the cranial or in the peripheral circulation. The levels of these neuropeptides were largely unrelated to the presence or absence of headache [72]. Another study [71] found higher levels of SP in platelets and lower levels of β-endorphin in peripheral blood mononuclear cells (PBMC) in patients with ETTH compared with control subjects, supplying further evidence of a failure of the pain-controlling and pain-processing systems in TTH, notably the endogenous opioid system. Some authors suggest that PBMCs seemed to reflect cerebral β-endorphin modulation closely and could be considered to be a mirror of the central opiatergic system [73]. In this study, PPT values were lower in patients with low levels of β-endorphin in PBMCs and high concentrations of SP in the platelets; the cellular levels of these two neurotransmitters appear to be negatively correlated in patients and in control subjects. A positive correlation between β-endorphin levels and PPT, and a negative correlation between SP in platelets and PPT, were found in patients and control subjects. These data suggest that the antinociceptive pathways are dysfunctional in TTH, even during the headache-free periods. It is also suggested that the modifications in the peripheral levels of those neurotransmitters could be the biochemical reflection of the low PPT in TTH (Figs. 2 and 3).

Serotonin

Considering that nucleus raphe magnus plays a central role in the control of ES2 inhibitory interneurons and that this nucleus is serotoninergic, our most interesting pharmacologic results on ES2 modulation were obtained with drugs that acted on serotonin mechanisms. They suggest that medullary inhibitory interneurons are inhibited by serotoninergic pathways and the receptors mediating this inhibition are probably of the 5-HT-1 type [74]. Although it is certain that 5-HT has important anti-nociceptive effects (*eg,* effects through many different 5-HT receptors subtypes and effects that may vary within the same 5-HT receptor subtype), the exact role of 5-HT in pain modulation is not well understood. Studies indicate that plasma 5-HT and platelet 5-HT levels are increased in patients with ETTH, although the peripheral 5-HT metabolism seems to be normal in patients with CTTH [75,76]. One study found lower levels of serotonin in platelets in patients with ETTH [71], concurring with the results of Shulka *et al.* [77] and Leira *et al.* [78]. The platelet 5-HT uptake has been reported to decrease in patients with ETTH and remain normal in patients with CTTH. Furthermore, the plasma 5-HT level increases during a headache in a mixed population (ETTH and CTTH) [79], although there is a significant negative correlation between the plasma 5-HT level and headache frequency [75]. Thus, patients with CTTH may have an impaired ability to increase plasma 5-HT and synaptic 5-

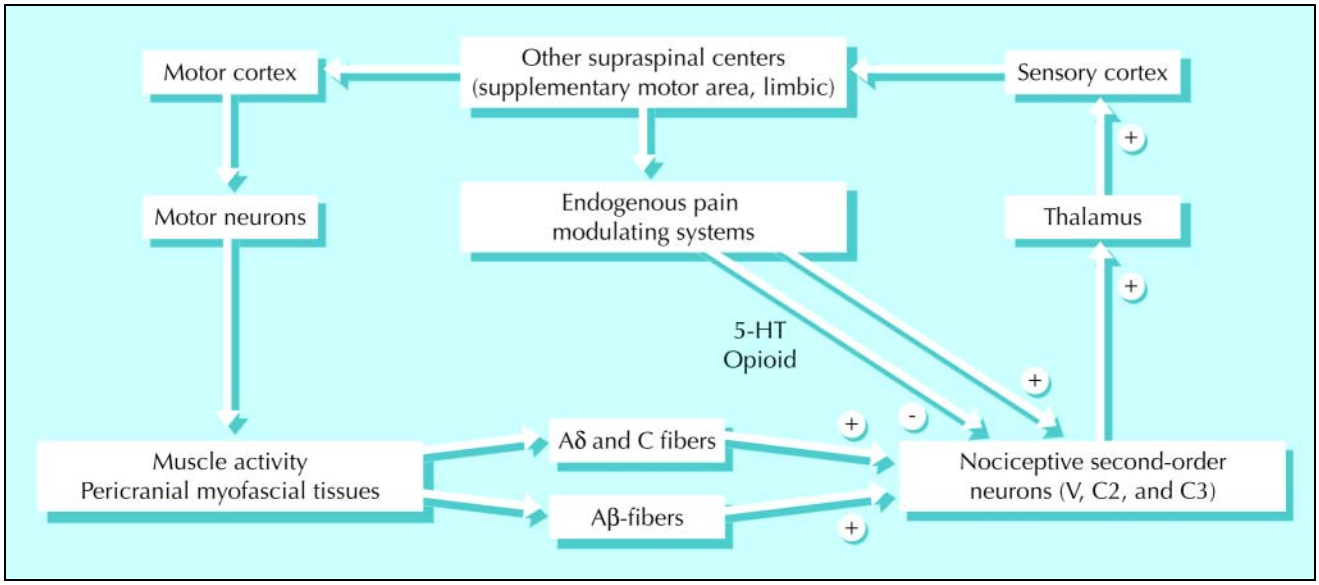

Figure 3. Pain processing in patients with tension-type headache.

HT levels (possibly) in response to increased nociceptive inputs from the periphery. This serotoninergic dysfunction could contribute to central sensitization at the level of the spinal dorsal horn and trigeminal nucleus and to the conversion from ETTH to CTTH.

β-Endorphin and met-enkephalin

Met-enkephalin levels in the cerebrospinal fluid were found to be increased in patients with CTTH, supporting a defect in the opioid system or in the production of neurotransmitters [80]; however, the β-endorphin concentration was normal [81]. β-endorphin levels in PBMC in patients with ETTH were lower compared with control subjects [71]. A positive correlation between β-endorphin levels and PPT was found in patients and control subjects. These data suggest that the anti-nociceptive pathways are dysfunctional in TTH, including the endogenous opioid system.

Pharmacotherapy and Neurotransmitter Systems

The most efficient drugs for the treatment of TTH are serotonin and noradrenalin re-uptake inhibiting anti-depressants. A placebo-controlled, double-blind, crossover study analyzing the effect of amitriptyline or citalopram in patients with CTTH demonstrated a reduction of muscle tenderness and headache intensity that was significantly higher with amitriptyline than with placebo [82]. Citalopram had no significant effects on any of the examined parameters. Studies on the effects of tricyclic anti-depressants on chronic pain conditions have yielded conflicting results. However, these studies are incomparable because the analgesic effect of the tricyclic antidepressants may differ among the various drugs, between acute and chronic dosing, between patients and healthy control subjects, and among various pain conditions [82]. The analgesic effects of amitriptyline cannot solely be explained by the inhibition of serotonin re-uptake because citalopram had no effects on the examined parameters. Amitriptyline effects the re-uptake of noradrenalin and the serotoninergic, adrenergic, cholinergic, and histaminergic receptors. Moreover, it potentiates the effects of endogenous opioids. It has been demonstrated that amitriptyline may act as an NMDA-receptor antagonist, and it has been suggested that the analgesic effects of amitriptyline in chronic pain may primarily result from this effect (*ie,* reduction of central sensitization) [83]. The reduction of tenderness exerted by amitriptyline is caused partly by segmental action in the central nervous system, probably at the level of the spinal dorsal horn and trigeminal nucleus. This was supported by the study of Ashina *et al.* [63••,64] in which the NOS inhibitor L-NMMA reduced headache and pericranial muscle hardness and tenderness. Recent studies demonstrated a peripheral analgesic effect of amitriptyline in addition to its central effect [84]. The authors suggested that the reduction of myofascial pain exerted by amitriptyline may be caused by the reduction of segmental central sensitization and a peripheral anti-nociceptive action.

What Do Psychologic Studies Tell Us About Neurotransmitter Systems Involved in Tension-type Headache?

Using the Tridimensional Personality Questionnaire, Di Piero *et al.* [85] found significantly higher harm-avoidance scores (serotoninergic) in patients with migraine and in patients with TTH; novelty-seeking (dopaminergic) and persistence (glutamatergic) scores were significantly different in patients with migraine. Reward-dependence scores

(noradrenergic) were similar in the control group, in patients with migraine, and in patients with TTH. This supports a role of the serotoninergic system in migraine and TTH. A dysfunction of dopaminergic and glutamatergic tone seems to be a specific feature of migraine. However, a randomized, double-blind, crossover study of sulpiride (dopamine antagonist) and paroxetine in the treatment of CTTH demonstrated better relief from sulpiride compared with paroxetine [86].

Proposal for a Pathogenic Model of Tension-type Headache

Under some conditions, the painful stimulus from the pericranial myofascial tissues may be more prolonged or more intense than normal. The mechanisms behind this are unknown, but may include increased muscle activity or the release of various chemical mediators that are secondary to local pathologic conditions. For most patients, these conditions will be self-limiting because of the central pain modulatory mechanisms and local reparative processes. These conditions will be experienced as frequent headache episodes for a limited period of time. However, the prolonged nociceptive input in patients who are predisposed may lead to sensitization of nociceptive second-order neurons at the level of the spinal dorsal horn and trigeminal nucleus [87]. The pathophysiologic basis for the increased susceptibility to central sensitization is unknown. Possible mechanisms include an impaired supraspinal inhibition of nociceptive transmission in the spinal dorsal horn and trigeminal nucleus that results from serotoninergic dysfunction. It has also been demonstrated that the endogenous opioid system is implied in this impaired balance between nociceptive and anti-nociceptive transmission. A genetic predisposition to CTTH has recently been reported [88]; future genetic studies may help to identify the mechanisms that make some patients susceptible to the development of central sensitization. In this sensitized state, the afferent Aβ-fibers that normally inhibit Aδ- and C-fibers by presynaptic mechanisms in the dorsal horn will stimulate the nociceptive second-order neurons. Furthermore, the effect of Aδ- and C-fiber stimulation will be potentiated and the receptive fields of the dorsal horn neurons will be expanded [67]. Recent data suggest that NMDA receptors and NO formation play an important role in the central sensitization process. Thus, the nociceptive input to supraspinal structures will increase considerably, which may result in increased excitability of supraspinal neurons [89] and a decreased inhibition or increased facilitation of nociceptive transmission in the spinal dorsal horn [90] (*ie*, generalized pain hypersensitivity). These neuroplastic changes may increase the drive in motor neurons at the supraspinal segmental levels [18], resulting in slightly increased muscle activity and in increased muscle hardness. The biochemical changes in the dorsal horn may alter the properties of the sensory afferents so that they release inflammatory mediators, (*eg*, SP and CGRP) from the receptive endings in the myofascial tissues, thus creating a vicious cycle. This proposed model is based mainly on experimental animal studies and observational clinical studies. However, in observational studies, it is difficult to clarify if an abnormal finding is a consequence or a cause of the disorder. Thus, experimental human studies are needed to bridge the gap between basic animal and clinical research and to study the cause-effect relationship between myofascial nociception and central sensitization (Figs. 1 and 2).

Patient selection seems crucial and it can be assumed that patients with moderate migraine without aura have been included in several studies of ETTH. However, some patients with chronic daily headache that evolved from migraine may have been included in studies of CTTH. New operational criteria, which allow clinicians to select cohorts of patients who are suffering from indisputable TTH, are necessary for future studies. Hopefully, these criteria will be available in the forthcoming revised Headache Classification of the IHS.

Conclusions

From experimental and clinical studies, it is obvious that there is an interrelation between peripheral and central mechanisms in the pathogenesis of TTH. The former may be important in initiating the headache and the latter (central sensitization) perpetuates it. Understanding the mechanisms of the central sensitization is a challenge for future studies in TTH and could allow for more efficient treatments to emerge, which is the "holy grail" in headache research.

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