Pathophysiology of Tension-type Headache

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Tension-type headache is one of the most common primary headache disorders. Advances in basic pain and clinical research have improved our understanding of pathophysiologic mechanisms of tension-type headache. Increased excitability of the central nervous system generated by repetitive and sustained pericranial myofascial input may be responsible for the transformation of episodic tension-type headache into the chronic form. Studies of nitric oxide (NO) mechanisms suggest that NO may play a key role in the pathophysiology of tension-type headache and that the antinociceptive effect of nitric oxide synthase inhibitors may become a novel principle in the future treatment of chronic headache. Future studies should focus on investigation of the source of peripheral nociception, the role of descending pain modulation, and the development of an animal model of tension-type headache to support the pathophysiologic importance of central sensitization in tension-type headache.

Introduction

Tension-type headache (TTH) is one of the most common primary headache disorders and has a large socioeconomic impact on the society [1]. According to the second edition of the International Classification of Headache Disorders [2], TTH can be divided into infrequent and frequent episodic (ETTH) and chronic (CTTH) subtypes. The scientific interest in TTH previously has been sparse; therefore, the pathophysiology of TTH has not been fully clarified. Understanding pathophysiology may be of importance in formulating the effective treatment and prevention of TTH [3]. The progress in the basic and clinical neuroscience in the past decade has increased our understanding of the pathophysiology of TTH. It is suggested that abnormalities in the peripheral and central nervous systems may be involved in the pathophysiology of TTH [4•,5••]. This article reviews the pathophysiologic mechanisms of TTH.

Emotional Factors

Emotional factors have been implicated as risk factors for the development of TTH. Findings of altered brain stem reflexes suggested that the limbic control of descending pain control systems may be abnormal in patients with CTTH [6]. Stress and mental tension have been reported to be the most common precipitating factors of TTH [7,8] and a positive correlation between headache and stress has been shown in patients with TTH [9]. Furthermore, experimental studies have demonstrated that tension–type-like headache can be induced by psychologic stress [10]. Moreover, behavioral and psychologic therapies have been shown to be effective for the treatment of TTH [11•]. Janke *et al.* [12] demonstrated that depression increased vulnerability to TTH in patients with frequent headaches during and following the laboratory stress test and was associated with elevated pericranial muscle tenderness. It was suggested that anxiety and depression may contribute to increased excitability in central nociceptive pathways in patients with CTTH [12,13]. The neurobiologic mechanisms through which emotional factors promote TTH are unknown and further studies are needed to explore the possible relation of corticolimbic circuits to sensitization of nociceptive pathways in TTH.

Genetic Factors

Ulrich *et al.* [14] examined the relative importance of genetic and environmental influence for the development of TTH by analyses of twins. It was concluded that environmental influence was of major importance for ETTH and a genetic factor was minor. In a Danish study, CTTH had an increased occurrence in first- and second-degree relatives, whereas spouses had no increased risk of CTTH [15,16]. It was demonstrated that first-degree relatives of 122 probands with CTTH had more than three times the risk of CTTH than the general population [15,16]. The mode of inheritance was investigated by complex segregation analysis, which indicated that CTTH has multifactorial inheritance and supported the view that CTTH has genetic components in pathophysiology because the multifactorial model had a better fit than the sporadic model [17]. It can be concluded that ETTH is a heterogeneous headache disorder and may be caused by multiple genes in combination with environmental factors or it may not have a genetic component [17].

Peripheral Factors

Muscular factors may play an important role in the development of TTH. Increased tenderness in pericranial muscles is a common clinical finding and the best documented abnormality in patients with ETTH and in patients with CTTH [18–22]. Tenderness has been demonstrated to be uniformly increased throughout the pericranial region and muscles, and tendons have been found excessively tender [18,19,21]. Moreover, pericranial tenderness is positively associated with the intensity and frequency of TTH [19]. It has been argued that the pericranial tenderness is an epiphenomenon and a consequence of head pain in patients with TTH [23]. However, findings of increased pericranial tenderness in patients with TTH during headache-free periods suggest that tenderness is not simply the consequence of an actual headache [24]. In addition to increased tenderness, it has been shown that the trapezius muscle in patients with CTTH is much harder than in control subjects [25,26]. Muscle hardness and tenderness are positively correlated in these patients [25]. Furthermore, hardness was increased on days with and without headache, indicating that increased hardness is not the consequence of actual headache [25].

Although the origin of increased muscle tenderness in TTH is unknown, nociceptors around vessels in striated muscle and in tendon insertions and fasciae have been suggested as possible sources of pain in TTH [4•,5••]. Muscle pain is mediated by thin myelinated (Aδ) fibers and unmyelinated (C) fibers, whereas the thick myelinated (Aα and Aβ) fibers normally mediate innocuous sensations [5••,27]. Noxious and innocuous stimuli such as mechanical stimuli, ischemia, and chemical mediators could excite and sensitize Aδ-fibers and C-fibers [5••,27]. The possible role of mechanical strain, ischemia, and inflammation has been extensively studied in TTH.

Muscle strain

Sustained contraction of pericranial muscles has long been thought to be a causative factor in patients with TTH. In one experimental study [5••,28], sustained tooth clenching with 10% of the maximal electromyographic (EMG) signal induced more TTH in patients with TTH than in control subjects. It has been demonstrated that patients with TTH are more likely to develop shoulder and neck pain in response to static exercise than healthy control subjects [29]. However, laboratory-based EMG studies with surface electrodes have reported normal or, more often, a slightly increased muscle activity in TTH [30–32]. The increased muscle activity may be a normal protective adaptation to pain, but slightly increased muscle activity in patients with TTH on headache-free days [20] makes this explanation less likely. Using needle electrodes, it was demonstrated that that EMG activity in so-called myofascial trigger points (trapezius muscle) was higher than in the adjacent non-tender muscles in patients with CTTH [33]. This study suggests that continuous activity in few motor units may be sufficient to induce peripheral sensitization of muscular nociceptors [5••] and that needle electrodes are needed to detect altered activity in small areas such as trigger points.

There is evidence of a substantial contribution of cervical proprioceptive input to ocular motor control and postural control in animals and humans [34]. In addition, it has been reported that patients with chronic cervicobrachial pain and concomitant dizziness manifest impaired postural performance compared with healthy subjects [35]. Giacomini *et al.* [36] suggested a proprioceptive disturbance in CTTH patients by investigating postural control with static posturography. However, contribution of impaired postural tone to nociception in patients with CTTH remains unclear.

Muscle blood flow and ischemia

It has been suggested that local muscle ischemia and disturbances in metabolism, microcirculation, and mitochondria function in the tender areas may explain myofascial pain in TTH and in other myofascial pain disorders [27,37]. Langemark *et al.* [38] found normal resting blood flow and relative flow increase during isometric work in the temporal muscle of patients with CTTH by using the ^{133}Xenon clearance technique. However, in that study, muscle blood flow was measured from a large muscle area, not in a tender point. Ashina *et al.* [39] measured blood flow and lactate levels in vivo in a tender point in the trapezius muscle in patients with CTTH by using the microdialysis technique. The increase in muscle blood flow from baseline to exercise and post-exercise periods was significantly lower in the tender points of patients than in control subjects. There was no difference in muscle lactate levels during static exercise, ruling out muscle ischemia in these patients. It was hypothesized that altered blood flow likely was caused by altered sympathetic outflow to blood vessels in striated muscle due to plastic changes in the central nervous system (central sensitization).

Inflammation

Endogenous substances such as serotonin, bradykinin, and potassium ions are effective chemical stimulants for skeletal muscle nociceptors [27]. Release of neuropeptides from muscle afferents may play a role in myofascial pain. The mode of action of inflammatory mediators in muscle pain is not fully clarified. Peripheral sensitization of muscular nociceptors likely is induced by the complex interaction of various chemical mediators [27]. Mork *et al.* [40] demonstrated that when a chemical mixture consisting of bradykinin, serotonin, histamine, and prostaglandin E_2 was slowly infused into the trapezius muscle, patients with frequent ETTH developed significantly more pain and also tended to develop more muscle tenderness than healthy control subjects. Concomitant psychophysical measures indicated that a peripheral sensitization of myofascial sensory afferents was responsible for the muscular hypersensitivity in these patients [41]. However, this hypothesis has

been challenged in a microdialysis study by Ashina *et al.* [42], who reported no difference in in vivo interstitial concentrations of inflammatory mediators and metabolites (bradykinin, adenosine 5-triphosphate, glutamate, glucose, pyruvate, urea, and prostaglandin E2) in a tender point between patients with CTTH and healthy control subjects. This study suggested that tender points are not sites of ongoing inflammation in patients with CTTH.

Conclusions on peripheral factors

Pericranial muscle tenderness and hardness are increased in patients with TTH and muscular factors may be of importance in the development TTH. Increased pain sensitivity in pericranial region of patients with TTH may be due partially to peripheral sensitization of nociceptors in myofascial tissues. However, the firm evidence for peripheral abnormalities in TTH is still lacking. The role of proprioceptive sensory fibers in muscle pain in TTH needs to be investigated.

Central Factors

Pain sensitivity

Studies of pain thresholds in patients with TTH revealed differences between ETTH and CTTH. Thus, a normal pressure-pain detection threshold was reported in patients with ETTH [19,30]. In contrast, studies of patients with CTTH showed that these patients are hypersensitive to stimuli applied in cephalic and extracephalic regions. The pressure, thermal, and electrical pain thresholds in cephalic region have been reported to be lower in patients with CTTH than in control subjects [18,20,43–45]. The differences in extracephalic pain thresholds between CTTH patients and healthy subjects were rather subtle and were found only in studies that included relatively large number of patients (*ie*, 32 to 50 patients) [18,20,44,45], whereas studies with small sample sizes (*ie*, 12 to 14 patients) [19,46] failed to detect any significant difference. Because of considerable inter-individual variation in pain thresholds [47], large sample size is required for group comparisons of pressure-pain detection thresholds. Stimulus-response functions of pressure pain in patients with CTTH exhibited a marked upward shift in rated pain intensity at suprathreshold stimulus intensities, whereas the pain threshold was shifted only marginally [48]. These data suggest increased excitability of neurons in the central nervous systems (*ie*, central sensitization in patients with CTTH). It has been suggested that suprathreshold testing may be more sensitive than threshold measurements in the evaluation of central sensitization in CTTH [5••]. The pressure-pain tolerance threshold (*ie*, the maximal pressure stimulus that is tolerated) generally is considered to be a better and more reproducible correlate to clinical pain than pain detection [45]. One study reported that pressure-pain tolerance thresholds in the finger were lower in patients with CTTH than in healthy control subjects [18]. A recent experimental study reported higher pain ratings to suprathreshold stimuli in patients with CTTH than in healthy control subjects [49]. This was true for single and repetitive (2 Hz) suprathreshold electrical stimulation in all of the examined locations (*ie*, temporal, trapezius, and anterior tibial regions) and for muscle and skin. These data clearly demonstrated generalized hyperalgesia in patients with CTTH.

The question is whether increased myofascial tenderness in patients with CTTH could be explained by general pain hypersensitivity. The increase in myofascial tenderness is more pronounced than the increase in general pain sensitivity in CTTH [5••]. A significant but not very high correlation between general pain hypersensitivity and pericranial tenderness has been demonstrated [18,20]. Thus, general hypersensitivity can explain only a minor part of the increased pericranial tenderness in patients with CTTH. Other factors thus may contribute to the increased tenderness. The demonstration of the qualitatively altered stimulus-response function for pressure versus pain recorded from a tender muscle in patients with CTTH indicates sensitization at the level of the spinal dorsal horn/trigeminal spinal nucleus [5••,48].

The lowered pressure pain detection, and electrical, thermal, and tolerance thresholds indicate the presence of allodynia (pain elicited by stimuli that normally are not perceived as painful) and hyperalgesia (increased sensitivity to painful stimuli) in patients with CTTH. The widespread and unspecific nature of the hypersensitivity indicates that the general pain sensitivity is affected at the central level in CTTH. Thus, it can be concluded that the general pain sensitivity in the central nervous system is increased in patients with CTTH, whereas the central pain processing seems to be normal in patients with ETTH.

Central pain modulation

The increased pain sensitivity in CTTH may be caused by decreased antinociceptive activity from supraspinal structures (*ie*, disturbed central pain modulation). Nociceptive flexion reflex is a spinally organized withdrawal reflex, which is subject to supraspinal influence and may be depressed (increased threshold) by diffuse noxious inhibitory control [50]. Diffuse noxious inhibitory control, which is triggered by peripheral Aδ- and C-fibers, may result from the physiologic activation of some brain structures putatively involved in descending inhibition [51]. Langemark *et al.* [52] found decreased nociceptive flexion reflex thresholds in patients with CTTH compared with control subjects. This finding indicated dysfunction of antinociceptive systems in CTTH. Further studies are required to test this hypothesis.

Biochemical Mechanisms

Serotonin

Serotonin (5-HT) is an important transmitter in the antinociceptive pathways descending from the dorsal raphe nucleus

in the brain stem to the spinal dorsal horn and it likely is involved in ascending antinociceptive pathways [53]. The role of 5-HT in TTH has been extensively investigated by studying 5-HT in peripheral blood, but the studies have given inconsistent results due to clinical and methodologic differences [5••]. It can be summarized that patients with ETTH have a decreased platelet 5-HT uptake and increased plasma 5-HT, whereas patients with CTTH have normal platelet 5-HT uptake, decreased platelet 5-HT, and normal plasma 5-HT [5••]. Moreover, there is a negative correlation between plasma 5-HT and headache frequency in patients with CTTH [54]. Thus, patients with CTTH may have an impaired ability to increase plasma 5-HT and thus possibly synaptic 5-HT levels in response to increased nociceptive inputs from the periphery. Such a serotonergic dysfunction could contribute to central sensitization of nociceptive pathways and thereby to the conversion from ETTH to chronic CTTH. However, this must be regarded only as a preliminary hypothesis. First, the above-mentioned results should be confirmed in future studies. Second, we do not know whether the peripheral changes in 5-HT actually reflect similar mechanisms in central neurons.

Neuropeptides

In the past decade, there has been increasing interest in the role of neuropeptides in primary headaches. Particularly, a role for calcitonin gene-related peptide (CGRP) has been implicated in the pathophysiology of migraine and cluster headache [55]. Studies of substance P (SP), neuropeptide Y (NPY), and vasoactive intestinal peptide (VIP) in patients with primary headaches or other chronic pain conditions have not led to consistent results that could be explained by different methodology [56]. Bach *et al.* [57] reported normal CGRP levels in the cerebrospinal fluid (CSF) in patients with CTTH. Ashina *et al.* [58] measured plasma levels of CGRP and SP, NPY, and VIP [56] in the cranial and peripheral circulation of patients and control subjects. It was demonstrated that plasma levels of CGRP, SP, NPY, and VIP are normal in the cranial and peripheral circulation of patients. In addition, plasma levels of neuropeptides were largely unrelated to headache state and no relationship between CGRP levels and muscular factors was demonstrated [56,58]. However, findings of normal levels of neuropeptides cannot exclude that abnormalities of these neuropeptides at the neuronal or peripheral or muscular levels play a role in the pathophysiology of CTTH. Further studies with new sensitive methods of analysis are necessary to clarify the role of neuropeptides in CTTH.

Other neurotransmitters

Plasma levels of the excitatory amino acid glutamate have been reported to be normal in patients with TTH [59]. In vivo concentrations of glutamate in a tender point of the trapezius muscle in patients with CTTH did not differ from control subjects in the resting state and in response to static exercise [42]. Sarchielli *et al.* [60] demonstrated an increase in platelet glutamate content in CTTH patients and hypothesized that glutamate in the central nervous system may be involved in the induction and maintenance of head pain.

The level of met-enkephalin in the CSF was found to be increased in patients with CTTH [61]. No correlation was found among CSF met-enkephalin-immunoreactivity and pericranial tenderness, nociceptive flexion-reflex threshold, or thermal pain threshold [61]. In contrast, β-endorphin level in the CSF did not differ between CTTH patients and control subjects [57]. In patients with ETTH, β-endorphin levels in peripheral blood mononuclear cells were lower than in control subjects [62]. In addition, a positive correlation was found between pressure-pain threshold values and β-endorphin levels in patients and control subjects [62]. These findings suggest that patients with TTH may have some dysfunction of the endogenous antinociceptive systems.

Mechanism-based Treatment

Antidepressants and tension-type headache

The only prophylactic treatment of CTTH with proven efficacy is the tricyclic antidepressant amitriptyline [63]. It was assumed previously that the analgesic effect of amitriptyline could be ascribed to the blockade of serotonin reuptake in the central nervous system. This was questioned first by animal studies and later by human studies showing that selective serotonin reuptake inhibitors have little or no clinical effect in patients with CTTH [64,65]. Findings of lower 5-HT reuptake inhibition and higher analgesic efficacy of amitriptyline than of citalopram suggest that 5-HT reuptake inhibition is not the major mechanism of action of amitriptyline in the treatment of CTTH [64]. Several mechanisms have been suggested to explain the antinociceptive action of amitriptyline. The antinociceptive effect of amitriptyline may be due to the augmentation of descending inhibitory influence on nociceptive pathways by inhibition of reuptake of biogenic amines at the spinal and supraspinal levels [64]. Other mechanisms of possible importance for the antinociceptive effect of amitriptyline are potentiation of the effect of endogenous opioids, and blocking of muscarinic cholinergic receptors, H_1 histamine receptors, α_1 adrenergic receptors, several 5-HT receptors, and Na^+, Ca^{2+}, and K^+ channels [66]. Acting as an *N*-methyl-D-aspartate receptor antagonist, amitriptyline has been shown to block the induction of long-term potentiation, a form of synaptic plasticity contributing to memory and sharing common mechanisms with central sensitization in pain pathways [67,68]. Action of amitriptyline in the peripheral nervous system by blocking Na^+ channels, adenosine A_1, receptor and 5-HT_{2A} receptors also have been recognized [69]. We previously demonstrated that the increased tenderness in patients with CTTH could be reduced by treatment with amitriptyline. Interestingly, the reduction in tenderness

could be ascribed solely to the group of patients who responded to amitriptyline treatment, whereas the smaller group of non-responders had unchanged levels of pericranial myofascial tenderness. The reduction of myofascial tenderness during treatment with amitriptyline likely is caused by a segmental reduction of central sensitization in combination with a peripheral antinociceptive action of the drug [70].

The noradrenergic and specific serotonergic antidepressant mirtazapine also has been reported to be effective in the treatment of CTTH [71]. The mechanism of action of mirtazapine is the blockade of α_2-adrenergic receptors on noradrenergic and serotonergic presynaptic neurons, which results in increased serotonergic and noradrenergic neurotransmission.

Nitric oxide

Animal studies have shown that sensitization of pain pathways may be caused by or associated with activation of nitric oxide synthase (NOS) and the generation of nitric oxide (NO) and that NOS inhibitors reduce central sensitization in animal models of persistent pain. On the basis of these findings and the hypothesis of central sensitization in CTTH, Ashina *et al.* [72••] investigated the analgesic effect of the NOS inhibitor N^G-monomethyl-L-arginine hydrochloride (L-NMMA). In a double-blind, placebo-controlled, crossover study [72••], patients received L-NMMA or placebo over 2 days. L-NMMA reduced headache intensity significantly more than placebo (Fig. 1). To explore the mechanisms of this analgesic effect, Ashina *et al.* [73] also studied the relationship between myofascial factors and NOS inhibition. This study showed that muscle hardness and tenderness were reduced after treatment with L-NMMA, whereas there was no significant reduction at any time after treatment with placebo. Another experimental study demonstrated that infusion of the NO donor glyceryl trinitrate induces TTH in these patients [74]. Collectively, pharmacologic studies of NO support the hypothesis that central sensitization may play an important role in the pathophysiology of CTTH and that inhibition of NO and thereby central sensitization may become a novel approach in the future treatment of CTTH.

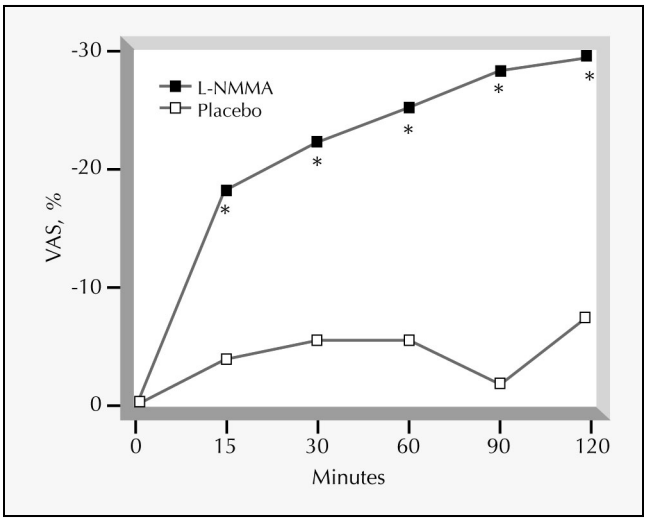

Figure 1. Percent changes from baseline pain intensity on a 100-mm visual analogue scale (VAS) in 16 patients with chronic tension-type headache. The pain intensity was significantly more reduced following treatment with L-NMMA (filled squares) compared with placebo (squares) ($P = 0.01$). *$P < 0.05$ compared with baseline (time = 0). The plots represent mean scores. (*Data modified from* Ashina *et al.* [72••], with permission).

Conclusions

Pericranial myofascial tenderness and muscle hardness are increased in TTH, and this increase may be caused by sensitization of peripheral nociceptors in myofascial tissues. Patients with CTTH exhibit signs of increased pain sensitivity due to increased excitability in the central nervous system at the level of the cervical spinal dorsal horn or trigeminal spinal nucleus, thalamus, and somatosensory cortex. Studies of NO mechanisms suggest that NO may play a key role in the pathophysiology of CTTH and that the antinociceptive effect of an NOS inhibitor, previously demonstrated only in animal models, may become a novel principle in the future treatment of chronic headache. The antinociceptive effect of NOS inhibition likely is due to a reduction of central sensitization. Future studies with selective NOS inhibitors are needed to determine which type of NOS is involved and its exact site of action.

Based on the available data of patients with TTH, it is plausible to suggest that frequent nociceptive input from muscles in the cephalic region of patients with infrequent and frequent ETTH induces sensitization of sensory afferents and second-order neurons in the trigeminal nucleus caudalis and dorsal horn of the cervical spinal cord. If the process or evolution is not blocked, the plastic changes would spread to supraspinal structures and result in sensitization of third-order neurons in the thalamus and neurons in the somatosensory cortex. Patients then would develop CTTH and exhibit signs of generalized hyperalgesia (Fig. 2).

Future research should focus on the identification of the source of peripheral nociception in patients with TTH. Progress in migraine research demonstrated the necessity of an interaction between basic research and clinical studies in humans. There is only one study that specifically focused on an animal model of TTH [75]. Unfortunately, the lack of validated animal models of TTH and sparse interest in the research community hampers the progress in TTH research and the development of mechanism-based treatment. Future human and animal studies are needed to support the pathophysiologic importance of central sensitization in CTTH and to explore a possible role of descending pain modulation in TTH.

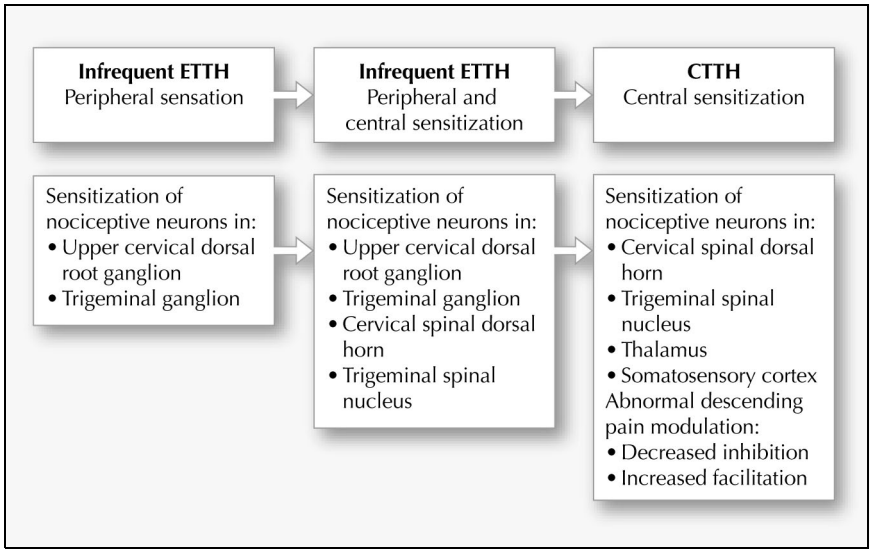

Figure 2. Hypothesis: transformation of episodic tension-type headache (ETTH) into the chronic form (CTTH). Because central sensitization is most likely correlated to frequency of headache, patients with headache frequency between 5 and 15 days per month would exhibit signs of sensitization of the second-order neurons.

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