Chapter 70

Sensitization of Myofascial Pain Pathways in Tension-Type Headaches

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Recent studies on tension-type headache indicate that the nociceptive input to the central nervous system may be increased because of activation or sensitization of peripheral sensory afferents. In addition, the responses of nociceptive neurons in the central nervous system to their synaptic inputs from peripheral sensory afferents appear to be enhanced in patients with chronic tension-type headache, as suggested by several pain perception studies and pharmacologic studies. Sensitization of second- and third-order neurons in the central nervous system may be induced by the barrage of nociceptive impulses from the periphery. In this way, both peripheral and central sensitization may play a role for initiation and maintenance of tension-type headache (Table 70-1). Recent studies demonstrate that treatment with drugs that counteract sensitization has an analgesic effect in tension-type headache. The evidence for sensitization of myofascial pain pathways in tension-type headache is discussed.

PERIPHERAL FACTORS

The most prominent clinical finding in patients with tension-type headache is a considerably increased tenderness to palpation of pericranial myofascial tissues (19,22,24). The increased pericranial tenderness has been found both in patients with episodic and in patients with chronic tension-type headache (18,22) and both during and outside headache (16,23). The tenderness seems to be uniformly increased throughout the pericranial region and both muscles and tendon insertions have been found excessively tender (10,13,19,22) (Fig. 70-1). In addition, it has been demonstrated that the pericranial tenderness is positively associated with both the intensity and the frequency of tension-type headache (19) and with muscle hardness (1).

What could be the pathophysiologic basis for the possible pain originating in the myofascial tissues? Under normal conditions, myofascial pain is mediated by thin myelinated (Aδ) fibers and unmyelinated (C) fibers, and the thick myelinated (Aα and Aβ) fibers normally mediate innocuous sensations (31). Various noxious and innocuous events such as mechanical stimuli, ischemia, and chemical mediators could excite and sensitize Aδ-fibers and C-fibers (26) and thereby play a role for the increased tenderness in tension-type headache.

The role of the first two events—mechanical strain and ischemia—has been extensively studied in tension-type headache. Numerous electromyographic (EMG) studies using surface electrodes have demonstrated that muscle activity is only slightly increased in tension-type headache (16). However, it has been reported that EMG activity is significantly increased in small localized areas of the muscle, the so-called myofascial trigger points (15). Continuous activity in a few motor units over long time could be sufficient for excitation or sensitization of peripheral nociceptors (7), but the findings by Hubbard and Berkoff (15) have not yet been reproduced by other groups. Muscle tenderness and hardness at tender muscle sites could also result from a local contracture (i.e., shortening of the contractile apparatus without action potentials in the muscle fibers) rather than normal contraction of motor units (33). This mechanism would explain the lack of EMG abnormalities in tension-type headache, but the mechanisms of peripheral nociceptor activation by a contracture have not yet been studied in enough detail (27). By use of the elegant microdialysis technique, Ashina et al. (5) demonstrated that lactate levels in a tender site in the trapezius muscle did not differ between patients and healthy subjects during rest and static exercise, ruling out muscle ischemia in these patients. Thus, it can be concluded that the muscle pain in tension-type headache is not caused by

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TABLE 70-1 Potential Mechanisms of Enhanced Pain Sensitivity (Hyperalgesia)

	Peripheral Sensitization	*Central Sensitization*	*Disinhibition*
Site of action	Peripheral tissue	Spinal or supraspinal	Spinal or supraspinal
Driven by	Inflammatory mediators	Synaptic input	Excitotoxicity?
Sensory signs	At site of tissue damage	Beyond site of damage	Widespread

excessive muscle contraction and muscle ischemia. However, it cannot be excluded that a locally increased muscle tone without EMG activity (contracture) may result in microtrauma of muscle fibers and tendon insertions or that excessive activity in a few motor units may excite or sensitize peripheral nociceptors.

Peripheral muscle afferents could be activated and sensitized by endogenous substances such as serotonin and bradykinin (26). Recently, Mork et al. demonstrated that when a combination of the endogenous substances bradykinin, serotonin, histamine, and prostaglandin E_2 was slowly infused into the trapezius muscle, patients with frequent episodic tension-type headache developed more pain (29) and tenderness (30) than healthy controls. Concomitant psychophysical measures indicated that peripheral sensitization of myofascial sensory afferents was responsible for the muscular hypersensitivity in these patients (30). However, Ashina et al. (6) demonstrated that the in vivo interstitial concentrations of adenosine 5-triphosphate, glutamate, glucose, pyruvate, urea, and prostaglandin E_2 in tender muscles during rest and static exercise did not differ between patients with chronic tension-type headache and healthy controls. The authors concluded that tender muscle sites in these patients are not sites of ongoing inflammation.

To summarize, pericranial myofascial tenderness and muscle hardness are frequently observed in tension-type headache. These findings are similar to trigger points in other myofascial diseases (35). Some studies indicate that the increased myofascial pain sensitivity in tension-type headache may be caused by activation or sensitization of peripheral nociceptors. However, firm evidence for peripheral abnormalities as a cause of myofascial tenderness is still lacking.

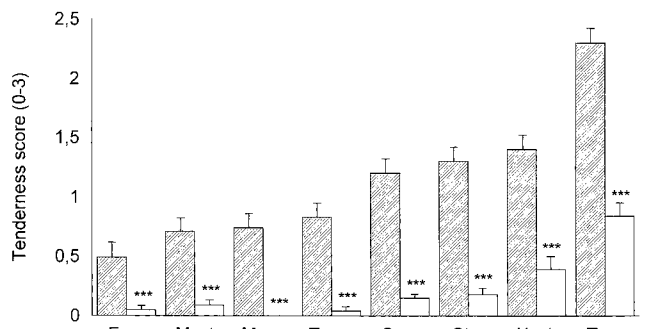

FIGURE 70-1. Local tenderness scores (mean ± SE) at eight pericranial locations in 40 patients with chronic tension-type headache (*hatched bars*) and in 40 healthy controls (*open bars*). The patients had significantly more tenderness than the controls at all locations. *Abbreviations:* Fron, frontal muscle; Mast, mastoid process; Mass, masseter muscle; Temp, temporal muscle; Coro, coronoid process; Ster, sternocleidomastoid muscle; Neck, neck muscle insertions; Trap, trapezius muscle. $***P \leq 0.0002$. (Reproduced from Bendtsen L, Jensen R, Olesen J. Decreased pain detection and tolerance thresholds in chronic tension-type headache. *Arch Neurol.* 1996;53:373–376, with permission.)

CENTRAL FACTORS

The increased myofascial pain sensitivity in tension-type headache could also be caused by central factors, such as (a) sensitization of second-order neurons at the level of the spinal dorsal horn/trigeminal nucleus, (b) sensitization of supraspinal neurons, and (c) decreased antinociceptive activity from supraspinal structures. The measurement of pain sensitivity to various types of stimuli applied to various parts of the body have provided important information about the nociceptive system in tension-type headache. Pain detection thresholds have been reported normal in patients with episodic tension-type headache (12,14,17,19) except for a recent study in patients with frequent episodic tension-type headache (30). In contrast, pain detection and tolerance thresholds have been found decreased in patients with chronic tension-type headache in all studies performed with sufficient sample size (10,20,21,32) (Fig. 70-2) (Table 70-2,).

Patients with chronic tension-type headache have been found hypersensitive to each of the different stimulus modalities examined, namely, pressure (10,21,32), thermal (21), and electrical (10,20) stimuli. Sensitivity to the various stimulus modalities is increased both at cephalic and extracephalic locations (10,20,21,32) and to stimulation of various tissues—muscle, skin, tendons, and peripheral nerves (10,20,21,32). The fact that chronic tension-type headache patients are hypersensitive to stimuli applied both at cephalic and at extracephalic, nonsymptomatic locations strongly indicates that synaptic

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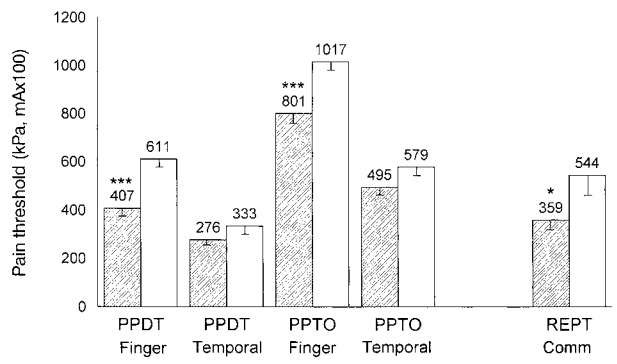

FIGURE 70-2. Pain thresholds to mechanical and electric stimuli in 40 patients with chronic tension-type headache (*hatched bars*) and in 40 healthy controls (*open bars*) (mean ± SE). *Abbreviations:* PPDT, pressure–pain detection threshold; PPTO, pressure–pain tolerance threshold; REPT, relative electric pain threshold; Finger, index finger; Temporal, temporal muscle; Comm, labial commissure. $***P \leq 0.0009$; $*P = 0.02$. (Reproduced from Bendtsen L, Jensen R, Olesen J. Decreased pain detection and tolerance thresholds in chronic tension-type headache. *Arch Neurol.*1996;53:373–376, with permission.)

transmission of nociceptive input within the central nervous system is increased in this group of patients, because peripheral sensitization would have more localized effects (28,34). The expansion of hypersensitivity to other tissues such as skin is consistent with referred hyperalgesia, which may be explained by convergence of multiple peripheral sensory afferents onto sensitized spinal cord neurons. The widespread and unspecific nature of the hypersensitivity, however, suggests that the central sensitization involves supraspinal neurons as well. Decreased activity of the endogenous antinociceptive systems would have similar effects (disinhibition). Thus, it can be concluded that nociceptive processing in the central nervous system is increased in patients with chronic tension-type headache, whereas central nociceptive processing seems to be relatively normal in patients with episodic tension-type headache.

The increase in myofascial tenderness is more pronounced than the increase in general pain sensitivity (7). Moreover, a significant but not very high correlation between general pain hypersensitivity and pericranial tenderness has been demonstrated (10,18). Thus, general hypersensitivity can explain only a part of the increased pericranial tenderness in patients with chronic tension-type headache. It has been demonstrated that the stimulus–response function for pressure versus pain in pericranial muscles is not only quantitatively but also qualitatively altered in patients with chronic tension-type headache (11). On the basis of results from animal studies, this is most likely explained by central sensitization at the level of the spinal dorsal horn/trigeminal nucleus. Thus, the increased tenderness in patients with chronic tension-type headache is probably partly caused by segmental central sensitization.

The hypothesis of central sensitization in tension-type headache is supported by clinical pharmacologic studies (8). It has been demonstrated that the increased tenderness in patients with chronic tension-type headache can be reduced by treatment with amitriptyline (9). Interestingly, the reduction in tenderness could be ascribed solely to the group of patients who responded to amitriptyline treatment, and the smaller group of nonresponders had unchanged levels of pericranial myofascial tenderness. The reduction of myofascial tenderness during treatment with amitriptyline may be caused by a segmental reduction of central sensitization in combination with an enhanced efficacy of noradrenergic or serotonergic descending inhibition (9).

TABLE 70-2 Pain Threshold Studies in Tension-Type Headache

Population	*Pain Threshold*	*Abnormal*	*N*	*Reference*
Episodic TH	Pressure–pain detection	No	20	Göbel et al., 1992 (14)
	Pressure–pain detection	No	28	Jensen et al., 1993 (19)
Frequent ETH	Pressure–pain detection	Yes	15	Mork et al., 2003 (30)
Mixed TH	Pressure–pain detection	No	17	Bovim et al., 1992 (12)
	Pressure–pain detection	No	28	Jensen et al., 1996 (17)
Chronic TH	Pressure–pain detection	Yes	40	Bendtsen et al., 1996 (10)
	Pressure–pain tolerance	Yes	40	Bendtsen et al., 1996 (10)
	Electric–pain detection	Yes	40	Bendtsen et al., 1996 (10)
	Electric–pain tolerance	Yes	40	Langemark et al., 1993 (20)
	Thermal–pain detection	Yes	32	Langemark et al., 1989 (21)
	Pressure–pain detection	Yes	32	Schoenen et al., 1991 (32)
	Pressure–pain detection	No	14	Jensen et al., 1993 (19)
	Thermal–pain detection	No		de Tommaso et al., 2003 (13)

Abbreviations: TH, tension-type headache. ETH, episodic tension-type headache; Mixed, populations consisting of both patients with episodic and patients with chronic tension-type headache; Abnormal, increased pain sensitivity; *N*, number of patients examined.

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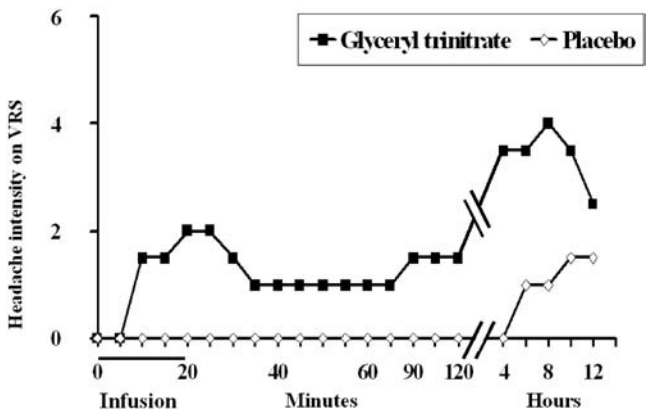

FIGURE 70-3. Median headache intensity during and after infusion of the nitric oxide donor glyceryl trinitrate (GTN) and placebo in 16 patients with chronic tension-type headache. Headache was scored on a 10-point verbal rating scale (VRS). The patients developed significantly more immediate and delayed tension-type headache on a GTN day (■) than on a placebo day (◇) ($P = 0.008$). (Reproduced from Ashina M, Bendtsen L, Jensen R, et al. Nitric oxide-induced headache in patients with chronic tension-type headache. *Brain*. 2000;123:1830–1837, with permission.)

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 (25). On the basis of these findings and the hypothesis of central sensitization in chronic tension-type headache, Ashina et al. demonstrated that infusion of the NO donor, glyceryl trinitrate, induces tension-type headache in these patients (2) (Fig. 70-3). In addition, the same group investigated the analgesic effect of the NOS inhibitor N^G-monomethyl-L-arginine hydrochloride (L-NMMA). This drug significantly reduced headache (4) as well as pericranial myofascial tenderness and hardness (3) in patients with chronic tension-type headache. These interesting studies support that central sensitization is involved in the pathophysiology of chronic tension-type headache. Moreover, these findings suggest that inhibition of NO and thereby central sensitization may become a novel means of future treatment of chronic tension-type headache.

To summarize, pain perception studies and pharmacologic studies strongly suggest that the central nervous system is sensitized in patients with chronic tension-type headache.

CONCLUSIONS

Sensitization of peripheral myofascial pain pathways may be of importance for the initiation and maintenance of tension-type headache, but more studies are needed to conclude this. Central sensitization is most likely of major importance in chronic tension-type headache. Central sensitization is facilitated if the activity of the descending inhibitory control systems is decreased; thus, disinhibition may contribute to the changes within the central nervous system. Further investigations of these mechanisms are essential for progress in the understanding and treatment of tension-type headache.

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