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Immunology Aspects in Tension-Type Headache Chronicity

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Abstract

Tension-Type Headache (TTH) headache is a type of primary headache which mostly complained by patients. The pain often ignored due to low mortality rates. Inadequate management makes the pain becoming chronic and causing a high disability rate. Many factors involved in transforming infrequent tension-type headache to chronic tension-type headache. A deeper understanding of the immune system's role in the pathophysiological process and modulation of chronic pain could be a potential target for developing therapies in managing chronic pain.

Keywords: chronic tension-type headache, immunology aspect, pathophysiology

Introduction

Tension-type headache (TTH) headache is a primary headache often complained of by all age groups with an incidence of 42% of all types of primary headache1-4. Nearly 90% of young adults have experienced one headache attack every month, 18-37% experience several monthly attacks, and 2-3% of patients become chronic TTH4-7. Based on gender, TTH is 1.5 times more common in women than men8.

Tension-type headache (TTH) is the most common health problem in the world2-4. It's caused by ignorance of the pain and self-medication attempts by TTH sufferers, which make it tends to become chronic and cause disability2,9-11. Reportedly 60% of TTH sufferers have decreased ability to work, increased absence rates followed by a decrease in the quality of life (both physical and psychosocial), which have a significant socio-economic impact.

The differentiation of TTH is based not only on the frequency of attacks but also on the different underlying pathophysiology.[11] The pathogenesis of TTH currently focused on the role of muscle tissue and the process of pain proprioception. It has been suggested that the role of muscle components contributes to the pain sensitization process associated with the changes in TTH from acute to chronic. [13,14]

Abnormalities in peripheral and central nociceptive systems combined with environmental, emotional, and genetic factors play a role in the pathophysiology of TTH. Allegedly in the episodic form, the peripheral mechanism is more dominant, whereas in the chronic type, in addition to the peripheral mechanism, central sensitization has occurred.[5,6,10,11]

It is essential to understand the pathophysiological mechanisms underlying the transformation of acute TTH into chronic from immunological and biomolecular aspects, which could be a consideration in pain management and chronic pain prevention. Later it will help the clinician to treat the headache appropriately, decrease patients' complaints, and increase patients' productivity.

Definition And Clinical Description

Tension-type headache (TTH) headache is a primary headache characterized by headaches lasting from 30 minutes to 7 days which meet the criteria: bilateral location, pressing or binding (not throbbing) nature, mild or moderate intensity, not exacerbated by routine activities such as walking or climbing stairs, no nausea or vomiting, may be accompanied by

photophobia or phonophobia.[12,15] Clinical manifestations of TTH can also be accompanied by pericranial tenderness during manual palpation[2].

Tension-type headache (TTH) is distinguished based on the attack episodes[7]. According to the International Headache Society Classification the Third Edition the Beta Version (ICHD-3 beta version). For infrequent episodic TTH there are at least 10 attack episodes with an average of <1 day/month (<12 days/year). For frequent episodic TTH there are at least 10 episodes of attack in 1-15 days/month for at least 3 months (12-180 days/year) and in chronic TTH headache occurs ≥ 15 days/month or lasts > 3 months (≥180 day/year).10,15

Myofascial Trigger Points in Chronic Tension-Type Headache

Chronic Tension-Type Headache (CTTH) is associated with active Trigger Points (TrPs) located in the muscles supplied by the C1-C3 segments (upper trapezius, lower trapezius, suboccipital, sternocleidomastoid) and by trigeminal nerves (temporalis, masseter, extraocular).[16,17]

During the headache phase, muscle pain increases and the threshold of thermal pain decreases in the temporal region. Pain hypersensitivity is found in those experiencing tension-type pain, with greater disturbances in individuals with chronic or more frequent headaches, implying that central sensitization can contribute to the synchronization of headaches.[18]

Under normal condition, myofascial pain mediated by thin myelinated fibers (Aδ) and nonmyelinated C fibers. Thick myelinated fibers (Aα and Aß) normally mediate harmless sensations. Whereas in abnormal circumstances, such as mechanical stimuli, ischemia, and chemical mediators, can excite and sensitize Aδ fibers and C fibers, therefore have a role in increasing tenderness in TTH.[19]

Prolonged input of the nociceptors from the pericranial myofascial tissue will cause central sensitization in second and third-order neurons (dorsal horn of spinal cord at the upper cervical and trigeminal levels, as well as the thalamus and somatosensory cortex). Patients with chronic TTH are hypersensitive to various cephalic and extracephalic stimuli, not limited to the location of symptoms. It is a strong indication of a central sensitization process because the hypersensitivity in peripheral sensitization is limited to a particular location.

The theory underlying chronic TTH is central sensitization process due to prolonged peripheral nociceptive input from muscle tissue. Trigger points actively induce chemical mediators (bradykinin, CGRP, substance P, TNFα, interleukin-1-b, serotonin or

norepinephrine), not only at the site of pain but also in areas of pain-free distant (referred pain).[9,17]

Immunology Aspects in Tension-Types Headache

There is not much research on the role of immunology in the chronicity of tension-type headaches. Verdova in 2017 found levels of Interleukin-1 β increased in chronic TTH. Aldy S Rambe in 2017 found levels of alpha TNF, IL-1 and IL-6 increased in chronic TTH. Amitriptyline and dexketoprofen are associated with a decrease in the value of the Numeric Rating Scale (NRS) in chronic TTH but not related to TNF levels of alpha, IL 1 and IL 6 levels.[20,21]

a. Peripheral Sensitization

After nociceptor stimulation, mast cell degranulation occurs. Interleukin 5 (IL-5), serotonin (5-HT), histamine, and nerve growth factor (NGF) are also released. They will bind with IL-5R, 5-HT2, histamine 2 (H2) receptors, and TrkA which causes pain sensitivity. In addition, mast cells also excrete Tumor Necrosis Factor Alpha (TNFα), IL-1β and IL-6. The activation of TNFα receptor 1 (TNFR1) will cause phosphorylation of the Nav1.9 channel[2,23]. The release of mediators by immune cells in the peripheral sensitization process is described in Figure 1.

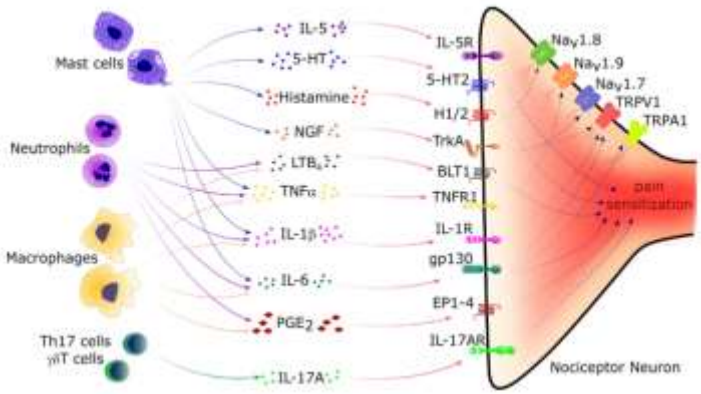

Figure 1. Immune Cells Release Mediators in the Peripheral Sensitization Process in Nociceptors[22]

The activation of IL-1 receptor 1 (IL-1R1) increases the expression of TRPV1. The IL-6 binds with gp130 and increases the expression of TRPV1 and TRPA1. They later will increase the neuron response to heat and chemicals which called sensitization[22,23]. Macrophages also release prostaglandin E2 (PGE2) which increases the nociceptors' sensitivity through PGE2

receptors 1-4 (EP1-4). Th17 cells and γδT cells release IL-17RA. IL-17RA neuronal signaling will cause nociceptive neuron sensitivity.[22]

Three examples of interactions between immune cells and nerve terminals are explained in figure 2: (1) Degradation of mast cells requires direct contact between mast cells and nerve terminals, mediated by N-cadherin (N-cad). MMP-24 metalloproteinases prevent mast cell degranulation by digesting N-cad. (2) The release of TNF-α and IL-15 by peripheral nerves and Schwann cells activates MMP-9 and facilitates the recruitment of macrophages. (3) Nociceptive nerve terminals can excrete Substance P (SP) and CGRP substances through antidromic activation from neighboring nerve terminal branches. Substance P and CGRP increase vasodilation and extravasation of immune cells. Neutral endopeptidase (NEP) inhibits nerve inflammation by decreasing substance P and CGRP.[24]

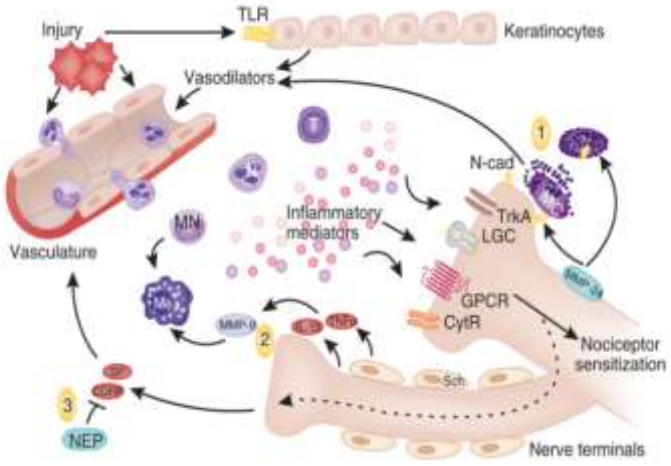

Figure 2. Immune System Activation and Nociceptors Sensitization in Pain[24]

b. Central Sensitization

Primary afferent nociceptive neurons alter the action potential from peripheral nerve to the dorsal horn of spinal cord, where synapses occur between first-order and second-order neurons. In chronic inflammatory or neuropathic pain, the nociceptive mediator including caspase 6 (Casp 6), adenosine triphosphate (ATP), chemokine ligand 2 (CCL2), TNFα, Colony Stimulating Factor 1 (CSF-1), and CGRP are released and activate microglia.[22]

c. Transformation of Peripheral Sensitization into Central Sensitization

Immune and glial cells interact with neurons to change pain sensitivity and mediate the transition from acute pain to chronic pain. This mechanism is the basis of transformation

in TTH. In response to injury, immune cells are activated and carried by blood flow to the site of injury. These cells not only contribute to protection but also initiate peripheral nociceptive sensitivity. Through the synthesis and release of inflammatory mediators and interactions with neurotransmitters and their receptors, immune cells, glial cells, and neurons form an integrated network that coordinates the immune response and modulates stimulation of the pain pathways[24].

The central sensitization process is explained in figure 3: [16,17,18].

a. Microglia are immune cells in the CNS that play a key role in mediating the central pain sensitivity. Primary afferent nociceptive neurons alter the action potential from the peripheral nerve to the dorsal horn of spinal cord (the site of synapses of neurons I & II). In chronic inflammation, there will be the release of mediators Casp 6, ATP, chemokine 2 (CCL2) ligands, TNFα, CSF-1, & CGRP which will activate microglia.
b. Microglia produce inflammatory mediators, namely IL-1β, TNFα, BDNF, PGE2 which are sensitive to first-order and second-order neurons and cause central sensitization that contributes to chronic pain. T cells also infiltrate the spinal cord, cross-talk with microglia, and nociceptive neurons which will strengthen the sensitivity of pain.
c. After peripheral nerve injury, primary afferent nociceptive neurons release CX3CL1 into the spinal cord which causes the following reactions:
    - Induces dorsal horn lobe microglia to produce TNFα
    - Activates astrocytes to produce CCL2 and CXCL1 which will induce changes in the spinal cord neurons that cause central sensitization.
d. In addition, oligodendrocytes produce IL-33 which works in cross-talk with microglia and astrocytes to increase pain sensitivity.

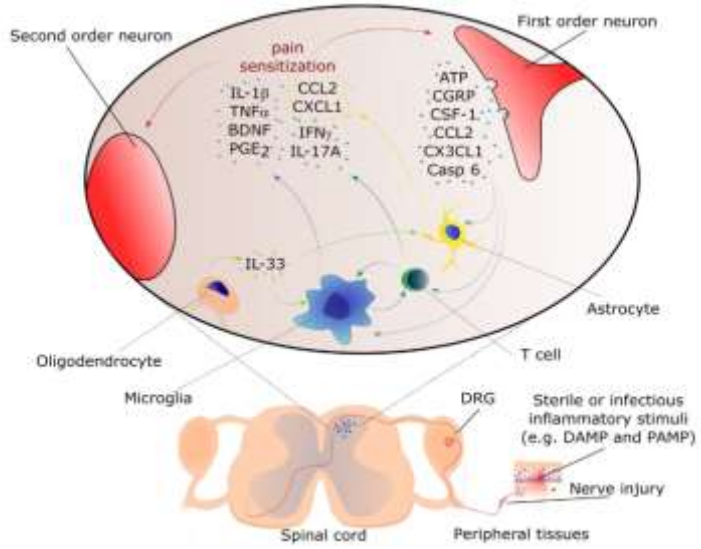

Figure 3. Microglia and T Cells mediate the Central Sensitization in the Spinal Cord[22]

Another concept that has emerged in pain research is that oxidative stress plays an important role in chronic pain due to central sensitization. The increasing of Reactive Oxygen Species (ROS) levels in the spinal cord along with the increasing of mitochondrial superoxide production cause central sensitization and consequently, pain without peripheral nerve injury or tissue inflammation. Superoxide can cause peripheral and central sensitization and alter nociception, producing hyperalgesia mediated by local and spinal oxidant mechanisms[23,25].

The immune system also reduces sensitivity by producing analgesia and anti-inflammatory or pro resolution-derived agents from the immune system. The immune system role in pain modulation process could be potential targets for the development of analgesic drugs and new therapies for managing chronic pain[24].

Conclusion

Tension-type headache is a type of primary headache often complained by patients. Many patients ignore the pain and do self-medication which makes the pain to become chronic. The focus of pathophysiology is the trigger points nociceptive stimulation that causes peripheral and central sensitization. Immune and glial cells play a role in this mechanism. So, a deeper understanding and further research are needed to assess its potential as a new therapeutic target in chronic TTH.

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