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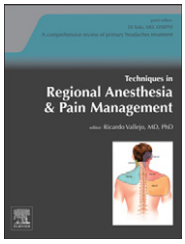

Pathophysiology of migraine and tension-type headache

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ARTICLE INFO

Keywords:
Migraine
Tension-type headache
Pathophysiology

ABSTRACT

Migraine and tension-type headache are common in general population. Recent progress in basic and clinical research has increased our understanding of pathophysiology of these headaches. New treatment modalities and drugs for the treatment of these headaches are emerging. Migraine is a neurovascular headache with complex pathophysiology, which has not been fully clarified. Genes for both migraines, with and without aura, are being identified. Current research indicates importance of cortical spreading depression and abnormal brain stem activity in the pathophysiology of migraine with aura. The migraine headache most likely originates in the sensory fibers innervating intracranial and extracranial blood vessels. Peripheral and central sensitization of trigeminovascular nociceptive pathways may develop during migraine attacks. Central sensitization of second- and third-order trigeminovascular nociceptive neurons may lead to transformation of episodic migraine to chronic migraine. Pericranial myofascial pain sensitivity is increased in patients with tension-type headache and may be of importance in the pathophysiology of this headache. Sensitization of second-order neurons at the level of the spinal dorsal horn or trigeminal nucleus, sensitization of supraspinal neurons, and decreased descending inhibition from supraspinal structures play a major role in the pathophysiology of chronic tension-type headache.

Introduction

Both migraine and tension-type headache (TTH) are common primary headache disorders in the population.[1,2] Both conditions have an enormous socioeconomic impact on individual and the society.[1,2] The pathophysiology of migraine and TTH is not fully clarified. However, the progress in basic and clinical research has increased our understanding of the mechanisms of migraine.[3] This has led to the development of new treatments for migraine.

In contrast to migraine, no significant improvement in treatment options has been seen in TTH within the last decades. This could be due to the TTH pathophysiology, which is less complete than that of migraine. Unfortunately, TTH has long been the least studied type of headache due to lack of scientific interest and acceptance among clinicians and researchers. Fortunately, we have gained a significant amount of knowledge on pathophysiology of TTH within the last two decades, and we are now beginning to understand some of the mechanisms of this condition.[4,5]

Pathophysiology of migraine

Migraine is regarded as a neurovascular disorder and is considered as a chronic headache disorder with episodic manifestations or attacks.[6] Migraine can be classified as migraine with and without aura. Aura refers to transient

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http://dx.doi.org/10.1053/j.trap.2012.11.002

focal neurologic symptoms, including visual disturbances, unilateral paresthesias, and language disturbance (dysphasia), and is experienced by up to 30% of migraine sufferers in the population.[7] Moreover, migraine is a complex headache condition occurring in a sequence of phases: premonitory phase, possible aura, headache, and postdrome followed by the resolution of headache. The pathophysiological mechanisms involved in each phase are probably mediated by different neuroanatomical structures.

Genetic studies demonstrate that migraine is a genetically complex primary headache disorder due to multiple mutations and variations. Approximately 50% of migraineurs have a first-degree relative who are also suffering from migraine.[8,9] A large population study in Denmark demonstrated that first-degree relatives of persons with migraine without aura had a 1.9-fold higher risk of migraine without aura while first-degree relatives of persons with migraine with aura had 4-fold higher risk of migraine with aura.[10] It has been suggested that both genetic and environmental factors are determinants for migraine without aura, whereas migraine with aura is mainly determined by genetic factors.[10] Sporadic and familial hemiplegic migraines (SHM and FHM) are rare paroxysmal migraine conditions which are characterized by motor aura and headache.[11,12] For FHM, 3 defects have been identified in genes coding for ion transporters or ion channels.[12] Based on these findings, FHM has been divided into 3 types.[12] In FHM type I, the affected gene is CACNA1A (on chromosome 19p13), coding for the α1A subunit of the Cav2.1 P/Q calcium channel. In FHM type II, the ATP1A2 gene (on chromosome 1q23) is affected, coding an a2-subunit of the astrocytic Na^+/K^+-ATPase. For FHM type III, the SCN1A gene (on chromosome 2q24) is affected, coding for voltage-gated sodium channel.

The initial events and factors leading to the development of migraine attack, as well as their neuroanatomical localization, are far from clarified and are subject to debate. It has been suggested that migraine headache originates in the nociceptive sensory fibers conveying pain signals from intracranial and extracranial blood vessels.[13] The strongest support for this hypothesis comes from the experiments showing that the stimulation of intra- and extracranial arteries evokes focal head pain.[14,15] Recent study using high resolution MRI angiography showed dilatation of intracranial and extracranial arteries on the headache side during experimentally calcitonin gene-related peptide (CGRP) induced migraine attacks.[16] Another group of scientists suggest that the initiation center for migraine without aura is in the brain stem nuclei[17,18] and hypothesize that pain could be generated without pathologic sensory afferent input.[19] The dorsal midbrain and dorsal pons structures were found to have increased concentrations of nonheme iron.[20] PET study has demonstrated activation of the dorsal midbrain, including the periaqueductal gray (PAG), and in the dorsal pons, near the locus coeruleus, in studies with migraine without aura.[21] However, it has recently been argued that activation of pons is not specific for migraine.[22]

For migraine with aura, cortical spreading depression (CSD) has long been considered as a pathophysiologic mechanism.[23] Initially described in rabbits by Leao, CSD is a propagating wave of depolarization of cortical neurons at a rate of approximately 3-5 mm/min across the cerebral cortex, followed by suppression of neuronal activity lasting for minutes.[23] Olesen et al.[24] were the first to show that regional cerebral blood flow was reduced in the posterior parietal and occipital lobes during visual aura symptoms. In humans, functional imaging studies, including blood oxygen level-dependent (BOLD) fMRI, consistently show a slowly propagating wave of hyperactivity followed by suppressed activity, beginning near the occipital pole and extending anteriorly at a rate of approximately 2-3 mm/min.[25] In animals, CSD caused long-lasting blood flow enhancement within the middle meningeal artery upon trigeminal and parasympathetic activation, and plasma protein leakage within the dura mater.[26] Thus, CSD waves can activate trigeminal nociceptive nerve fibers in the affected hemisphere, leading to the development of lateralized headache.[26] In addition, in animals, CSD frequency was suppressed by 40%-80% by treating with commonly used migraine prophylactic medications such as topiramate, valproate, propranolol, amitriptyline, and methysergide.[27]

Pain in migraine may originate from intra- and extracranial perivascular nociceptors innervated by trigeminal afferent fibers.[13] When activated, trigeminal nociceptive fibers in animals release proinflammatory and pronociceptive vasoactive neuropeptides such as substance P, neurokinin A, and CGRP from their peripheral ending.[28,29] Elevated plasma CGRP is reported in external jugular vein during acute migraine in humans,[28,30] but findings were not confirmed in a study comparing plasma CGRP in ictal vs interictal state.[31] These findings have led to the development of highly specific CGRP receptor antagonists with positive results in the treatment of acute migraine.[32]

Sensitization of trigeminovascular nociceptive second- and third-order neurons or central sensitization has been demonstrated in migraineurs[33] and animal models of migraine. Clinic-based studies suggest that up to two-thirds of migraine sufferers develop cutaneous allodynia, a marker of central sensitization, during their attacks.[33,34] In a population study, prevalence of allodynia was higher in transformed migraine (68.3%) than in episodic migraine (63.2%).[35] Central sensitization plays an important role in the pathophysiology of chronic migraine and may be a most important mechanism of migraine chronification. Presence of cutaneous allodynia may be a risk factor for transformation of episodic to chronic migraine, possibly through the mechanisms of neuronal damage in the region of the periaqueductal gray matter.[36,37]

Triptans, disease-specific headache abortive medications used in treatment of migraine, are serotonin 5-HT1B/1D/1F receptor agonists.[38] Based on the anatomical localization of these receptors, triptans may act through cranial vasoconstriction (5-HT1B receptors), peripheral neuronal inhibition (5-HT1D receptors), and inhibition of transmission between first- and second-order neurons of the trigeminal spinal nucleus (5-HT1B/1D/1F receptors).[38] However, the last mechanism has been challenged by the impermeability of blood-brain barrier to triptans.[13] In animals, CDS has been shown to disrupt blood-brain barrier by a matrix metalloproteinase-9-dependent mechanism.[39] However, it is not clear how these findings apply to humans. Interestingly, in a clinic-based study, when cutaneous allodynia developed within a migraine attack, it was also associated with triptan