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MIGRAINE – PATHOPHYSIOLOGY OF PAIN

Vlasta Vuković, Maja Strineka, Arijana Lovrenčić-Huzjan, Vida Demarin

Department of neurology, University hospital Sestre milosrdnice
Refference center for neurovascular disorders of the Ministry of health of Croatia
Refference center for headache of the Ministry of health of Croatia

Summary

Migraine is a primary episodic headache disorder characterized by a cascade of events that involve various combinations of neurologic, gastrointestinal and autonomic changes. Headache is probably caused by activation of meningeal and blood vessel nociceptors combined with an alteration in central pain modulation. Headache and its associated neuro-vascular changes are subserved by the trigeminal system. A link also exists between the migraine aura and headache. Cortical spreading depression (CSD) activates trigeminovascular afferents, causing a long-lasting increase in middle meningeal arterial blood flow and polypeptide release within the dura mater. The neuropeptides interact with the blood vessel wall, producing dilatation, plasma protein extravasation, and platelet activation. Neurogenic inflammation sensitizes nerve fibers (peripheral sensitization) that now respond to previously innocuous st imuli, such as blood vessel pulsations, causing, in part, the pain of migraine.

Key words: migraine; pathophysiology; pain.

INTRODUCTION

Migraine is a disabling neurologic disorder that affects more than 10% of the adult population [1]. Migraine is characterized by headache and associated symptoms. Typical attacks are characterized by severe, throbbing head pain; sensitivity to light (photophobia); sensitivity to sound (phonophobia); and/or exacerbation of pain by head movement; nausea and vomiting also occur in majority of patients [2].Approximately a quarter of patients also has vertigo associated with migraine [3].

Corresponding author: Vlasta Vuković
e-mail: vlasta.vukovic@uclmail.net

There are 2 major subtypes of migraine [4]. The most common is migraine without aura, accounting for around *75%* of cases. The second major subtype is migraine with aura, which occurs in approximately 25% of cases [5]. Migraine aura is defined as a focal, fully reversible neurological disturbance of relatively short duration (<60 minutes) that usualy precedes or accompanies the headache and manifests itself as visual, sensory or motor symptoms [6]. It is observed in 30% of migraine patients, and it is clearly neuraly driven. The hypothesis that the aura is the human equivalent of CSD has been well established [7]. Some data show that migraine with aura may be associated with vertebral artery hypoplasia [8].

GENETIC MECHANISM OF MIGRAINE

Over the past 15 years there has been enormous scientific and clinical progress in the field of headache. Is is beleived that migraine attacks are caused by environmental factors (70%) and genetic factors (30%). Understanding of the genetics of migraine has advanced quickly, due primarily to findings relating to the rare, dominantly inherited sub-form called familial hemiplegics migraine (FHM). Three genes have now been identified in which mutations can cause FHM, as discussed in the article by Moskowitz and co-workers. The CACNA1A gene is located on chromosome 19 and encodes the [alpha]1 subunit of a voltage-dependent calcium channel of the P/Q type; the type of FHM caused by mutation of this gene is now called FHM-1. The next type (FHM-2) is caused by mutation of the ATP1A2 gene on chromosome 1, which encodes the [alpha]2 subunit of the sodium–potassium pump. The third gene encodes a voltage-dependent sodium channel, IA (mutation leads to FHM-3). There is evidence of yet more genetic mechanisms of FHM, since not all families with this disorder link to the three demonstrated loci. The fact that all three gene products are involved in the regulation of ion homeostasis has led to the suggestion that all migraine may be caused by disturbed ion homeostasis. So far, however, no genes have been demonstrated for the more common types of migraine: migraine with typical aura and migraine without aura [9]. Therefore, the treatment for various subtypes of migraine is recommended [10].

CORTICAL SPREADING DEPRESSION

Although the first neurologic event in migraine is still a point of controversy, it is recognized that migraine arises from primary dysfunction of the central

nervous system occurring in the brain and/or the brainstem, which leads to activation and further sensitization of the trigeminal system (TGS) [4]. Activation of the TGS can cause pain and central sensitization directly and it may also induce extracephalic vascular inflammation, which may further contribute to the pain. Even though what causes the activation of the TGS is still not fully understood, it is now generally recognized that migraine arises from a primary brain and/ or brainstem dysfunction [4]. Two neurologic events have been proposed to account for the origination of migraine: cortical spreading depression (CSD) and brainstem dysfunctions.

CSD is a wave of sustained cortical neuronal depolarization followed by potent, relatively long-lasting neural suppression. CSD slowly propagates (2-6 mm/min) over the cortex. The short depolarization phase is associated with an increase in regional cerebral blood flow, whereas the phase of reduced neural activity is associated with a reduction in cerebral blood flow [4,11]. It is important to emphasize that the changes in the blood flow are secondary to the changes in neuronal activity.

CSD is likely the physiologic correlate of human migraine aura [2,4] and could be key to the initiation of migraine in humans. In humans, CSD could arise as a result of the hyperexcitability of the cortex of susceptible patients [11].

The primary cause of a migraine attack was proposed to be an episodic dysfunction in brainstem nuclei involved in the central control of nociception [11]. Brainstem dysfunctions could directly activate the TGS or exert a permissive role to facilitate the activation of the TGS [11].

CSD and brainstem dysfunctions are 2 fundamental physiologic events that could interact with each other to initiate migraine [11]. CSD may activate the TGS, whereas activation of the brainstem may lower the threshold of the brain and predispose patients to CSD.

HIGHER ORDER PROCESSING/ CENTRAL MODULATING OF TRIGEMINAL PAIN

Following transmission in the caudal brain stem and high cervical spinal cord, information is relayed rostrally. Processing of vascular nociceptive signals in the thalamus occurs in the ventroposteromedial thalamus , medial nucleus of the posterior complex and in the intralaminar thalamus. Zagami and Goadsby have shown, by application of capsaicin to the superior sagittal sinus, that trigeminal projections with a high degree of nociceptive input are processed in neurons particulary in the VPM thalamus and its ventral periphery [12].

These VPM neurons can be modulated by activation of γ-aminobutryc acid (GABA) inhibitory receptors and by propranolol but with β1- adrenoceptor mechanism [13].

Functional brain imaging with positron emission tomography (PET) in humans has shown activation of the dorsal midbrain, including the periacqueductal grey (PAG) and the dorsal pons close to the locus coeruleus, in studies during migraine without aura [14]. Dorsolateral pontine activation is observed with PET in spontaneus episodic [15] and chronic [16] migraine and with nitrogylcerine triggered attacks [17].

NEUROPEPTIDE RELEASE AND MIGRAINE

In the past, the "vascular theory of migraine" proposed that transient ischemia induced by vasoconstriction was the cause of the symptoms of migraine aura, whereas the headache pain reflected rebound abnormal vasodilation and mechanical activation of perivascular TGS nerve endings [6]. The vascular theory, which linked migraine headache pain and vasodilation, is not supported by experimental data [4].

For instance, functional brain imaging during migraine with aura demonstrated that headache pain can start when cerebral blood flow remains decreased – that is, when blood vessels are constricted. Conversely, headache sometimes disappears even though cerebral blood flow remains increased [18]. Likewise, pharmacologic experiments demonstrated that migraine can be induced without dilation of the middle cerebral artery and that profound vasodilation of cranial arteries can fail to trigger migraine attacks. Furthermore, an increase in diameter of the middle cerebral artery during migraine attacks could not be demonstrated [11].

These data show that the vascular theory is untenable [4]. Many researchers now believe that change in vascular tone is a secondary phenomenon, not a primary cause of migraine and headache pain. Therefore nowadays, the neurovascular theory is propsed as the explanation for all known chemical and vascular events that occur during migraine attack.

An important event in migraine is the release of neuropeptides. Trigeminal sensory neurons contain substance P (SP), calcitonin gene-related peptide (CGRP), and neurokinin A. Stimulation of the trigeminal sensory neurons causes the release of SP and CGRP from sensory C-fiber terminals and the start of neuro-genic inflammation, suggested by one study to occur in humans [19,20]. IV administration of CGRP causes headache and migraine in migraineurs, suggest-

ing that the increase in CGRP observed during spontaneous migraine attacks may play a causative role. Almost all SP-positive trigeminal ganglion neurons contain CGRP, whereas more than half of the CGRP-positive neurons are not SP-positive, suggesting that SP is always co-released with CGRP. SP is contained predominantly in small-diameter sensory C-fibers, whereas CGRP is contained in both small- and larger-diameter neurons (corresponding presumably to C- and A8-fibers, respectively). A8-fibers are activated at lower stimulus intensities than C-fibers I and, when activated, release only CGRP, whereas activation at higher intensities activates both A8-J and C-fibers, resulting in the release of both CGRP and neurokinins [21,22].

In the cat, trigeminal ganglion stimulation also increases cerebral blood flow by a pathway traversing the greater superficial petrosal branch of the facial nerve releasing a powerful vasodilator peptide, vasoactive intestinal polypeptide (VIP) [23]. Stimulation of the more specifically vascular pain producing superior sagittal sinus increases cerebral blood flow and jugular vein CGRP level.

According to this neurogenic inflammation theory, ions and inflammatory agents are released in the vicinity of sensory fibers innervating the meninges, where they activate and sensitize peripheral nociceptors [24,25]. This cascade of events is characterized by vasodilatation, plasma protein extravasation, and the release of pro-inflammatory mediators such as bradykinin, prostanoids, and protons.

Exposure of perivascular fibers to chemical agents alters their sensitivity to subsequent stimuli and leads to the sensation of head pain [26]. The cause of the initial release of these chemicals has not been established but may arise from brain, within blood, or from meningeal tissues.

Evidence from humans that CGRP level is elevated in the headache phase of migraine [27], cluster headache [28] and chronic paroxysmal hemicrania [29] supports the vieww that the trigeminovascular system might be activated for a protective role in these conditions. Moreover, NO-donor-triggered migraine, which is the typical form of migraine, also results in increased levels of CGRP that are inhibited by sumatriptan, as in spontaneous migraine.

SENSITISATION AND ALLODYNIA

Patients desribe various sensations of pain. The pain may be diffuse with a dull, burning quality and may move, radiate or spread through different innervation territories. Patients with migraine usually report pain that involves the front of the head, in the cutaneus distribution of the first (ophtalmic) branch

of the trigeminal nerve. However, pain from the back of the head, innervated by great occipital nerve, which is a branch of C2 spinal root, is also described [30,31].

The term sensitisation reffers to increased afferent activity for an unchanged stimulus. For an example, activation of C fibers by heat or chemical stimulation would produce sensitisation.

Sensitisation may occur in three primary ways:

1) Peripheral sensitisation which implies increased primary afferent activity from an unchanged stimulus due to some local activating process,
2) Central sensitisation and
3) Disinhibitory sensitisation

In recent years it has become apparent that many types of prolonged or chronic pain are associated with long-lasting activation and sensitization of peripheral nociceptors and/or central nociceptive neurons in the dorsal horn. By incorporating these concepts into basic research on migraine pathophysiology, a new animal model for long-lasting headache of migraine was developed. This model involves prolonged activation and subsequent sensitization of the trigeminovascular system in response to a brief exposure of the dura to a mixture of inflammatory agents consisting of serotonin (5-HT), bradykinin, histamine, and prostaglandin (PG) [26]. These agents activate and sensitize somatic and visceral nociceptors in the rat and are potent algesics in humans, capable of inducing headache [32]. With this animal model, it was found that a brief chemical irritation of the dura activates and sensitizes meningeal nociceptors over a long period of time, rendering them responsive to mechanical stimuli to which they showed only minimal or no response before their sensitization. During migraine, such peripheral sensitization is likely to mediate the throbbing pain and its aggravation during routine physical activities.

Brief stimulation of the dura with inflammatory agents also activates and sensitizes second-order trigeminovascular neurons located in the spinal trigeminal nucleus that receive convergent input from the dura and the skin [24]. In this paradigm, the central trigeminovascular neurons develop hypersensitivity in the periorbital skin, manifested as increased responsiveness to mild stimuli (brush, heat, cold) to which they showed only minimal or no response before their sensitization. The induction of central sensitization by intracranial stimulation of the dura and the ensuing extracranial hypersensitivity were taken to suggest that a similar process occurs in patients, during migraine.

Therefore the current view is that extracranial hypersensitivity is a manifestation of central neuronal sensitization. Recent quantitative stimulation applied to the surface of the skin showed that pain thresholds to mechanical, heat, and cold skin stimuli decrease significantly during migraine in the majority of patients. This skin hypersensitivity, termed cutaneous allodynia, is typically found in the periorbital area on the side of the migraine headache. Patients commonly notice cutaneous allodynia during migraine when they become irritated by innocuous activities such as combing, shaving, taking a shower, wearing eyeglasses or earrings, or resting the head on a pillow on the headache side. Ipsilateral cephalic allodynia is likely to be mediated by sensitization of trigeminovascular neurons in the spinal trigeminal nucleus that process sensory inputs from dura and periorbital skin.

Allthough all molecular mechanisms involeved in the migraine attack are not fully understood, unravelling the physiology and pharmacology of migraine and searching for its basic molecular mechanisms will provide new treatments for this disabling headache.

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Sažetak

Migrena – patofiziologija boli

Migrena je primarna glavobolja epizodnog karaktera karakterizirana nizom događaja koji uključuju kombinacije neuroloških, gastrointestinalnih i autonomnih promjena. Glavobolja je vjerojatno uzrokovana aktivacijom nociceptora u meningama i u stjenci krvnih žila, u kombinaciji s poremećajem u centralnoj modulaciji boli. Glavobolja i pridružene neurovaskularne promjene povezane su s trigeminalnim sustavom. Postoji također veza između migrenske aure i glavobolje. Kortikalna šireća depresija aktivira trigeminovaskularna aferentna vlakna, uslijed čega dolazi do dugotrajnog porasta protoka u srednjoj meningealnoj arteriji kao i u otpuštanju polipeptida unutar dure. Uslijed interakcije neuropeptida i stijenke krvne žile dolazi do dilatacije, ekstravazacije proteina plazme te aktivacije trombocita. Upala senzitizira živčana vlakna (periferna senzitizacija) te oni sad reagiraju na prethodno bezazlen podražaj, npr. pulzacije krvne žile, uzrokujući, barem djelomično, migrensku bol.

Ključne riječi: migrena; patofiziologija; bol.