6. BIOCHEMICAL MECHANISMS OF MIGRAINE

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Introduction. Migraine is a neurovascular disorder with paroxysmal manifestations of headache lasting from 4 to 72 hours, often unilateral at onset, pulsatile, moderate or severe, which frequently alters daily activity and amplifies physical exertion. Is one of the primary types of headaches that affects one billion people worldwide, mostly women. The signaling molecules related to the biochemistry of migraine are widespread in the trigemino-vascular pathways and include: calcitonin gene-related peptide (CGRP), adenylate cyclase activating peptide (PACAP-38), nitric oxide (NO). Moreover, cortical spreading depression plays an essential role in generating migraine pain.

Aim of study. To research the biochemical pathways of migraine with possible therapeutic targets for these conditions.

Methods and materials. A wide area of articles from PubMed, NCBI, HINARI, Google Scholar databases over the last ten years describing the biochemical appearance of migraine, also potential therapeutic targets acting on these mechanisms were explored. Usual used keywords: migraine attack, biochemical mechanism, ion channel, nociceptive transmission..

Results. The CGRP and PACAP-38 molecules increase intracellular cAMP, while NO molecule increases cGMP. This suggests direct involvement in the biochemical pathways that initiate migraine. A preclinical evidence implicates that activation of cAMP and cGMP leads to the opening of ATP-dependent K+ channels with massive efflux of K+ ions, which produce vasodilatation, initiating the perivascular trigeminal afferents, generating nociceptive impulses. Through the ascending pathways of trigeminal pain are transmitted to the cortical and subcortical brain parts. This led to the hypothesis of modulation of nociceptive transmission through ion channels, mainly K + dependent, which may be a common pathway in the genesis of migraine attacks. New methods of treatment act by inhibiting the CGRP pathway by binding to its ligand or receptor (e.g. Erenumab, Fremanezumab, Galcanezumab, Eptinezumab). Moreover, studies revealed that the ionic gradient is also disturbed by cortical spreading depression, a self-propagating wave, producing an extended depolarization over the cerebral cortex, resulting in cerebral hypoperfusion. This wave activates the peripheral and central trigeminal neurons and opening, at the same time of the neural channels - Pannexin1, with the release of proinflammatory mediators, which induce the expression in astrocytes of COX2 and iNOS. Later on cytokines, prostanoids and NO are released in the subarachnoid space, a process that activates trigeminal nerve fibers and produces migraine pain.

Conclusion. Migraine is a common disabling brain disorder whose key biochemical mechanisms remain incompletely studied. Increasing evidence from literature supports the idea that cortical spreading can cause sustained activation of meningeal nociceptors and central trigeminovascular neurons and can thus initiate the headache mechanisms. Several findings support a fundamental role of calcitonin gene–related peptide (CGRP), adenylate cyclase activating peptide (PACAP-38), nitric oxide (NO) , but the mechanisms of action of these molecules in a migraine attack and the mechanisms underlying the hypersensitivity of migraineurs to modulation of nociceptive pathways remain unclear.