

MIGRAINE AND THE ENDOCANNABINOID SYSTEM: A STORMY RELATIONSHIP

Abstract

Migraine is a neurological disorder with high incidence characterized by peripheral and central sensitization. The trigemino-vascular system is implicated in the genesis of the migraine attack. CGRP is one of the main determinants of the migraine pain. CGRP-targeting drugs like anti-CGRP monoclonal antibodies (anti-CGRP and anti-CGRP-receptor monoclonal antibodies) and CGRP-receptor antagonists named “gepants” are effective and safe drugs recently introduced into clinical practice. The endocannabinoid system is a lipid-based neurotransmitter complex that has been linked to migraine. The CB1 receptor is localized in the presynaptic synapses of the trigeminal terminals and is activated by the endocannabinoid anandamide. It acts as a negative regulator of the CGRP release. Anandamide has been found in reduced amounts in subjects suffering from migraine. This review will summarize the evidence in the literature regarding the relationship between migraine and the endocannabinoid system, particularly the clinical data.

Keywords: Migraine; Headache; Chronic Migraine; Medication Overuse Headache; Endocannabinoids; Endocannabinoid System; Anandamide; 2-Arachidonoylglycerol.

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I. INTRODUCTION

The diagnosis of migraine is made using the criteria established by the International Classification of Headaches Third Edition (ICHD-3). Migraine without aura (1.1) is described by ICHD-3 as a recurrent headache that occurs with at least 5 crisis with a duration of 4-72 hours. Typical features of migraine are unilateral localization of pain, moderate-to-severe intensity, pulsating pattern, exacerbation following usual physical activity, and association with neurovegetative symptoms such as photophobia, phonophobia, nausea and vomiting. [1]. Migraine with aura (1.2), on the other hand, is characterized by recurrent attacks, lasting between 5 and 60 minutes of completely reversible unilateral central nervous system symptoms like visual, sensory, speech that usually develop slowly and are generally followed by headache that meets the characteristics of a migraine [1]. Based on the frequency of attacks, migraine can be distinguished into episodic and chronic. Episodic migraine includes 1-14 migraine days per month. Chronic migraine (1.3; CM) is a disorder characterized by 15 or more headache days per month for at least three months, which includes at least 8 headache days per month, with the characteristics of a migraine. If a patient consumes many symptomatic drugs for pain control, he will develop a medication overuse headache (8.2; MOH) in the long run. MOH due to excessive use of acetaminophen (8.2.3.1) or nonsteroidal anti-inflammatory drugs (NSAIDs) (8.2.3.2) is defined by taking more than 15 drugs per month, while MOH due to excessive use of triptans (8.2.2) occurs when the person takes more than 10 triptans per month [1].

The diagnosis of migraine, as it is a primary headache, is basically clinical, relying on the collection of the patient's anamnesis, and through the exclusion of secondary forms of headache. The patient should undergo a general physical examination and neurological examination, which must be normal to suppose a primary headache [2]. A headache diary is usually requested to assess the frequency of attacks. Pain intensity is determined by the patient's completion of a numeric rating scale (NRS) or a visual analog scale (VAS). Instrumental analysis and other visits, such as a magnetic resonance imaging of the brain (MRI), both with or without contrast agents, an ultrasonography of supra-aortic trunks, a complete ophthalmological examination, blood pressure tests, may be necessary to exclude a secondary cause of headache.

Migraine is among the most disabling neurological disorders of the youth and adult population age groups. It ranks as the second highest cause of disability worldwide in the 10-24 age group and the fifth highest in the 25-49 age group as attested by the Global Burden of Disease 2019 [3]. Migraine, therefore, affects a population of education and working age, which is the most productive component of society. It afflicts people in the most active period of their lives, leading to a significant loss of productive capacity from both personal and social perspectives. Epidemiological studies have attempted to estimate the prevalence and incidence of migraine by means of various methodologies, concluding that it affects about 14 percent of the population, while chronic migraine affects 4.6 percent of people [4]. Migraine most prevalently affects the female sex, with a female/male ratio of 3:1 [5]. According to the latest global epidemiological estimates, in 2019, the overall incidence of migraine was 87.6 million new cases/year, an increase of 40.1% since 1990 [6].

II. ETIOPATHOGENESIS

The pathogenesis of migraine has yet to be fully explained. Since it is a complex disease, both genetic and environmental factors are involved. Genetic inheritance of migraine is polygenic. The only exception is familial hemiplegic migraine (FHM), for which a single-gene Mendelian inheritance involving 4 genes (*CACNA1A*, *ATP1A2*, *SCN1A*, *PRRT2*) has been established, determining four forms of this rare disease respectively (FHM1, FHM2, FHM3, FHM4) [7]. FHM (1.2.3.1) is defined by ICHD-3 as a migraine with aura comprising motor weakness, in which at least one family member has had hemiplegic migraine attacks [1].

A pivotal role in the pathogenesis of the migraine attack is attributed to the alerting of the trigeminovascular system. The trigeminal nerve is composed of fibers A δ and fibers C, which innervate the intracranial arteries, including the vessels of the meninges and the dura mater [8]. Various triggers of migraine attack, including alterations in sleep-wake rhythm, fasting, weather variations, certain foods, psychophysical stress, can activate the trigeminal nerve endings both in an orthodromic way (from the peripheral stimuli to the central structure) and in an antidromic way (from the central areas to the periphery). The debate about the origin of the migraine attack is still ongoing. There are arguments both pros and cons regarding its peripheral or central origin. Particularly, the sensory nerve fibers activated in migraine are in the periphery, differently, cortical spreading depression, the widely accepted mechanism of aura is a typical central trigger of migraine [9]. Meanwhile, sensitization of the 1st-order trigeminal sensory neuron occurs, which in turn causes the sensitization of the 2nd- and the 3rd-order neurons that make synapses in the thalamus, which transmit pain information directly to the somatosensory cortex's areas [5].

The search for a biological correlate of migraine began a long time ago. Since its discovery in 1982, calcitonin gene-related peptide (CGRP) has been recognized as the major player of the migraine attack. CGRP- α is derived from an alternative splicing of the calcitonin gene. Its receptor is composed of a transmembrane protein coupled with a G_s protein (calcitonin receptor like receptor, CALCRL), which binds to the receptor activity modifying protein (RAMP1) to form a heterotrimer. CGRP is released from trigeminal nerve endings peripherally and produces arterial vasodilation of extra-cranial meningeal vessels. CGRP is released during a migraine attack [10]. Subsequently, it was demonstrated that triptans, specifically sumatriptan, serotonin 5-HT_{1B/D} receptor agonist drugs, can block CGRP's emission from the trigeminal nerve endings and concomitantly extinguish pain during a migraine attack [11]. Based on experimental observations on the role of CGRP in the genesis of migraine attack, monoclonal antibodies that block CGRP peptide or its receptor have been developed. These drugs are: erenumab (antibody targeting the CGRP receptor), galcanezumab, fremanezumab, and eptinezumab (antibodies that directly block CGRP peptide). Monoclonal antibodies for migraine preventive therapy have been tested to be safe and well-tolerated in most patients in both clinical and real-world studies [8]. Other CGRP drugs called "gepants", which are small molecule CGRP receptor antagonists, are approved or under investigation in the US and UE market: these are ubrogepant, rimegepant, atogepant (with oral administration), and zavegepant (with intranasal or subcutaneous administration). Ubrogepant has been designed for acute treatment, whereas atogepant has been developed for

migraine preventive therapy; finally, rimegepant can be used for both acute and preventive therapy [12].

Neuropeptides and other signaling pathways are being actively studied in the pathogenesis of migraine, and new therapies directed toward these novel targets are expected [13]. In particular, a relevant role seems to be attributed to pituitary adenylate cyclase-activating polypeptide-38 (PACAP38). It is observed, among other things, that sumatriptan reduces PACAP-38-induced sensitization of parasympathetic neurons and the development of allodynia, characteristics of severe migraine [14].

III. ENDOCANNABINOID SYSTEM AND MIGRAINE

The endocannabinoid system (ECS) is a complex lipid network comprising endogenous ligands, their respective receptors, and the proteins that catalyze the production and the catabolism of endocannabinoids. The biological activity of endocannabinoids is mediated mainly by CB1 and CB2 receptors, but other receptors also mediate some actions of endocannabinoids, particularly acylethanolamides. CB1 and CB2 are receptors coupled to $G_{i/o}$ inhibitory proteins. Consequently, their activation inhibits adenylate cyclase and some voltage-dependent calcium channels. CB1 receptors are abundant in the central structures: basal nuclei, hippocampus, cortex, and cerebellum. Most receptors are expressed on axons and in pre-synaptic neurons. CB2 receptors, on the other hand, are found mainly in the immune system, microglia, and vessels [15].

Alterations in the ECS have been associated with numerous neuropsychiatric disorders, including substance abuse [16]. Modifications of the ECS has been found in CM and MOH [17–22]. Specifically, in subjects with CM and MOH, a deficit of anandamide (AEA) and 2-arachidonoylglycerol (2-AG) has been shown in peripheral blood and cerebrospinal fluid (CSF) [17-20]. Early studies in humans have confirmed the presence of a clear alteration of the ECS in migraine subjects. Italian authors analyzed AEA and 2-AG in platelets extracted from the plasma of 20 CM, 20 MOH patients, compared with 20 healthy controls. The laboratory analysis showed a strong reduction in 2-AG and AEA amounts in CM and MOH patients compared with controls ($p < 0.0001$ for both), but no significant differences has been revealed between the two groups of patients. In the two groups of migraineurs, endocannabinoid levels were significantly lower in women than men. In addition, the 2-AG content in the platelets of both groups was 20 times higher than that of AEA [20].

These observations may be the consequence of the difference in activity of the endocannabinoid-degrading enzymes in migraine. These are the fatty acid amide hydrolase enzyme (FAAH), which metabolizes AEA, and the monoacylglycerol lipase (MAGL) enzyme, which in turn degrades 2-AG. The amounts of ECS enzymes were found to be reduced in CM patients with MOH compared with EM, and even more in comparison to controls [19-22]. Moreover, AEA, 2-AG and CGRP in CSF of subjects with CM and probable CM or MOH were determined. AEA concentrations were significantly lower than controls, while CGRP concentrations were higher, with a negative correlation between the two variables for both CM and probable CM or MOH [17].

The deficiency of the ECS in chronic migraine configures a possible pharmacological strategy for the treatment of chronic pain. A new challenge is restoring deficient endocannabinoid transmission by inhibiting the enzymes which catabolize AEA and 2-AG [21,23,24]. To date, pharmacological blocking of the fatty acid amide hydrolase enzyme (FAAH), which metabolizes AEA, has been tested in preclinical models as a possible target for migraine [23,24].

IV. CONCLUSIONS

Migraine is a disabling condition that afflicts a large proportion of the population. Fundamental discoveries in its pathogenesis have enabled the development of new drugs directed against CGRP, the leading algogenic neuropeptide. Preclinical and clinical discoveries have identified the endocannabinoid system as one of the regulators of the release of this peptide. The impairment of the ECS involved in pain regulation in the peripheral nervous system appears to be one of the pathogenic mechanisms of migraine onset. Future research in this field could explain the complex interplay between migraine pain and the endocannabinoid components.

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