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# Potential Therapeutic Role of the Endocannabinoid System for Migraine

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*Identified implications of the endocannabinoid system in migraine physiology suggest that this pathway might hold therapeutic potential for some headache disorders.*

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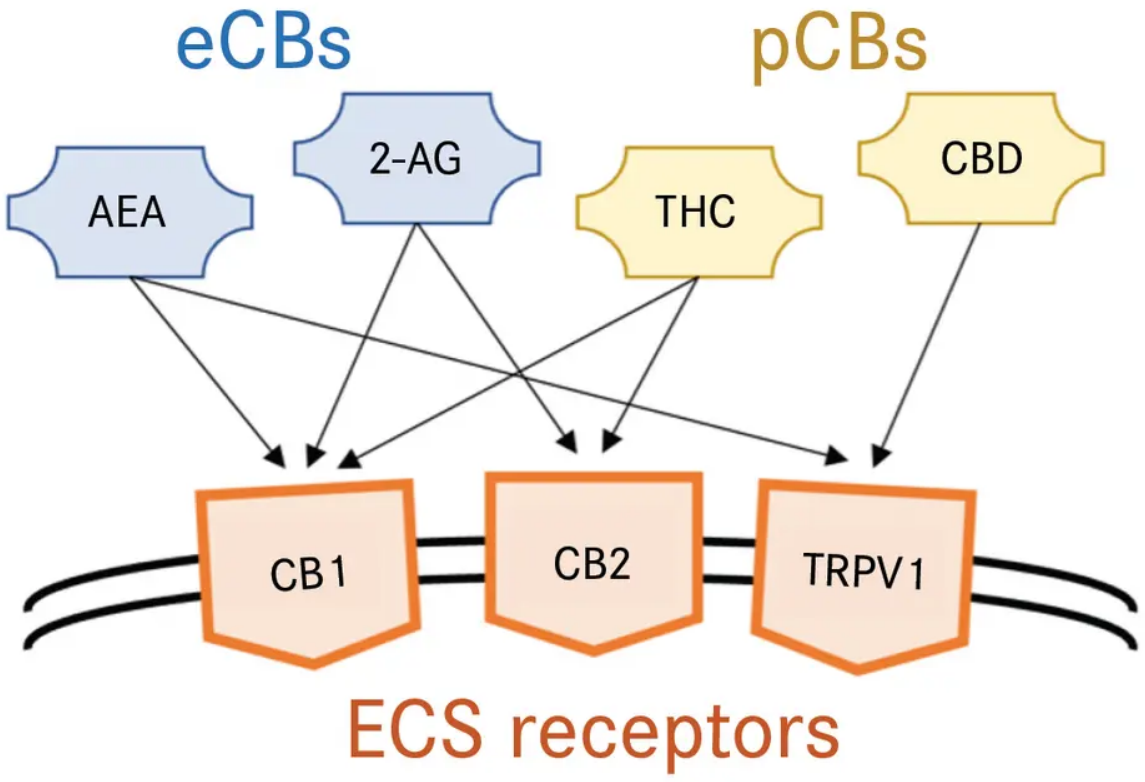
**MIGRAINE IS A HIGHLY PREVALENT** and debilitating disorder characterized by a unilateral hemicranial pulsating headache with accompanying symptoms (ie, sensory disturbances and nausea).[1] Migraines occur most often in persons aged 20 to 50 years and are more common in women.[2] Migraines are currently treated with acute and preventive therapy[3]; however, because the pathophysiology of migraine is still largely elusive,[4] treatment response remains difficult to predict.[1] Migraine pain is widely recognized to be caused by a lowered threshold of nociceptive signaling in response to proinflammatory agents, and environmental and hormonal triggers have been linked to migraine initiation.[1] Prolonged activation of the trigeminovascular system can, in turn, lead to persistent nociceptive signaling, which creates a positive feedback loop[1] whereby the persistent release of neuropeptides from sensory neurons increases pain impulses that are transmitted to the nucleus trigeminalis caudalis.[4] This clinical endocannabinoid (eCB) deficiency is also common in other major functional pain disorders.[2]

Current standards of care for migraine include ß-blockers, antiepileptic drugs, triptans, and analgesics, which exhibit moderate effectiveness, limited tolerability, and may induce weight gain, depression, chest pain, and gastrointestinal and cardio-renal effects.[4] Investigational migraine treatment aims to abort attacks or to reduce attack frequency, duration, and intensity[3]; however, only a minority of patients actually achieve these outcomes in clinical trials.[3] Potential

novel targets for antimigraine drugs include those that reduce central sensitization and suppress cortical spreading depression (CSD).[3]

The eCB system (ECS) is a comprehensive signaling system present in nearly every cell type that functions to reduce pain and alleviate neurodegenerative and inflammatory damage.[1] The ECS regulates pain signals by inhibiting the release of neurotransmitters controlling nociceptive inputs and the levels of inputs known to be involved in transmission and modulation of pain signals.[5] The ECS consists of endogenous phospholipid-based ligands, their molecular targets (G protein–coupled cannabinoid receptors: type 1 [CB1] and type 2 cannabinoid receptors [CB2]), protein transporters, and synthetic and degradation enzymes (**FIGURE**).[6] Whereas CB1 is expressed abundantly in the brain, CB2 is primarily expressed in peripheral tissues.[1] CB1 and CB2 receptors also form heteroreceptor complexes in microglia, which are activated by CSD and thus may contribute to the pathogenesis of migraine with aura.[1] Indeed, CB1 receptor gene variants increase the risk of migraine with aura.[7] Targeting CB1 receptors is an attractive strategy for migraine treatment, promising block peripheral and central nociceptive traffic to reduce pathologically enhanced cortical excitability.[1]

**FIGURE.** Biological pathways implicated in migraine, which serve as potential targets for modulating the activity of the endocannabinoid system to reduce migraine-related pain.[6]




2-AG, 2-arachidonoylglycerol; AEA, anandamide; CB1, type 1 cannabinoid receptor; CB2, type 2 cannabinoid receptor; CBD, cannabidiol; eCBs, endocannabinoids; ECS, endocannabinoid system; pCBs, phytocannabinoids; THC, tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid 1

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The best-characterized ECS signaling molecules are the eCBs arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), which typically act to amplify or dampen the perception of pain.[1,2,4,5,8] *N*-acylphosphatidylethanolamine-phospholipase D and *sn*-1-specific diacylglycerol lipase synthesize AEA and 2-AG, respectively, from precursors in the phospholipid membrane.[3] These eCBs are synthesized on demand and are not stored.[4,6] After

binding to the CB1 and CB2 receptors, cannabinoids are enzymatically degraded and removed from the body.[2,8] Disturbances in the supply or functionality of eCB ligands have been connected to mental state disturbances, including migraine, suggesting a correlation between deficient levels of eCBs and pain.[1] Indeed, aberrant catabolic pathways have been identified in patients with migraine.[7] In fact, evidence suggests that lower levels of AEA and 2-AG in women may correspond with increased incidence of migraines.[2,4,7]

Additional targets for eCBs include the CB3 receptor GPR55, peroxisome proliferator-activated receptors alpha and gamma, and the transient receptor potential vanilloid 1 (TRPV1) ion channel.[7] Cannabinoid and TRPV1 receptors are often found in the same organs, tissues, and cells, where they can have opposing or similar functions in pain and inflammation.[5,6] Whereas 2-AG is a full agonist for CB1 and CB[2,3] AEA is largely selective for the CB1 receptor, though it also binds to TRPV1, suggesting an alternative strategy for managing migraine.[4,7]

PPAR

Apart from eCBs, other sources of cannabinoids include the phytocannabinoids (pCBs) produced by plants of the genus *Cannabis* and synthetic cannabinoids that can interact with cannabinoid receptors.[9] Both CB1 and CB2 respond to endogenous ECS signals from eCBs, as well as signals from pCBs, which are propagated by exogenous cannabinoids, most notably tetrahydrocannabinol (THC).[1]

Cannabis exhibits analgesic, immunomodulatory, and anti-inflammatory effects.[7] Only a few cannabinoid drugs have been rigorously tested for safety and efficacy and have been approved for use at the national level: dronabinol (Marinol) for anorexia and weight loss and for chemotherapy-induced nausea and vomiting (CINV); nabilone (Cesamet) for CINV; rimonabant (Acomplia) for weight management, dyslipidemia, and type II diabetes; nabiximols (Sativex) for spasticity; and cannabidiol (Epidiolex) for seizures.[9] A growing number of US states and other nations have legalized the use of *Cannabis* sativa for medicinal purposes, although evidence-based data regarding its clinical utility remain incomplete.[3,9] A major concern about this therapeutic approach is that long-term use of cannabis can cause a physical reliance on pCBs (eg, THC) and drug tolerance, which may result in reduction or loss of experienced pain relief.[1] Moreover, headache itself is an adverse effect (AE) associated with cannabinoid medications and is common with cannabis withdrawal.[7] Indeed, cannabinoid overuse in rodent models induced latent sensitization, which increased their sensitivity to stress, suggesting that vulnerable individuals using cannabinoids may have increased risk of developing medication overuse headache.[3] Nonetheless, short-term exposure to eCBs is capable of evoking plastic changes to brain regions that regulate pain sensation.[1] Preclinical and clinical findings suggest a possible role for eCBs and related lipids, such as palmitoylethanolamide (PEA), in migraine-related pain treatment.[3] A multicenter, double-blind, placebo-controlled study (NCT00123201) of the safety and efficacy of dronabinol, which was delivered with a metered dose inhaler for the treatment of migraine, was completed in 2015 but no results have been published.[7]

Alternative strategies for leveraging cannabinoid drugs in migraine management include using low-dose, selective, or alternative ligands and/or targeting alternative pain-implicated pathways, all of which can overcome the psychotropic AEs of CB1 receptor activation.[1,2,5,6,8] Lowered inhibitory activity of eCBs in migraine, possibly due to reduced CB1 and CB2 receptor expression, supports the contention that compensatory therapy with exogenous cannabinoids at

low doses is enough.[1] Low-dose cannabinoids combined with nonsteroidal anti-inflammatory drugs (NSAIDs) could result in analgesia without the AEs associated with large doses of either cannabinoids or NSAIDs alone.[5] Aside from modulating CB1 receptors, targeting CB2 receptors in immune cells can also reduce inflammation.[1] Other endogenously produced molecules (eg, oleamide, *O*-arachidonoyl ethanolamine, 2-AG ether, and *N*-arachidonoyl-dopamine) influence the function of CB receptors.[8] eCB-like mediators (eg, N-acyl-taurines, N-acyl-serotonins, N-acyl-dopamines, fatty acid primary amides, and N-acyl-amino acids) have heterogeneous targets, such that they can affect biological processes in the central nervous system without acting primarily through CB1/CB2 receptors.[3] The pCB cannabidiol, unlike THC, also acts on non–CB1/CB2 receptors such as TRPV1 to reduce inflammation and neuropathic pain without concerns about intoxication and psychoactive effects.[1,7] Structural analogues of eCBs (ie, *N*-oleoylethanolamine and PEA) exhibit low affinity for cannabinoid receptors, instead serving as alternative substrates for catalytic enzymes and thus increasing the potency of eCBs.[6] Preliminary evidence suggests that inhibiting enzymes that break down 2-AG is also effective for reducing headache-like pain.[2,7] Overall, cannabinoid-based migraine treatment should be a successful contender as a new migraine therapy, as cannabinoid treatment may overcome the AEs of existing antimigraine drugs, provide a more inclusive and effective mode of therapy, and provide anticonvulsive, analgesic, antiemetic, and anti-inflammatory effects to combat migraine-associated pain.[1]

Ultimately, the successful development of compounds that modulate the ECS for pain relief in humans will depend on the ability to separate psychotropic effects from therapeutic ones and to limit potential off-target interactions.[4] The ECS may be dysfunctional in migraine and may interact with numerous parallel pathways.[3] As such, additional studies are required to explore the neurobiological mechanisms and neural circuits of the ECS that are implicated in migraine.[7]

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**REFERENCES**

**1. Leimuranta P, Khiroug L, Giniatullin R. Emerging Role of (Endo)Cannabinoids in Migraine. *Front Pharmacol*. 2018;9. Accessed June 26, 2022. https://www.frontiersin.org/article/10.3389/fphar.2018.00420**
**2. Uncovering a Connection Between Cannabinoids and Migraine. UArizona Health Sciences. Published April 11, 2022. Accessed June 21, 2022. https://uahs.arizona.edu/tomorrow/uncovering-connection-between-cannabinoids-and-migraine**
**3. Greco R, Demartini C, Zanaboni AM, et al. The endocannabinoid system and related lipids as potential targets for the treatment of migraine-related pain. *Headache*. 2022;62(3):227-240. doi:10.1111/head.14267**
**4. Greco R, Demartini C, Zanaboni AM, Piomelli D, Tassorelli C. Endocannabinoid System and Migraine Pain: An Update. *Front Neurosci*. 2018;12:172. doi:10.3389/fnins.2018.00172**
**5. Greco R, Gasperi V, Maccarrone M, Tassorelli C. The endocannabinoid system and migraine. *Exp Neurol*. 2010;224(1):85-91. doi:10.1016/j.expneurol.2010.03.029**
**6. Tanaka K, Mayne L, Khalil A, et al. The role of the endocannabinoid system in aetiopathogenesis of endometriosis: A potential therapeutic target. *Eur J Obstet Gynecol Reprod Biol*. 2020;244:87-94. doi:10.1016/j.ejogrb.2019.11.012**
**7. Tassorelli C, Greco R, Silberstein SD. The endocannabinoid system in migraine: from bench to pharmacy and back. *Curr Opin Neurol*. 2019;32(3):405-412. doi:10.1097/WCO.0000000000000688**
**8. Huang WJ, Chen WW, Zhang X. Endocannabinoid system: Role in depression, reward and pain control (Review). *Mol Med Rep*. 2016;14(4):2899-2903. doi:10.3892/mmr.2016.5585**
**9. Legare CA, Raup-Konsavage WM, Vrana KE. Therapeutic Potential of Cannabis, Cannabidiol, and Cannabinoid-Based Pharmaceuticals. *Pharmacology*. 2022;107(3-4):131-149. doi:10.1159/000521683**

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