Headache Medicine 2026, Supplement ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

ID: 172

Endocannabinoid system and modulation of trigeminovascular sensitization in migraine: a systematic review

Roberta Silva Conceição, Maria Eduarda Amorim Brandao, Maria Julia Barreto Garcez, Layane Nicoly Andrade Silva, Lara Nascimento de Mendonça, Maria Clara Barreto Garcez, Laura Stephane Nunes dos Passos, Marcella Nascimento Andrade, Marina Rocha Barreto de Almeida, Luana de Sousa Sobral, Ana Claudia Rodrigues Santos, Maria Eduarda Silva Macedo, Bruna Oliveira Carvalho, Arthur Magalhães Rodrigues, Renan Guedes de Brito

Tiradentes University, Aracaju, Sergipe, Brazil

Roberta Silva Conceição
silva.robertaconceicao@gmail.com

Introduction
Migraine is a prevalent and disabling neurological disorder associated with the activation of the trigeminovascular pathway and central pain sensitization. In this context, the endocannabinoid system stands out for its potential to modulate nociceptive neurotransmission and neuroinflammation, making cannabinoids a promising therapeutic strategy for migraine management.

Objective
To evaluate the action of cannabinoids on the modulation of the trigeminovascular pathway and its impact on the therapeutic management of migraine.

Methods
This is a systematic review guided by the question: "Do cannabinoids exert a modulatory effect on the trigeminovascular pathway capable of reducing the frequency, intensity, or clinical impact of migraine?". The question was structured based on the PICO strategy: population (patients with migraine), intervention (use of cannabinoids), comparison (placebo or conventional treatment), and outcome (modulation of the trigeminovascular pathway and reduction of migraine attacks). The search was conducted in the PubMed database using the DeCS/MeSH descriptors ("Migraine Disorders" AND "Cannabinoids"). 28 studies were identified, of which 10 met the eligibility criteria and were included in the analysis. Original articles published in the last 5 years in the English language were included. Selection followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results
Modulation of the trigeminovascular pathway by cannabinoids demonstrated clinical and preclinical efficacy in reducing migraine symptoms. In humans, the combined vaporization of 6% tetrahydrocannabinol (THC) + 11% cannabidiol (CBD) outperformed placebo in pain relief (67.2%) and pain-free status (34.5%) at 2 hours. In mice, a 100:1 ratio (CBD:THC) mitigated photophobia induced by calcitonin gene-related peptide (CGRP) and sodium nitroprusside (SNP), as well as reduced pain grimaces associated with cortical spreading depression. In female rats, CBD/THC prevented periorbital allodynia and chronic photosensitivity. Mechanistically, peripherally restricted cannabinoids (PRCBs) prevented trigeminal sensitization induced by nitroglycerin (GTN) and sumatriptan overuse, while inhibition of fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) reduced hyperalgesia and serum CGRP levels. Methanandamide attenuated CGRP via cannabinoid type 1 (CB1) receptors and inhibited dural mast cell degranulation via cannabinoid type 2 (CB2) receptors. Finally, baseline sex differences were identified in 2-arachidonoylglycerol (2-AG) concentrations within the periaqueductal gray.

Conclusion
Cannabinoids demonstrated therapeutic potential in migraine by modulating the trigeminovascular pathway, reducing neuroinflammation, and attenuating central sensitization. The findings reinforce the endocannabinoid system as a promising target for novel and personalized therapeutic approaches.

Keywords:
Headache disorders
Trigeminovascular system
Cannabinoids
Pain modulation

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