

6-1-2019

# The endocannabinoid system in migraine: from bench to pharmacy and back.

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**The endocannabinoid system in migraine: from bench to pharmacy and back**

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**Funding:**

No funding was received for this manuscript

**Abstract**

*Purpose of the review*:

Migraine is a common, highly disabling disorder. Its treatment involves acute and preventive therapy. Many of available preventive medications are not well tolerated, which results in poor compliance and limited effectiveness. Cannabinoids have been proposed for the treatment of migraine but their efficacy and tolerability are controversial.

*Recent findings:* Cannabinoids modulate functions and activity of signaling pathways that have a key role in pain control. Growing preclinical evidence and initial clinical findings suggest that modulation of the endocannabinoid system, via endogenous or exogenous cannabinoids may be relevant for migraine via multiple mechanisms.

*Summary:* The endocannabinoid system qualifies as an interesting area of research worth exploration in the quest for therapeutic targets for the treatment of migraine.

**Key words:** endogenous and exogenous cannabinoids, trigeminovascular system, pain

## Introduction

Our knowledge of the endocannabinoid system (ES) largely originated from studies aimed at identifying the mechanism of action and the properties the plant *Cannabis sativa*, better known as marijuana. The identification of its main active psychoactive ingredients led to the discovery of the cannabinoid receptors and their endogenous agonists, the endocannabinoids (ECs).

In recent years, much attention has been drawn to the use cannabinoids in several areas of medicine, including pain. It is an area still controversial and debatable that requires careful and focused research.

## Cannabinoids

*C. sativa L*, an annual wind-pollinated dioecious (male and female reproductive organs in separate plants) herb, is one of the world's oldest cultivated plants. L is an abbreviation for Linnaeus who invented the botanical classification scheme [1]**.** *C. sativa L* is usually called "hemp" when used as a source of fiber, "hempseed" when used as a source of seed oil, and "marijuana" (sometimes spelled "marihuana") when used as a drug for therapeutic or recreational purposes. Previously it was believed that there were at least two species; *C. sativa L* (narrow leaves, branches apart, light green, and tall with few flowers) and *Cannabis indica L* (wide broad leaves, branches close together, deep green, and short and bushy with dense flowers*)*. *Cannabis ruderalis L* (varied leaflets and short stature) is sometimes considered a third species.

Many now believe that there is just one species of C. sativa L with subgroups called cultivars. These are selected for a characteristic or combination of characteristics, are distinct, uniform, and stable in these characteristics, and when propagated by appropriate means, retains those characteristics [2,3].

*C. sativa L* is the species and sativa, indica, and ruderalis are subspecies. Pisupati and colleagues [4] analyzed the nuclear genomic diversity among cannabis varieties, including fiber hemp and seed oil hemp, high cannabinoid drug-types, and feral populations. They found the existence of

at least three major groups of diversity with European hemp varieties, with genetic groups having different cannabinoid and terpenoid content.

It took more than 100 years to identify the chemical components in cannabis flowers. Over 104 different phytocannabinoids (plant cannabinoids) have been identified including D9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Other compounds include terpenes, flavonoids, steroids, noncannabinoid phenols, vitamins, and pigments. These have independent beneficial effects which must be considered when being used therapeutically. CBD and THC are both present in the plant as their carboxylic precursors (D9-tetrahydrocannabinolic acid [THCA] and cannabidiolic acid). They are produced after the heating or drying of the flowers. THCA is synthesized within the glandular trichomes present in the flowers, leaves, and bracts (modified or specialized leaf, associated with a reproductive structure such as a flower) of the female plant. Terpenes are volatile compounds responsible for the typical smell and taste of cannabis. More than 120 different types of terpenes have been identified in cannabis. Terpenes have a wide range of known biological effects. Prior, cannabis classification systems did not take the terpenes into account [5,6].

Today's cannabis plants are hybrid descendants of two genetically divergent gene pools – narrow leaf drug (NLD) and broad-leaflet drug (BLD). The original NLD plants had a relatively high THC and low CBD content. BLD later introduced from Afghanistan were short bushy plants with broad, dark green leaflets. BLD plants could produce phytocannabinoids varying from all THC to all CBD. In the late 1970s, growers began to call the original NLD varieties 'sativas' because they resembled narrow leaf hemp fiber varieties. The Afghan BLD hashish varieties were called "indicas." But both NLD and BLD populations belong to different subspecies of *C. indica*, subspecies indica (NLD) and subspecies afghanica (BLD) [7,8].

There is a large disparity between patients, growers, and scientists to describe this plant. Scientists often use the term sativa for low THC content plants and the term "*indica"* for plants with high THC content. In the "cultural" language "*sativa*" refers to plants with very high THC content and low or no CBD content whereas *indica* refers to plants with moderate THC and CBD content. It

is important to recognize that popular literature about marijuana strains uses the terms *indica* and *sativa* in a way that is distinct from the scientific usage and both are inaccurate since form does not determine chemistry[3].

Classifications now take into account the chemical content (chemotype/chemovars) of C. sativa L. Cannabis plants typically exhibit one of the three different chemotypes based on the absolute and relative concentrations of THCA and cannabidiolic acid. Type I refers to high THC chemovars, Type II refers to mixed THC/CBD chemovars, and Type III refers to CBD-predominant chemovars. With modern analytical techniques, rapid and comprehensive analysis of all cannabinoids and terpenes present in cannabis products can be done. This allows an expanded cannabis classification scheme that considers the primary cannabinoid (THC or CBD) and their concentration, terpenoid content and concentration, plant shape, scent, taste, and use.

**From cannabis to endocannabinoids**

The search for the site of action of THC led to the discovery of 2 G protein-coupled receptors for THC, named cannabinoid receptor type-1 (CB1) and type-2 (CB2) and the endogenous cannabinoids. endocannabinoids are endogenous lipids that engage cannabinoid receptors. The best-characterized endocannabinoids are arachidonoyl ethanolamide, best known as anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). AEA is metabolized mostly by fatty acid amide hydrolase (FAAH), whereas 2-AG by monoglyceride lipase (MAGL) [9]. Precursors of AEA and 2-AG are present in lipid membranes, where they are transformed on demand into the final product and then released into the extracellular space.

Accumulated evidence suggests the existence of additional targets for endocannabinoids in addition to CB1 and CB2. This seems the case for the purported ‘CB3’ receptor GPR55 and the transient receptor potential vanilloid 1 (TRPV1) ion channel. Other potential endocannabinoid targets, such as peroxisome proliferator-activated receptor a and g are localized in the nucleus, where they shuttle from/to the cytosol in a ligand-dependent manner.

CB receptors, endogenous ligands that activate them, and the enzymes responsible for the synthesis and degradation of the endocannabinoids constitute altogether the endocannabinoid system.

AEA is responsible for maintaining basal endocannabinoid tone and has a high selectivity for the CB1 receptor over the peripheral CB2 receptor [9]. AEA also binds to the TRPV1, an ionotropic receptor that is responsible for the integration of noxious stimuli that cause pain [10]. In contrast to AEA, 2-AG is a full agonist for both CB1 and CB2 [9]. CB1 receptors are found in neuroanatomical regions involved in pain processing and modulate the release of several neurotransmitters [11]. They are also expressed in afferent fibers and in many nonneural cells. CB1 receptors are involved in pain transmission and modulation at multiple levels of the neuroaxis from periphery to central nervous system [9,12]. CB2 receptors are located primarily in immune cells, even though CB2 mRNA was detected within the spinal cord and CB2 protein in the brain [13]. CB receptors co-localize with opioid receptors and augment the analgesic effects of opioids, probably via pharmacodynamics mechanisms. GPR55 is located in the brain, in the peripheral nervous system and in mast cells [14]. The enzymes involved in the synthesis of AEA and 2-AG are the N-acylphosphatidylethanolaminephospholipase D and the sn-1-specific diacylglycerol lipase, respectively [9]. Once synthesized and released, endocannabinoids are removed from the extracellular space through an endocannabinoid membrane transporter (EMT) and subsequently hydrolyzed. AEA is mostly hydrolyzed by FAAH, which releases, arachidonic acid and ethanolamine or arachidonic acid and glycerol, whereas 2-AG degradation is mainly because of a cytosolic MAGL [9].

**The theoretical bases for a role of the endocannabinoid system in migraine pain: Cannabinoids and Endocannabinoids**

THC, the constituent responsible for the mind-altering and intoxicating effects of C. Sativa, acts on CB1 and CB2 receptors. CBD binds to other receptors, and is devoid of the psychoactive effects associated with THC. CBD is the most abundant cannabis-derived non-CB1/CB2 receptor ligand, that may exert some effects via inhibition of FAAH [15,16]. In addition to its psychotropic properties,

cannabis has long been known to have analgesic, immunomodulatory, and anti-inflammatory effects [17]. CBD reduces inflammatory and neuropathic pain by modulation of 5-HT$1_A$ (serotonin 1A) receptors and TRPV1 channels [18&]. Similarly, to some other cannabinoids, CBD suppresses cytokines and chemokines release, decreases production of reactive oxygen species and modulates immune cell system [19] (Table 1).

Experimental studies show that THC is effective in reducing multiple types of pain including pain caused by acute noxious stimuli and chronic inflammation [43]. THC prevents depression of home cage wheel running caused by migraine-like pain after dural TRPA1 agonist microinjection, in a time- and dose-dependent manner [44,45]. Moreover, THC and other CB1 agonists dose-dependently reduce cortical spreading depression amplitude, duration, and propagation velocity in a rat model [26]. WIN 55,212-2, a potent CB1 agonist, inhibits trigeminocervical complex A and C-fiber afferent activity [46].

Theoretically, the endocannabinoid system may target migraine in multiple pathways (glutamatergic, serotoninergic, opiatergic and inflammatory) [47–49] and at multiple anatomic levels. In the periphery, endocannabinoids may affect neurogenic inflammation mediated by the trigeminovascular system in the meninges via their stabilizing effect on mast cells [14,50] and the inhibition of calcitonin gene-related peptide (CGRP)-induced dilatation of dural blood vessels and neuronal pronociceptive activity [51]. Centrally, activation of CB1 receptors in the ventrolateral periaqueductal gray (PAG) modulates nociceptive trigeminovascular transmission in the trigeminocervical complex via a mechanism mediated by 5HT1B/1D receptors [52]. Endocannabinoid system also affects the descending pathways of pain control by acting at either CB1 or TRPV1 receptors [53,54]. Consistently, microinjections within the PAG and rostral ventrolateral medulla of URB597 (cyclohexylcarbamic acid 3’-carbamoylbiphenyl-3-yl ester), a global FAAH inhibitor, enhance analgesia via TRPV1 and CB1 receptors in animal models of neuropathic pain [53]. Again, the levels of AEA and 2-AG are significantly increased in animal models of neuropathic pain, to suggest a compensatory upregulation of endocannabinoids directed at the inhibition of pain

in pathological conditions [55]. AEA acts presynaptically to prevent release of nitric oxide by CGRP in the dura mater [51]. Also, artificially increased levels of 2-AG and AEA in the dorsal PAG enhance stress induced analgesia [56].

Studies conductedonthemigraine-specific animal model based on nitroglycerin (NTG) administration showed increased FAAH activity and up-regulation of CB1 receptor binding sites in the rat hypothalamus and in the medulla [57]. In NTG-treated rats, activity of FAAH and MAGL hydrolases increased in the mesencephalon, a key area in migraine pathophysiology [57], to suggest a decrease in the endocannabinoid tone. Consistently, we observed that AEA administration significantly reduced NTG-induced nocifensive behavioural and neuronal activation in the nucleus trigeminal caudalis (NTC), another key area for migraine [58], and others reported reduced central sensitization through TRPV1, cyclooxygenase-2 expression, and nuclear factor kappa B inhibition in NTC [59]. If AEA and CB1-mediated mechanisms are important, we must not overlook the possible role of CB2-mediated mechanisms when considering that the activation of these receptors significantly decreases nocifensive behaviour in rats previously made hyperalgesic by NTG [60]. Modulation of CB2 receptor activity seems particularly appealing, as they induce analgesic effects without producing tolerance or central side-effects [61,62].

FAAH inhibition causes analgesia and reduces inflammation in animal models of migraine pain [63,64]. NTG-induced mechanical allodynia and c-Fos protein in the NTC are both suppressed in FAAH deficient mice or after URB597 treatment, thus strongly indicating a role for AEA in migraine pain [64]. In agreement, URB937, a peripherally restricted FAAH inhibitor, reduces NTG-induced nocifensive behavior, and c-Fos expression in the NTC and locus coeruleus [63], thus underscoring the role of peripheral mechanisms, possibly related to the anti-inflammatory activity of endocannabinoids [65&&]. Indeed, URB937 acts only peripherally, maintaining higher levels of AEA released by nervous terminal located in the injured peripheral tissues or in the dura, via CB1 receptor activation in trigeminovascular endings [66]. It is worth noting that similar effects have been reported with biphenyl-3-ylcarbamic acid cyclohexyl ester (URB602), a reversible MAGL inhibitor that significantly

decreases NTG induced neuronal activation in PAG and NTC, to suggest once more that modulation of CB2 may also play a role in migraine [67&&]. These findings support the hypothesis that modulation of the endocannabinoid system may be an extremely valuable approach for the treatment of migraine-related pain and hyperalgesia [68]. However, controversy exists as regards the safety of the modulation of the endocannabinoid system, in particular as regards the inhibition of endocannabinoids catabolism when off-target effect is not properly ruled out [69]. Technological advances allow a full characterization of protein interaction landscape and warrants further investigation along this promising pathway.

**Clinical data**

Clinical evidence in favor of the need to further investigate the role of the endocannabinoid system in migraine is more scattered, but nonetheless compelling. Women with migraine without aura bear increased activities of FAAH and EMT, to suggest reduced AEA levels [70]. In another study based on PET detection of CB1 receptors, women with episodic migraine showed increased binding in pain-modulating areas of the brain [71]. Variants in the CB1 receptor gene increase the risk of migraine attack with nausea in life stress exposed patients [72&]. A more recent study failed to detect significant changes in the plasma levels of AEA and other fatty acid ethanolamides in episodic migraineurs [73], probably as a consequence of a high interpatient variability in the evaluated cohorts.

A more consistent alteration of endocannabinoid system seems to be implicated in chronic migraine. FAAH and EMT levels were lower in the platelets of patients with chronic migraine when compared to either controls or episodic migraine [74]. Furthermore, FAAH levels decreased in patients with chronic migraine and acute medication overuse after detoxification, in parallel with the clinical improvement and with the restored pain control, to suggest that the catabolizing pathway is altered in these patients [75]. Increased levels of N-palmitoylethanolamine (PEA), a fatty acid amide belonging to the endocannabinoid system, were found in the cerebrospinal fluid of chronic migraine patients [76], a finding interpreted by the authors as a compensatory mechanism.

**Cannabinoids in the management of migraine: Clinical effects and Tolerability**

PEA has showed properties that may be useful in pain conditions [77,78]. Limited evidence suggests the possible efficacy of ultramicronized PEA in reducing the number of migraine attacks/month, regardless of age or sex, and the use of acute medications [79,80].

Cannabis-based medicines are approved only for a few indications. None are approved for pain or headache. The Health Effects of Cannabis and Cannabinoid report [81] concluded that there is substantial evidence that cannabinoids are effective for the treatment chronic pain in adults. But little is known about the efficacy, dose, routes of administration, or side effects of available cannabis. Anecdotal evidence suggests a role for cannabis in the treatment of headache and migraine [82,83], but no controlled clinical studies have been done. Anecdotal benefit has been reported in pseudotumor cerebri [84] and refractory cluster headaches [85]. Cannabis use is very frequent in French cluster headache patients; most had variable, uncertain, or even negative effects of cannabis smoking [86]. Headache is an adverse event associated with cannabinoid medications, and is very common with cannabis withdrawal [87]**.** It is therefore possible that using cannabis simply relieves headache caused by cannabis withdrawal.

Rhyne et al. [88] did a retrospective chart review of 121 adults with migraine headache referred for treatment with medical marijuana and had at least one follow-up visit. Migraine headache frequency decreased from 10.4 to 4.6 headaches per month ($P$<0.0001) and self-reported positive effects were recorded in 48 patients (39.7%). The scientific validity of this study is however limited by multiple issues: high rate of drop-outs, inconsistent chart documentation, and so on.

Nabilone is a synthetic cannabinoid with a highly selective agonistic activity for CB1 and CB2 receptors. It decreased analgesic intake and improved pain in a small double-blind, placebo-controlled trial of 26 patients with treatment refractory medication overuse headache, a frequent complication of chronic migraine [89]. They were given nabilone (0.5mg) or ibuprofen (400 mg) for 8 weeks, then after a week-long washout period, switched to the other drug for a second 8-week course. Nabilone was significantly more effective than ibuprofen in reducing pain intensity, analgesic intake, as well as in improving quality of life. Patients only had mild adverse effects. A different

multicenter, double-blind, placebo-controlled study of the safety and efficacy of a dronabinol, a synthetic form of THC, delivered with a metered dose inhaler for the treatment of migraine (clincaltrials.gov, The national clinical trial (NCT) Identifier: NCT00123201) has been completed for several years, without publication of results from the sponsor Solvay Pharmaceuticals, Brussels, Belgium.

Tolerability is a concern in the use of cannabinoids. Dosing is individualized and requires titration. Those with no prior experience should start with a very low dose and stop if undesirable side-effects occur. Psychoactive effects occur at doses above the individual consumer's psychotropic threshold. They are generally pleasurable and relaxing. However, this can turn into dysphoria, anxiety, or even panic. Impairment of memory, reductions in psychomotor and cognitive performance, and disordered perception of the passage of time can occur. Common physical effects are tiredness, dizziness, tachycardia, orthostatic hypotension, dry mouth, reduced lacrimation, muscle relaxation, and increased appetite. Tolerance develops too many of these undesired effects of cannabinoids particularly tiredness, dizziness, and cardiovascular and psychoactive effects over a period of days or weeks [90].

There is an association between cannabis use and the development of psychosis, at least in vulnerable subjects [91], with the highest risk among the most frequent users. The evidence is unclear as to whether and how cannabis use is associated with heart attack, stroke, and diabetes, but tachycardia often occurs with acute dosage; tolerance developing with chronic exposure. Cannabis use increases the risk of being involved in a motor vehicle accident. Smoking cannabis during pregnancy is linked to lower birth weight in the offspring. The relationship between smoking cannabis during pregnancy and other pregnancy and childhood outcomes is unclear. The hyperemesis syndrome can occur in chronic daily cannabis users. It is characterized by severe, intractable episodes of nausea and cyclic vomiting accompanied by abdominal pain (typically epigastric or periumbilical); relieved by compulsive hot water bathing or showering [92]. Treatment includes: cessation of cannabis use, rehydration, and psychological counseling.

## Conclusions

C. sativa is one of the world's oldest cultivated plants. It has been used for thousands of years. Many believe it is effective for migraine and headache, but controlled clinical trials are missing. Anecdotal information does not provide THC and CBD content or the amount and type of terpenes. Cannabis is effective for pain, we still need to know if it is effective for headache.

The modulation of the endocannabinoid system, in particular in the processing of nociceptive signals in the trigeminovascular system, may prove a well-tolerated and pharmacologically sound therapeutic option for migraine [93]. Additional studies are needed to explore the neurobiological mechanisms and neural circuits involved.

## KEY POINTS

1) Alterations in the Endocannabinoid System seem to be implicated in migraine pathogenesis and progression

2) Exogenous and endogenous cannabinoids may have therapeutic benefits in migraine, provided that tolerability issues are addressed

3) More research is necessary for the complete characterization of the multiple components of Cannabis and for the identification of safe modulators of the endogenous cannabinoid system as suitable targets for migraine treatment.

## Acknowledgements

We are grateful to Prof. Daniele Piomelli for providing well characterized multiple inhibitors of the degrading enzymes of endocannabinoids for our experiments in animal models of migraine.

## Financial support and sponsorship

None

## Conflicts of interest

Cristina Tassorelli has received honoraria for participation in clinical trials, contribution to advisory boards or scientific presentations from: Allergan, Electrocore, Eli-Lilly, Novartis, Teva and Medscape, LLC. CT has received independent support from the Italian Ministry of Health, Italian Ministry of Research and European Community. CT has no ownership interest and does not own stocks of any pharmaceutical company. CT serves as Chief Section Editor of Frontiers in Neurology – Section Headache Medicine and Facial Pain and on the editorial board of Journal of Headache and Pain. CT is the chairman of the Clinical Trials Committee of the IHS.

Rosaria Greco has no conflict of interest to declare.

Stephen Silberstein is the Director of the Jefferson Headache Center in Philadelphia, PA. As a consultant and/or advisory panel member, he receives, or has received, honoraria from Abide Therapeutics; Alder Biopharmaceuticals; Allergan, Inc.; Amgen; Avanir Pharmaceuticals, Inc.; Biohaven Pharmaceuticals; Cefaly; Curelator, Inc.; Dr. Reddy's Laboratories; Egalet Corporation; GlaxoSmithKline Consumer Health Holdings, LLC.; eNeura Inc.; electroCore Medical, LLC; Impel NeuroPharma, Inc.; Lilly USA, LLC; Medscape, LLC; Novartis, Inc.; Satsuma Pharmaceuticals; Supernus Pharmaceuticals, Inc.; Teva Pharmaceuticals; Theranica; and Trigemina, Inc.
The Authors have no conflicts of interest to declare as regards the substances mentioned in this manuscript.

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