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REVIEW ARTICLE

Clinical Endocannabinoid Deficiency (CECD):
Can this Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and other Treatment-Resistant Conditions?

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Abstract

OBJECTIVES: This study examines the concept of clinical endocannabinoid deficiency (CECD), and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis.

METHODS: Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other resources.

RESULTS: Migraine has numerous relationships to endocannabinoid function. Anandamide (AEA) potentiates 5-HT1A and inhibits 5-HT2A receptors supporting therapeutic efficacy in acute and preventive migraine treatment. Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. AEA is tonically active in the periaqueductal gray matter, a migraine generator. THC modulates glutamatergic neurotransmission via NMDA receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, IBS and related disorders. The past and potential clinical utility of cannabis-based medicines in their treatment is discussed, as are further suggestions for experimental investigation of CECD via CSF examination and neuro-imaging.

CONCLUSION: Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines.

Abbreviations

AEA:	arachidonylethanolamide, anandamide
2-AG:	2-arachidonylglycerol
CB_1:	cannabinoid 1 receptor
CBD:	cannabidiol
CECD:	clinical endocannabinoid deficiency
CGRP:	calcitonin gene-related peptide
CNS:	central nervous system
CRP:	complex regional pain
ECT:	electroconvulsive therapy
FAAH:	fatty acid amide hydrolase
fMRI:	functional magnetic resonance imaging
5-HT:	5-hydroxytryptamine, serotonin
GI:	gastrointestinal
IBS:	irritable bowel syndrome
NMDA:	N-methyl-d-aspartate
PAG:	periaqueductal gray
PET:	positron emission tomography
PTSD:	post-traumatic stress disorder
RSD:	reflex sympathetic dystrophy
THC:	Δ^9-tetrahydrocannabinol
TMJ:	temporomandibular joint
VR_1:	vanilloid 1 receptor

Introduction

In the initial lines of his 1895 work, *Project for a Scientific Psychology,* Sigmund Freud stated [1] (p. 295), "The intention is to furnish a psychology that shall be a natural science: that is, to represent psychical processes as quantitatively determinate states of specifiable material particles, thus making those processes perspicuous and free from contradiction." Freud was frustrated in this effort, and found that available science at the twilight of the 19th century was not capable of providing biochemical explanations for cerebral processes, leading him to pursue psychodynamic theory alternatively.

At the dawn of the 21st century, despite astounding progress in psychopharmacology, medicine remains challenged in its attempts to understand and successfully treat a large number of recalcitrant syndromes, noteworthy among them, migraine, fibromyalgia, and irritable bowel syndrome (IBS). For many physicians these problematic entities suggest a psychosomatic or "functional" etiology that remains shorthand for a diagnosis where our biochemical understanding and therapeutic vigor fall short of the mark.

In the last fifteen years, however, the discovery of the endogenous cannabinoid (endocannabinoid) system [2] has provided new insights into a neuromodulatory scheme that portends to provide better explanations of, and treatments for, a wide variety of previously intractable disorders, particularly painful conditions (reviewed in [3; 4]).

After all, for each neurotransmitter system there are pathological conditions attributable to its deficiency: dementia in Alzheimer disease due to loss of acetylcholine activity, Parkinsonism due to dopamine deficiency, depression secondary to lowered levels of serotonin, norepinephrine or other amines, etc. Should the situation be any different for the endocannabinoid system, whose receptor density is in fact greater than many of the others? This article will explore that question and propose a concept first articulated in prior publications [5; 6], that a clinical endocannabinoid deficiency (CECD), whether congenital or acquired may help to explain the pathophysiology of certain diagnostic pitfalls, especially those characterized by hyperalgesia, and thereby provide a basis for their treatment with cannabinoid medicines.

Mechanisms of action of cannabis and THC have recently been elucidated with the discovery of cannabinoid receptors and an endogenous ligand, arachidonylethanolamide, nicknamed anandamide, from the Sanskrit word *ananda,* or "bliss" [7]. Anandamide (AEA) inhibits cyclic AMP mediated through G-protein coupling in target cells, which cluster in nociceptive areas of the CNS [8]. Preliminary tests of its pharmacological action and behavioral activity support similarity of AEA to THC [9], and both entities are partial agonists at the CB_1 receptor. Pertwee [4] has examined the pharmacology of cannabinoid receptors and pain in detail.

Methods

Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other Internet resources.

Results

Migraine

Migraine is a public health issue of astounding societal cost. There are an estimated 23 million sufferers in the USA [10], with an economic impact of $1.2 to $17.2 billion annually [11]. The neurochemistry of migraine is among the most complex of any human malady, and its relation to cannabinoid mechanisms has been examined previously in brief [12] and in depth [5].

Serotonergic pathways are considered integral to migraine pathogenesis and treatment. Numerous points of intersection with cannabinoid mechanisms are evident: THC inhibits serotonin release from the platelets of human migraineurs [13]; THC stimulates 5-HT synthesis, inhibits synaptosomal uptake, and promotes its release [14]; AEA and CB_1 agonists inhibit rat serotonin type 3 ($5\text{-}HT_3$) receptors [15] involved in emetic and pain responses. Additionally, AEA produces an 89% relative potentiation of the $5\text{-}HT_{1A}$ receptor response, and a 36% inhibition of the $5\text{-}HT_{2A}$ receptor response [16]. Another endocannabinoid, 2-arachidonylglycerol (2-AG) inhibited $5\text{-}HT_{2A}$ by 28%. Recently, mild but significant similar activity on $5\text{-}HT_{2A}$ has been demonstrated for cannabidiol [17], and cannabis terpenoids [18]. Higher concentrations of anandamide decreased serotonin and ketanserin binding (the latter being a $5\text{-}HT_{2A}$ antagonist) [19]. These observations support putative efficacy of therapeutic cannabinoids in acute migraine (agonistic activity at $5\text{-}HT_{1A}$ or D) and in its prophylactic treatment (antagonistic activity at $5\text{-}HT_{2A}$) [20].

The importance of dopaminergic mechanisms in migraine has also been explored [21]. 6-hydroxydopamine, which causes degeneration of catecholamine

terminals, blocked THC antinociception [22]. AEA stimulates nitric oxide formation through inhibition of presynaptic dopamine release [23]. Dopamine blocking and modulatory effects of cannabis and THC have been demonstrated in studies of Tourette syndrome [24; 25], and schizophrenia in Germany [26], suggesting that THC may similarly modulate dopaminergic imbalances in headache.

Inflammatory mechanisms affected by cannabis are legion (reviewed [27–31]. THC and cannabinoids inhibit prostaglandin E-2 synthesis [32]; smoked cannabis reduces platelet aggregation [33]; THC demonstrated an oral potency as an anti-inflammatory 20 times that of aspirin and twice that of hydrocortisone [34], and cannabidiol (CBD) inhibited both cyclooxygenase and lipoxygenase. Similarly, anandamide and metabolites are substrates for brain lipoxygenase [35]. Opiates, cannabinoids and eicosanoids signal through common nitric acid coupling [36], while THC blocks the conversion of arachidonate into metabolites derived by cyclooxygenase activity, and stimulates lipoxygenase, promoting down-regulation of inflammation.

CNS beta-endorphin levels are depleted during migraine attacks [37], but THC experimentally increases them [38]. THC additionally regulates substance P and enkephalin mRNA levels in the basal ganglia [39]. THC affects an analgesic brainstem circuit in the rostral ventromedial medulla that interacts with opiate pathways [40], mediating antinociception after activation of neurons in the midbrain periaqueductal grey matter (PAG), a putative migraine generator area [41], wherein THC and other cannabinoids are antinociceptive [42]. The PAG is an integral processor of ascending and descending pain pathways, fear and anxiety [43]. Additional support is provided by studies demonstrating tritiated sumatriptan binding in human PAG [44], and that THC administration elevates proenkephalin gene expression in the PAG [45]. Most compelling is data supporting tonic activity of anandamide in the PAG with production of analgesia, and hyperalgesia upon cannabinoid antagonism [46].

Cannabinoids may represent a therapeutic advantage over opiates, particularly in treatment of neuropathic pain [47]. Opiates commonly aggravate migraine or even provoke its appearance [48], as observed therapeutic doses of morphine failed to alleviate acute attack and increased hyperalgesia in migraineurs during inter-ictal periods.

A trigeminovascular system has long been implicated as integral to the pain, inflammation and secondary vascular effects of migraine, linked through the NMDA/glutamate system [49]. Cannabinoid agonists inhibit voltage-gated calcium channels, and activate potassium channels to produce presynaptic inhibition of glutamate release [50], without dissociative effects noted with other NMDA inhibitors, such as ketamine. Subsequently, THC was shown to modulate glutamatergic transmission through a reduction without blockade [51]. NMDA antagonism was felt to be effective in eliminating hyperalgesia associated with migraine [52], as well a "secondary hyperalgesia" with exaggerated responses to noxious stimuli in areas adjacent to the pain. NMDA blockade was recommended to treat chronic daily headache [53]. This group also addressed how a genetic predisposition ("third hyperalgesia") may lead to a "chronicization" of migraine through NMDA stimulation [54].

THC and CBD phytocannabinoids also act as neuroprotective antioxidants against glutamate neurotoxicity and cell death mediated via NMDA, AMPA and kainate receptors [55], independently of cannabinoid receptors, and exceed the antioxidant potency of vitamins C and E.

Migraine is a complex neurochemical disorder with myriad effects beyond pain. Its tendency to produce photophobia and phonophobia, even between discreet attacks [56], may be considered suggestive of a "sensory hyperalgesia," as these normally tolerated sensations take on painful proportions.

The combination of endocannabinoids and their inactive precursors have been dubbed an entourage effect [57], and an analogous synergy of phytocannabinoids, cannabis terpenoids and flavonoids has also been suggested and analyzed at some length [58]. The unique attributes of cannabis to affect serotonergic, dopaminergic, opioid, anti-inflammatory, and NMDA mechanisms of migraine, both acutely and prophylactically, have rendered it a proposed "ideal drug" for its treatment [5].

Migraine is a strongly genetic disorder, but similar symptoms are acquired under conditions of closed head injury, where the "post-traumatic syndrome" displays similar symptoms. A protective role of endocannabinoids in such settings is evident in the findings that 2-AG is elevated after experimental brain injury, and that it plays an important neuroprotective role [59].

Unfortunately, no organized clinical trials of cannabis in migraine have been performed. While documentation of the use of cannabis for migraine suggests a 4000 year history, and it was a major indication for cannabis medicines in Western society between 1842 and 1942 [5], there have been few modern studies beyond the "anecdotal" [5; 60–62]. Surveys in California indicate that of 2480 patients served by the Oakland Cannabis Buyers' Club, 127, or 5%, sought cannabis for treatment of chronic migraines [63]. Success rates of some 80% with North American strains of cannabis have been estimated based on clinical contact [5]. Experience in prophylactic use of Marinol® (synthetic THC) in some ten patients was disappointing, with some decrement in frequency and severity of attacks, but not total remission or "cures" claimed by 19th century authors with extracts of Indian hemp [5]. The difference may well be due to a nearly total dearth of cannabidiol in North American cannabis strains [64] (see discussion below), and the observed possibility of CBD modulation of serotonergic function [17]. More formal documentation of clinical efficacy would be distinctly welcome.

Fibromyalgia

Fibromyalgia, or myofascial pain syndrome, is an extremely common but controversial condition, whose very basis has been questioned, particularly among neurologists [65]. Even this author must admit to past prejudice in labeling it a "semi-mythical pseudo-disease." Notwithstanding these opinions, the condition is the most frequent diagnosis in American rheumatology practices. Bennett has provided an excellent review [66], emphasizing new insights into fibromyalgia as a condition indicative of "central sensitization" and amplification of somatic nociception. While no clear chemical or anatomical pathology has been clarified in tender muscle points, these present a self-sustaining and amplifying influence on pain perception in the brain over time, and lead to a concomitant disturbances in restful sleep, manifestations of dysautonomia, and prevalent secondary depression. Interestingly, the application of standard antidepressant medication to the latter, and pharmacotherapy in general, provide disappointing results in fibromyalgia treatment. Has a promising therapeutic avenue been missed?

Returning to the work of Nicolodi and Sicuteri, the "secondary hyperalgesia" manifested by an increased response to noxious stimuli in areas adjacent to the pain is common to migraine and fibromyalgia (see below). These authors suggested NMDA blockade as an approach to pain in defects of serotonergic analgesia in fibromyalgia [67].

Several studies of Richardson and her group provide key support for a relation of fibromyalgia and similar conditions to a clinical endocannanabinoid deficiency. An initial study [68] demonstrated that intrathecal injection of SR141716A, a powerful cannabinoid antagonist/inverse agonist, resulted in thermal hyperalgesia in mice. This suggests that the endocannabinoid system regulates nociceptive thresholds, and that absence of such regulation, or endocannabinoid hypofunction, underlies hyperalgesia and related chronic pain conditions. In a subsequent study [69], oligonucleotides directed against CB_1 mRNA produced significant hyperalgesia. Additionally, the hyperalgesic effect of SR141716A was blocked in a dose-dependent manner by co-administration of two NMDA receptor antagonists, again supporting tonic activity of the endocannabinoid system under normal conditions. On this basis, it was suggested that cannabinoid agonists would be applicable to treatment of chronic pain conditions unresponsive to opioid analgesics.

Further investigation demonstrated that intrathecal AEA totally blocked carrageenan-induced spinal thermal hyperalgesia, while having no effect on normal thermal sensory and antinociceptive thresholds [70]. Additionally, AEA inhibited K^+ and capsaicin-evoked calcitonin gene-related peptide (CGRP) release, and CB_1 receptors were identified in rat sensory neurons and trigeminal ganglion. On this basis, the authors recommended cannabinoids for disorders driven by a primary afferent barrage (e.g., allodynia, visceral hyperalgesia, temporomandibular joint pain (TMJ), and reflex sympathetic dystrophy (RSD)), and that such treatment could be effective a sub-psychoactive dosages.

Another study examined peripheral mechanisms [71], wherein AEA acted on CB_1 to reduce hyperalgesia and inflammation via inhibition of CGRP neurosecretion in capsaicin activated nerve terminals. This is akin to mechanisms of "sterile inflammation" observed centrally in migraine, where CGRP is felt to be an important mediator [5]. Overall the results supported the notion that endocannabinoids modulate neurogenic inflammation through inhibition of peripheral terminal neurosecretion in capsaicin-sensitive fibers. AEA demonstrated anti-edema effects in addition to anti-hyperalgesia. Similar implications were provided by another study [72], in which WIN 55,212–2, a powerful CB_1 agonist, blocked capsaicin-induced hyperalgesia in rat paws. Once more, the benefit occurred at a dosage that did not produce analgesia or motor impairment, suggesting therapeutic benefit of cannabinoids without adverse effects. Similarly, local THC administration was evaluated in capsaicin-induced pain in rhesus monkeys [73], where, once more, pain was effectively reduced at low dosage, and was blocked by a CB_1 antagonist.

Another concept that is important to understanding of fibromyalgia is "wind-up," a central sensitization of posterior horn neurons in pain pathways that occurs secondarily to tonic impulses form nociceptive afferent C fibers dependent on NMDA and substance P synaptic mechanisms in the spinal cord [74]. Similar mechanisms were implicated in TMJ dysfunction and RSD/CRP syndromes. The authors felt that some unknown peripheral tonic mechanism maintains allodynia, hyperalgesia, central sensitization and enhanced wind-up. Unfortunately, an obvious explanation was overlooked. In a previous publication [75], it was demonstrated that of wind-up was decreased in dose-dependent fashion by WIN 55,212 in spinal wide dynamic range and nociceptive-specific neurons. Thus, cannabinoids were able to suppress facilitation of spinal responses after repetitive noxious stimuli without impairment of non-nociceptive functions.

On a practical level, once more there have been no formal clinical trials of cannabis or THC in treatment of fibromyalgia. However, 21 California patients listed fibromyalgia and 11 myofascial pain (1.3% of a clinical population of 2480 subjects) as primary diagnoses leading to their usage of clinical cannabis [63]. Anecdotal reports to this author and other clinicians support unique efficacy of cannabis beyond conventional pharmacotherapy for alleviation of pain, dysphoria and sleep disturbances.

Irritable Bowel Syndrome (IBS)

IBS is another difficult clinical syndrome for patients and their physicians. It is characterized by fluctuating symptoms of gastrointestinal pain, spasm, distention, and varying degrees of constipation or especially diarrhea. These may be triggered by infection,

but dietary indiscretions also figure prominently in discrete attacks. Although many clinicians regard it as a "diagnostic wastebasket," irritable bowel syndrome represents the most frequent referral diagnosis for American gastroenterologists. Once more, a wide variety of treatments including atropinic agents, antidepressants and others affecting a myriad of neurotransmitter systems are prescribed, often with inadequate clinical benefits.

That endocannabinoids are important in GI function was powerfully underlined by the fact that 2-arachidonylglycerol (2-AG) was first isolated in canine gut [76].

In a recent review [77], the concept of "functional" bowel disorders as disturbances displaying "visceral hypersensitivity" was emphasized, involving a veritable symphony of neuroactive and pro-inflammatory modulators. In the susceptible subject, these lead to gastrointestinal allodynia and hyperalgesia to stimuli that would not discomfit the unaffected individual. The role of vanilloid mechanisms in IBS was also explored, and it is worth emphasizing that anandamide is an endogenous agonist at VR_1 receptors, as is the phytocannabinoid cannabidiol (CBD) [78]. Repetitive VR_1 stimulation rapidly produces a sensory neuron refractory state that would be a clinical advantage in treatment of visceral hypersensitivity.

Pertwee has examined the relationship of cannabinoids to gastrointestinal function in depth [79]. To summarize: The enteric nervous systems of mammals express CB_1 and stimulation depresses gastrointestinal motility, especially through inhibition of contractile neurotransmitter release. Observed effects include delayed gastric emptying, some decrease in peptic acid production, and slowed enteric motility, inhibition of stimulated acetylcholine release, peristalsis, and both cholinergic and non-adrenergic non-cholinergic (NANC) contractions of smooth muscle, whether circular or longitudinal. These effects are mediated at the brain level as well as in the GI tract (This supports a chestnut frequently invoked by this author, 'The brain and the gut speak the same language."). These effects are opposed by CB_1 antagonists (e.g., SR141716A). This would strongly support the notion that GI motility is under tonic control of the endocannabinoid system. The latter concept was reinforced by additional investigation from the same laboratory [80], in which it was demonstrated that the virtually all of the immunoreactive myenteric neurons in the ganglia of rat and guinea pig expressed CB_1 receptors, and that there was a close correlation of such receptors to fibers labeled for synaptic protein, suggesting a fundamental role in neurotransmitter release. Additionally, it has been shown that chronic intestinal inflammation results in an up-regulation or sensitization of cannabinoid receptors [81]. CBD has little effect on intestinal motility on its own, but synergizes the effect of THC in slowing transit of a charcoal meal when used in concert [82].

In the basis of available data, Di Carlo and Izzo recommended the application of cannabinoid drugs in treatment of IBS in humans [83]. To date, those studies have not eventuated, but cannabis has a long history in treating cholera, intestinal colic and related disorders (reviewed in [84]), and cannabis figures prominently in IBS treatment in testimonials on the Internet. Though anecdotal, reports suggest unique efficacy of symptomatic relief at cannabis dosages that do not impair activities of daily living. In comparison, recent trends in pharmacotherapy provide interesting contrasts. Alosetron, a $5\text{-}HT_3$ receptor antagonist marketed for females with diarrhea-predominant IBS produces only a 12–17% therapeutic gain [85], and was temporarily removed from the American market due to fatal cases of ischemic colitis with attendant obstipation. Tegaserod, a $5\text{-}HT_4$ receptor agonist marketed to women with constipation-predominant IBS, is reportedly well tolerated, but provides only a 5–15% improvement over placebo [85]. This "push-pull" dichotomy of serotonergic function in IBS is strongly suggestive that such efforts are barking up the wrong neurotransmitter tree. Rational analysis suggests that endocannabinoids may well be the more likely therapeutic neuromodulatory target, and that phytocannabinoid treatment might represent a more efficacious and safer therapeutic approach. In particularly severe IBS cases, the employment of a foaming rectal preparation of a whole cannabis extract might be considered.

Comorbidities of Migraine, Fibromyalgia and Irritable Bowel Syndrome

Further examination of pertinent literature supports that there are very interesting relationships between migraine, fibromyalgia and IBS. Recently, a syndrome of cutaneous allodynia associated with migraine has been reported [86], and experimentally, repetitive noxious stimulation of the skin in migraineurs between attacks facilitates pain perception [87]. Nicolodi, Sicuteri et al. similarly noted a decreased pain threshold in migraineurs tested with over-distension of upper extremity veins, but not mere pressure from a sphygmomanometer cuff [88], meriting a label for migraine as a "visceral systemic sensory disorder." The same team noted a baseline fragility of serotonergic systems in migraine and fibromyalgia [89], plus the co-occurrence of primary headache in 97% of 201 fibromyalgia patients. In a later study [67], they supported the concept that both disorders represented a failure of serotonergic analgesia and NMDA-mediated neuronal plasticity. Other observations included the induction of fibromyalgic symptoms by the drug fenclonine in migraineurs but not others, and the production of migraine *de novo* in fibromyalgia patients without prior history after administration of nitroglycerine 0.6 mg sublingually. Similarly, an American group [90] examined 101 patients with the transformed migraine form of chronic daily headache, and were able to diagnose 35.6% as having comorbid fibromyalgia. Similarly, a high lifetime prevalence of migraine, IBS, depression and panic disorder were observed in 33 women meeting American College of Rheumatology criteria of fibromyalgia [91].

Sperber et al. examined separate groups of IBS and fibromyalgia patients [92]. Of the IBS cohort, 31.6% had fibromyalgia with significant numbers of tender muscle points compared to controls. Similarly, 32% of fibromyalgia patients met diagnostic criteria of IBS. In addition to these correlations, Bennett added irritable bladder syndrome to the comorbidities of fibromyalgia [66], supporting a concomitant visceral hyperalgesia [93; 94] in a condition where cannabis extracts have already proven efficacious [95].

Most recently, in an experimental protocol, it was demonstrated that IBS patients displayed cutaneous hyperalgesia that was suppressed by temporary rectal anesthesia with lidocaine [96], indicating central sensitization.

Broadening the Concept of Clinical Endocannabinoid Deficiency

One may quickly see that certain patients display symptoms of all three disorders, or additional ones considered "functional." With accrual of sufficient numbers of complaints lacking objective medical support, one assigns the label of somatization disorder. Given the above data, however, one might reasonably ask three questions in such contexts: 1) Are there as yet unelucidated biochemical explanations for these disorders? 2) Might endocannabinoid deficiency explain their pathophysiology? 3) Are the symptoms alleviated by clinical cannabis?

Globus hystericus and similar symptoms are frequently relegated to the psychogenic realm, but as a spasmodic disorder, it may well represent an endocannabinoid deficiency (CECD), as muscle tone (and tremor associated with demyelination) have been demonstrated to be under tonic endocannabinoid control in experimental animals [97]. Cannabis extracts have already proven efficacious in treatment of spasticity [98; 99].

Similarly, premature ejaculation in men is conventionally perceived as "psychological." This seems less tenable, when anecdotes support that cannabis prolongs latency, and proof is apparent in the dose responsive delay in ejaculation in rats noted in experiments with HU 210, a powerful CB_1 agonist [100].

A more obvious set of correlating conditions would be those of causalgia, allodynia and phantom limb pain, where application of cannabis based medicine extracts has already proven medically effective [99; 101]. Perhaps it will be demonstrable in the future that such conditions are associated with focal or spinal CECD states.

It has long been known that cannabinoids lower intraocular pressure in glaucoma (reviewed [102]), but only recently noted that that the mechanism is under tonic endocannabinoid control. Glaucoma also represents a vascular retinopathy for which cannabis may be neuroprotective. Perhaps an endocannabinoid deficiency is operative here as well.

Cannabis has had numerous historical applications to obstetrics and gynecology (reviewed [103]). This suggests usage of cannabinoid treatment in spasmodic dysmenorrhea, hyperemesis gravidarum, and regulation of the uterine milieu in fertilization and unexplained fetal wastage, where endocannabinoid mechanisms have been demonstrated or implicated. Further investigation may shed light on whether dysregulation of the system underlies their pathophysiology.

In the pediatric realm, the entity of infantile colic has remained enigmatic. This disturbing anomaly is associated with apparent visceral sensitivity and distinct dysphoria, and is frequently medically recalcitrant to even desperate treatment measures with medications with serious adverse effect profiles. This author posits this to be another developmental endocannabinoid deficiency state that is likely amenable to phytocannabinoid treatment.

Endocannabinoid mechanisms also regulate bronchial function [104], and therapeutic efficacy in asthma treatment with cannabis preparations has been long known [105]. Based on similar analyses of the multi-organ involvement of cystic fibrosis [106], Fride has proposed endocannabinoid deficiencies as underlying the pathophysiology of that disorder, and its treatment with phytocannabinoids.

In the psychiatric realm, bipolar disorder has been therapeutically recalcitrant to high dose antidepressants, but anecdotal data support cannabis efficacy [107]. Whether endocannabinoid tone is too low in the disorder would be conjectural at this time, but in the instance of post-traumatic stress disorder (PTSD), such a foundation seems likely, as endocannabinoids have been demonstrated as essential to the extinction of aversive memories in experimental animals [108].

Recent work by Wallace et al. has also demonstrated that convulsive thresholds are also under endocannabinoid control [109; 110], and that THC prevents 100% of subsequent seizures, far in excess of the capabilities of phenobarbital and phenytoin. Affected rats demonstrated both acute increases in endocannabinoid production and a long-term up-regulation of CB_1 production as apparent compensatory effects counteracting glutamate excitotoxicity. Based on this, one might conjecture that similar changes accrue when seizures are employed therapeutically as electroconvulsive therapy (ECT), in treatment of intractable depression. It seems that the resultant memory loss and prolonged improvement in mood may well be attributable to an increase in endocannabinoid levels rectifying their previous inadequacy.

Recent theory on depression suggests that mere deficiencies of serotonin and norepinephrine may be insufficient explanations of the disorder, but rather, innate neuroplasticity is inherently impaired and requires specific treatment [111]. Cannabinoids certainly seem to enhance that plasticity with their neuroprotective abilities [112; 113], and should be further explored therapeutically.

The apoptotic and anti-angiogenic properties of endo- and phytocannabinoids in various cancers (reviewed [114; 115]) raise the hypothesis that certain people who are especially susceptible to malignancy may be endocannabinoid deficient.

Conclusions

Clinical Endocannabinoid Deficiency: Is It a Provable Concept?

The preceding material has pertained to conjectural and experimental evidence of a conceptual alternative biochemical explanation for certain disease manifestations, but one must ask how these would obtain? Baker et al. have described how endocannabinoids may demonstrate an impairment threshold if too high, and a range of normal function below which a deficit threshold may be crossed [112]. Syndromes of CECD may be congenital or acquired. In the former case, one could posit that genetically-susceptible individuals might produce inadequate endocannabinoids, or that their degradation is too rapid. The same conditions might be acquired in injury or infection. Unfortunately, the regulation of endocannabinoid synthesis and degradation are far from fully elucidated (reviewed [116]). While a single enzyme, anandamide synthase, catalyzes AEA production, its degradation by fatty acid amidohydrolase (FAAH), is shared with many substrates. To complicate matters, an endocannabinoid with antagonistic properties at CB_1 called virodhamine (*virodha,* Sanskrit for "opposition") has recently been discovered [117]. Further research may shed light on these relationships.

In the meantime, a clinical agent that modifies endocannabinoid function will soon be clinically available in the form of cannabidiol. Recent research has demonstrated that although THC does not share VR_1 agonistic activity with AEA, CBD does so to a similar degree as capsaicin [78]. What is more, CBD inhibits uptake of the endocannabinoid anandamide (AEA), and weakly inhibits its hydrolysis. The presence of this component in available cannabis based medicine extracts portends to vastly extend the clinical applications and therapeutic efficacy of this re-emerging modality [118–120].

It is highly likely that additional regulatory roles for endocannabinoids will be discovered for this neuro- and immunomodulatory system. Some simple human experiments may be valuable, such as cerebrospinal fluid assay of AEA and 2-AG before and after ECT treatment. It is likely in the future that positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) for cannabinoid ligands may clarify these concepts.

This article has examined the inter-relationships of three clinical syndromes and biochemical basis in endocannabinoid function, as well as reflecting on other conditions that may display similar correlations. Only time and the scientific method will ascertain whether a new paradigm is applicable to human physiology and treatment of its derangements. Our insight into these possibilities is dependent on the contribution of one unique healing plant; for clinical cannabis has become a therapeutic compass to what modern medicine fails to cure.

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