



Endocannabinoid System: Neuropharmacological Implications

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Abstract

Marijuana or cannabis has been part of humanity's medicine chest for almost as long as history has been recorded. Cannabinoids are a class of diverse chemical compounds isolated from cannabis that act on cannabinoid receptors (CB1 & CB2). The ligands for these receptor proteins include the endocannabinoids (produced naturally in the body by humans and animals), the phytocannabinoids (found in cannabis and some other plants) and synthetic cannabinoids (manufactured artificially). The endogenous cannabinoid system, named after the plant that led to its discovery, is perhaps the most important physiologic system involved in establishing and maintaining human health. The human body's neurological, circulatory, endocrine, digestive and musculoskeletal systems have now all been shown to possess cannabinoid receptor sites. Indeed, even cartilage tissue has cannabinoid receptors, which makes cannabis a prime therapeutic agent to treat various complicated ailments. In each tissue, the cannabinoid system performs different tasks, but the goal is always the same: homeostasis, the maintenance of a stable internal environment despite fluctuations in the external environment. The endocannabinoid system, with its presence in almost all organs especially in CNS makes it a bridge between body and mind. By understanding this system we begin to see a mechanism that explains how states of consciousness can promote health and sense of well being. Nausea, vomiting, stimulation of appetite, symptomatic relief of cancer pain and/or management of neuropathic pain, stroke, cancer, drug dependence, glaucoma, autoimmune uveitis, osteoporosis, sepsis, hepatic, renal, intestinal and cardiovascular disorders are the various diverse areas where cannabinoids have shown their therapeutic presence and potential. In present work cannabinoids are presented as a viable therapeutic target in CNS disorders that include Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, Parkinson's and Huntington's disease.

Keywords: Anandamide, cannabis, endocannabinoids, THC, neurodegeneration

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Introduction and Historical Perspective

The present review tries to investigate the past evidences of cannabinoids and endocannabinoid system in the field of pharmacology in general and in neuropharmacology in particular. Based on the past results, future possibilities in this field for treatment of various neurodegenerative disorders is searched. The diverse and almost universal presence of cannabinoid receptors and their endogenous ligands make them a viable therapeutic option that holds a great promise in the treatment of majority of disorders particularly neurodegenerative disorders.

Marijuana or cannabis is in the class of psychotropic substances, which are substances that act on an individual's psyche and cause different changes in his or her mental functioning. Cannabis is in the group of psychodysleptic drugs or hallucinogens [1] which is a very popular recreational drug due to its ability to alter sensory perception and cause euphoria. However, it has also been recognized thousands of years ago that extracts of *Cannabis sativa* can exert medicinal effects [2].

Cannabis sativa probably originates from neolithic China [3]. Cannabis was first used for medicinal purposes in 2737 B.C. [3,4]. However the exact period of its domestication is unknown. The first known record of the use of cannabis as a medicine was published in China 5000 years ago in the reign of the Emperor Chen Nung. It was recommended for malaria, constipation, rheumatic pains, absent-mindedness and female disorders. Later its use spread into India and other Asian countries, the Middle East, Asia, South Africa and South America. It was highly valued in medieval Europe. In Western Europe, particularly in England, cannabis was extensively used as a medicine during the 19th century, while in France it was mostly known as a “recreational” drug [5].

All the parts of the *cannabis sativa* contain cannabinoids but the quantity varies from one part to another. The resin secreted by the female glandular hairs contains up to 90 percent cannabinoids, the bracts of the flowers and fruits contain an average of 3 to 6 percent, and the leaves contain only one to 3 percent [6]. Marijuana is a colloquial term used to refer to the dried flowers of the female *Cannabis Sativa* and *Cannabis Indica* plants.

The United States Pharmacopeia initially classified marijuana as a legitimate medical compound in 1851. Although criminalized in the United States in 1937 against the advice of the American Medical Association, cannabis was not removed from the United States Pharmacopoeia until 1942 [4].

In Europe cannabinoids were used at the end of the 19th century to treat pain, spasms, asthma, sleep disorders, depression and loss of appetite. In the first half of the 20th century cannabinoid medications fell into almost complete disuse, partly because scientists were unable to establish the chemical structure of the ingredients of the cannabis plant. It was only in 1964 that (-)-trans-delta-9-tetrahydrocannabinol (THC, dronabinol), the principal active ingredient of cannabis, was stereochemically defined [7].

All forms of cannabis plants are quite complex, containing over 400 chemicals. Approximately 60 of these chemicals are classified as cannabinoids. Among the most psychoactive of the cannabinoids is delta-9-tetrahydrocannabinol (THC), the active ingredient in the prescription medications dronabinol (Marinol) and naboline (Cesamet). Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which are non-psychoactive but possess distinct pharmacological effects.

Cannabinoids were originally regarded as any of a class of typical C-21 groups of compounds present in *Cannabis sativa* L. The modern definition emphasizes on synthetic chemistry and on pharmacology and encompasses kindred structures or any other compound that affects cannabinoid receptors. It has been proposed to use the term phytocannabinoid for the natural plant compounds and endocannabinoids for the natural animal compounds, the endogenous ligands of the cannabinoid receptors. In contrast to most other drugs, including opiates, cocaine, nicotine and caffeine, they do not contain nitrogen, and hence are not alkaloids.

Cannabinoid receptors and endocannabinoids, compounds produced by the body that bind to these receptors, together constitute the endocannabinoid system. This system is of great importance for the normal function of the body and is millions of years old. It has been found in mammals, birds, amphibians, fish, sea urchins, molluscs and leeches [8].

Thirty years after the identification of THC by Dr. Mechoulam, a scientist working with him, William Devane, identified a brain chemical, anandamide - a chemical -which binds to the

cannabinoid receptor and causes changes which are qualitatively similar to those provoked by THC. Over the last few decades, the endocannabinoid system (eCBs) has emerged as a topic of great interest in pharmacology. Sea squirts, tiny nematodes, and all vertebrate species share the eCBs as an essential part of life and adaptation to environmental changes. By comparing the genetics of cannabinoid receptors in different species, scientists estimate that the eCBs evolved in primitive animals over 600 million years ago. The basic functions of the eCBs were summarized in 1998 by Professor Di Marzo as, “relax, eat, sleep, forget and protect.

The eCBs refers to a group of neuromodulatory lipids and their receptors which are implicated in a wide variety of physiological and pathological processes [9]. Endocannabinoid system is a neurotransmitter system, which includes several neuromodulatory lipids their receptors (cannabinoid receptor type 1, CB1, and 2, CB2) and a set of enzymes that synthesize and degrade endocannabinoids.

The first guanine-nucleotide-binding protein (G protein)-coupled receptor (GPCR) activated by THC, cannabinoid receptor 1 (CB1; encoded by gene CNR1), was discovered in the brain in 1988 [10] and cloned in 1990 [11]. The second GPCR, CB2, was identified in immune cells in 1993 [12]. Out of several phytocannabinoids present in Cannabis plants (in varying amounts depending on strain or growing conditions), only THC potently activates CB1 and CB2. The existence of these two receptors, of which one (CB1) is the most abundant GPCR in the brain, could only be explained by the presence of endogenous ligands; the eCBs. These were discovered in the early nineties, shortly after the discoveries of CB1 and CB2, as derivatives of the non-oxidative metabolism of the polyunsaturated fatty acid, arachidonic acid. N-arachidonoyl-ethanolamine (anandamide) 9 and 2-arachidonoyl-glycerol (2-AG) are the two best-studied eCBs so far, and together with enzymes involved in their biosynthesis and inactivation, and the two cannabinoid receptors, they form the ‘eCB system [9].

Both CB1 and CB2 receptors are members of the 7 transmembrane G protein coupled receptor (GPCR) superfamily [13]. CB 1 receptors are now considered the most abundant metabotropic receptor in the mammalian brain and are also present in peripheral tissues [14]. The CB1 receptors are found in high densities in the neuron terminals of the basal ganglia (affecting motor activity), cerebellum (motor coordination), hippocampus (short-term memory), neocortex (thinking), and hypothalamus and limbic cortex (appetite and sedation).

To a lesser extent, the CB 1 receptors are found in periaqueductal gray dorsal horn (pain) and immune cells. CB1 receptors being present in both neurons and glial cells, regulate important brain functions including cognition and memory, emotion, motor control, feeding, and pain perception [15]. They act as modulators of excitatory and inhibitory neurotransmission. Moreover, CB 1 receptors are also found in peripheral tissues, playing an important role in energy balance and metabolism [16]. CB1 receptors are among the most abundant GPCRs in the mammalian CNS. Outside the brain, CB1 receptors are expressed at lower levels in a variety of peripheral tissues including fat, heart, intestine, liver, endocrine, pancreas and uterus [17]. Endocannabinoids are released from the postsynaptic neurons and act on the presynaptic CB 1 receptors (retrograde signaling) and suppress the release of the inhibitory and excitatory neurotransmitters via their inhibitory effect on calcium channels. The modulatory action of the eCBs on neuronal differentiation and survival as well as synaptic remodeling indicates the critical role of this signaling system in the development of brain circuits and information processing [18].

CB2 receptors are primarily expressed in peripheral tissues, such as liver, lung, and kidney, and are closely associated with the immune and hematopoietic system [19]. More recently, increasing evidence supports the existence of CB2 receptors in the brain, strengthening the idea of a functional significance of CB2 receptors in the central nervous system (CNS) [20,21]. CB 2 receptors are primarily found on immune cells and tissues and, when activated, can affect inflammatory and immunosuppressive activity [22]. CB2 receptors are localized in cells of the immune system and modulate the immune cell migration and the release of cytokines; within the nervous system CB2 receptors are mainly located in microglia [23]. Relatively low CB 2 receptor expression has also recently been identified in some neurons [24]. CB 1 and CB 2, have been fully characterized and cloned. However, cannabinoid compounds may also bind to other receptors, such as GPR55, peroxisome proliferator-activated receptors PPAR alpha and PPAR gamma and transient receptor potential vanilloid-1 (TRPV1) channels [22,25].

Cannabinoid receptors regulate the activation of adenylyl cyclase isozymes, protein kinase A, phosphatidylinositol 3-kinase (PI 3-K), mitogen activated protein kinase (MAPK), and nitric oxide (NO). They may also be coupled to the ion channels via the Golf protein leading to the inhibition of Ca²⁺ influx through L, N, and P/Q type calcium channels and activation of

inwardly rectifying potassium conductance [9]. Activation of CB1 receptors also inhibits L-,N- and P/Q-type voltage-activated Ca²⁺ channels and stimulates inwardly rectifying K⁺ channels, the result of which is to reduce neurotransmitter release [26].

Cannabis, Endocannabinoids and Brain

Endocannabinoids act as neurotransmitters since they are synthesized and released by neurons, are able to bind and activate membrane receptors, and are inactivated by reuptake and enzymatic degradation within the cell. However, endocannabinoids have two fundamental characteristics that differentiate them from other neurotransmitters: they act as retrograde messengers and they do not accumulate in the interior of synaptic vesicles [15].

Employing modern brain imaging technologies, such as the CAT scan, researchers have found no evidence of brain damage in human cannabis users [27], even in subjects smoking an average of nine cannabis cigarettes per day. Brain wave patterns of chronic cannabis users and non-users, produced by standard electroencephalographic (EEG) tests, cannot be distinguished by visual examination [28]. The available evidence suggests that even long-term heavy use of cannabis produces no severe or grossly debilitating impairment of cognitive function [29,30].

There are 4 major chemical classes of exogenous cannabinoid ligands that differ structurally. Classical cannabinoids include Δ^9 -THC, AM2389, cannabitol, nabilone, HU-210 and other tricyclic terpenoid derivatives bearing a benzopyran moiety. Non classical cannabinoids include CP 55,940, HU-308 and other bicyclic and tricyclic analogs of Δ^9 -THC lacking the pyran ring of classical cannabinoids. Aminoalkylindoles including WIN55,212-2, JWH-018, JWH-073, and AM1241 differ in structure, lipophilicity, and binding activity at the cannabinoid receptors in comparison with the above-mentioned classes. Many of the aminoalkylindoles are currently found in commercial SCB products. Finally, 1,5 biarylpyrazole ligands act as cannabinoid receptor antagonists, and include compounds such as rimonabant and AM251, which are both CB1-receptor selective, and SR144528, which is CB2- receptor selective.

A number of therapeutic actions of these compounds have been reported and thought to be mediated via eCBs. Unfortunately, THC-based drugs produce both therapeutic and

undesirable psychotropic actions by activating cannabinoid receptors type 1 (CB1) in the CNS. Interestingly, some other components such as cannabidiol (CBD) are devoid of the typical psychological effects. CBD constitutes up to 40% of cannabis extracts with some pharmacological effects without the undesirable psychoactive side effects [31].

In 1992, the first endogenous compound to exert activity at cannabinoid 1 receptors, arachidonylethanolamide, an N- acylethanolamine, was extracted from pig brain and named anandamide after the Sanskrit word for bliss, ananda [13]. Three years later, 2-arachidonoylglycerol, a monoacylglycerol involved as an intermediate in a variety of signalling pathways, was reported to interact with cannabinoid receptors [15]. This compound is present in the brain in higher concentrations than anandamide, but since it is also involved as an intermediate in a number of signalling pathways, the amount of 2-arachidonoyl glycerol involved in endocannabinoid signalling may be similar to that of anandamide. It is believed that 2-arachidonoylglycerol has a lower affinity, but higher efficacy for cannabinoid receptors than anandamide [32]. In addition, anandamide is by no means a specific ligand for cannabinoid receptors, and can activate other targets such as TRPV1 receptors and PPAR [33,34]

Both anandamide and 2-AG are generated on demand via phospholipid-dependent distinct pathways in response to a rise in intracellular calcium or metabotropic receptor activation [35]. Once released, they remain largely membrane-associated because of their hydrophobic nature. Clearance of eCBs relies on cellular uptake and enzymatic degradation (for anandamide through membrane-associated fatty acid amide hydrolase (FAAH) [36] while 2-AG by monoacylglycerol lipase) [37].

Cannabinoids have shown interesting and encouraging results and effects in several complicated neurodegenerative and neuropsychiatric disorders. Substantial bulk of information has been accumulated that suggests a strong potential for cannabinoid compounds that could provide neuroprotection against acute or chronic neurodegenerative disorders. Cannabinoids interact with a multitude of neurotransmitters and neuromodulators [38,39] among them acetylcholine, dopamine, γ -aminobutyric acid (GABA), histamine, serotonin, glutamate, norepinephrine, prostaglandins and opioid peptides are most important one which are implicated in pathogenesis of several neurodegenerative and neuropsychiatric disorders.

Out of various diseases cannabinoids are implicated in some of disorders where component of neuro-viability is involved.

Cannabinoids in Parkinson's Disease

Parkinson's disease (PD) is one of the common neurodegenerative disorders affecting 1% of the elderly population [40]. The exclusive hallmark feature of PD is the accumulation of α -synuclein protein, loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which leads to depletion of dopamine in the striatum [41]. Several critical advances have been made in understanding the pathways that lead to cell dysfunction and death in PD. The number of pathways which have shown to play important role in PD include neuro-inflammation, mitochondrial dysfunction, oxidative stress, kinase pathways, calcium dysregulation, protein aggregation and prion-like processes. These pathways have helped to identify molecular targets [42].

Two prominent areas involved in the control of movement, such as the globus pallidus and the substantia nigra, not only contain the highest densities of CB1 receptors [43] but also the highest levels of eCBs, specifically anandamide [44]. Their presence in these areas suggests their involvement in the regulation of motor activity. Furthermore, there is evidence that endogenous cannabinoid transmission plays a role in the manipulation of other transmitter systems within the basal ganglia by increasing GABAergic transmission, inhibiting glutamate release and affecting dopaminergic uptake. Most hyperkinetic and hypokinetic movement disorders are caused by a dysfunction of basal ganglia-thalamo-cortical loops. It has been suggested that an endogenous cannabinoid tone participates in the control of movements and therefore, the central cannabinoid system might play a role in the pathophysiology of these diseases [45].

Since CB1 receptors are highly expressed in both D1 and D2 receptor containing neurons and they antagonize D1 and D2 receptor mediated behaviors, mounting evidences have suggested the involvement of endocannabinoid system in dyskinesia [46]. This is the central motive to hypothesize CB1 receptor as a therapeutic target to regulate the imbalance of glutamatergic or GABAergic neurons in PD and dyskinesia [47]. There is also a report that eCBs and cannabinoid agonists decrease dopamine re-uptake by inhibiting dopamine transporters [48]

and hence may have applications for fine tuning the striatal neuronal network involved in dyskinesia [49].

Furthermore, augmented oxidative stress has long been linked with PD [50]. Reactive oxygen species (ROS) derived from mitochondria is involved in PD pathology as weakened mitochondrial function and increased oxidative marker. The phenolic ring moieties in cannabinoids have been found to display antioxidant activity and guard against glutamate-induced neurotoxicity in a cellular model [51].

Supplementary mechanisms related to the direct improvement of endogenous antioxidant enzymes involve the activation of the anti-oxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf-2) [52]]. In a recent report, cannabidiol was found to up-regulate the transcription of Nrf-2 in BV-2 microglial cells [53]. Cannabidiol also increased the subsequent downstream enzymes including heme oxygenase-1, glutathione S-transferase, glutathione S-transferase peroxidase, NAD (P)H:quinone oxidoreductase and glutamate-cysteine ligase, which play central role in providing defense against cytotoxic and electrophile induced oxidative stress [54].

Therapeutic effects in movement and spastic disorders could be ascribed in part to interactions with GABAergic, glutamergic and dopaminergic transmitters systems [55].

Thus development of safe, effective cannabis-based medicines targeting different mechanisms may have a significant impact in PD therapy [56].

Cannabinoids in Alzheimer's Disease

Endocannabinoid signaling has been demonstrated to modulate the main pathological processes occurring during the silent period of the neurodegenerative process, including protein misfolding, neuroinflammation, excitotoxicity, mitochondrial dysfunction, and oxidative stress. The analysis of human post-mortem samples revealed some alterations in eCBs composition and signaling in patients of Alzheimer's disease (AD), although the bestowal of such modifications in the pathophysiology of the disease remains to be elucidated [57]. Recent scientific evidences indicate that cannabinoid therapy may provide symptomatic relief to patients afflicted with AD while also moderating the progression of the disease.

During the last few years, targeting the endogenous cannabinoid system has emerged as a potential therapeutic approach to treat AD in such first stages.

In AD the activation and accumulation of microglial cells around β -Amyloid ($A\beta$) plaques has long been described and is believed to result in chronic neuroinflammation. It has been demonstrated that in microglia of AD patients, CB1 and CB2 receptor expression is significantly increased, while in basal ganglia and hippocampus neuronal CB1 receptor expression is decreased [58]. Therefore, endocannabinoid system might play an important role in AD pathogenesis [59].

THC inhibits the enzyme responsible for the aggregation of amyloid plaque — the primary marker for Alzheimer's disease—in a manner "considerably superior" to approved Alzheimer's drugs such as donepezil and tacrine [60].

In study older rats administered daily doses of WIN 55,212-2 for a period of three weeks performed significantly better than non-treated controls on a water-maze memory test. Researchers reported that rats treated with the compound experienced a 50 percent improvement in memory and a 40 to 50 percent reduction in inflammation compared to controls. [61].

Also, using mice inoculated with human $A\beta$ (1–42) peptide into the right dorsal hippocampus, Esposito et al. [62] have demonstrated anti-inflammatory and antioxidant actions of CBD. Indeed, CBD is able to attenuate a β -amyloid plaques formation modulating iNOS expression and also decreasing p38MAP kinase and NF- κ B levels. Thus, limiting propagation of neuroinflammation and oxidative stress. Also, CBD appears able to exert a beneficial effect in the amyloidogenic pathway, through a specific molecular mechanism involving peroxisome proliferator-activated receptor- γ (PPAR γ) [63].

Cannabinoids in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a fatal neurodegenerative disorder that is characterized by the selective loss of motor neurons in the spinal cord, brain stem, and motor cortex. However, recent preclinical findings indicate that cannabinoids can delay ALS progression, lending support to anecdotal reports by patients that

cannabinoids may be efficacious in moderating the disease's development and in alleviating certain ALS-related symptoms such as pain, appetite loss, depression and drooling [64].

Additional trials in animal models of ALS have shown that the administration of other naturally occurring and synthetic cannabinoids can also moderate ALS progression but not necessarily impact survival [65]. One recent study demonstrated that blocking the CB1 cannabinoid receptor did extend life span in an ALS mouse model, suggesting that cannabinoids' beneficial effects on ALS may be mediated by non-CB1 receptor mechanisms. An overwhelming amount of preclinical and clinical evidence to warrant initiating a multicenter randomized, double-blind, placebo-controlled trial of cannabis as a disease-modifying compound in ALS[66]. There is rapidly emerging evidence that the cannabinoid receptor system has the potential to reduce both excitotoxic and oxidative cell damage which plays an important role in damage of motor neurons in ALS. In a recent study, Moreno-Martet et al. [67] evaluated neuroprotective effects of Sativex (The formula for Sativex includes a 1:1 equal ratio of THC to CBD) in (G93A) transgenic mice. Sativex has proven to be effective in delaying ALS progression in the early stages of disease and in animal survival, although the efficacy was decreased during progression of disease.

Cannabinoids in Epilepsy

Epilepsy is a central nervous system disorder characterized by uncontrollable twitching of the arms or legs and/or seizures. Conventional treatment to mitigate symptoms of this disorder includes medications or sometimes surgery.

Clinicians have begun to focus specifically on the ability of cannabidiol to potentially mitigate symptoms associated with intractable pediatric epilepsy after several case reports attracted prominent attention [68] . Parents of children with severe epilepsy also report in on line surveys successful experiences with cannabidiol-enriched cannabis [69]. In 2013, the United States Food and Drug Administration granted orphan drug status to imported, pharmaceutically standardized CBD extracts for use in experimental pediatric treatment. Clinical trials assessing the safety and efficacy of the treatment in children with severe forms of the disease, such as Dravet syndrome have begun in 2014 [70].

The molecular basis for the antiepileptic action of CBD might involve are induction of $[Ca^{2+}]$, via interaction with the mitochondrial Na^{2+}/Ca^{2+} -exchanger [71]. Another phytocannabinoid that might exert antiepileptic actions is D9-THCV. This compound acts in a manner similar to “standard” CB 1 receptor antagonists to increase—in a GABA A antagonist-sensitive manner—miniature inhibitory postsynaptic currents at interneuron–Purkinje cell synapses, and to decrease Purkinje cell spike firing in the mouse cerebellum in vitro [72]. Collectively, such results suggest that D 9 -THCV acts to limit excitation via increase in GABA release, an idea that is consistent with its efficacy in an experimental model of epilepsy [73].

The anti-convulsant effect of CBD may depend at least in part on an ability to block the spread of seizure activity in the brain, possibly through suppression of post-tetanic potentiation [74].

Cannabinoids in Huntington's Disease

Huntington's disease (HD) is an autosomal dominant inheritable disorder that leads to excessive body movements and cognitive decline [75]. HD is produced by selective lesions in the cerebral cortex and in particular, the striatum. There are presently no known conventional therapies available to alleviate HD symptoms or delay HD-associated striatal degeneration. Worldwide a prevalence of 5–8/100,000 is observed, with highest frequencies in Europe and India. HD patients have longer CAG repeats in the DNA of the huntingtin gene. The neurodegenerative process is driven by neurotransmitter changes (mainly loss of GABA transmission) and focuses on basal ganglia projections [76].

Although the administration of cannabidiol in HD patients provided little symptomatic relief compared to placebo in a single clinical trial, [77] more recent preclinical data indicates that cannabinoids may possess potential to moderate the advancement of the disease and similar neurodegenerative disorders [78].

Specifically, experimental data published in the Journal of Neuroscience Research in 2011 reported that the combined administration of the plant cannabinoids THC and CBD provide neuroprotection in rat models of Huntington's Disease. Authors reported, that combination of THC and CBD-enriched botanical extracts protected striatal neurons against ... toxicity.” By

contrast, the administration of individual, selective synthetic cannabinoid agonists did not produce similarly favorable outcomes.

Investigators concluded, "In our opinion, these data provide sufficient preclinical evidence to justify a clinical evaluation of [one to one THC to CBD] cannabis-based medicine ... as a neuroprotective agent capable of delaying disease progression in patients affected by HD, a disorder that is currently poorly managed in the clinic, prompting an urgent need for clinical trials with agents showing positive results in preclinical studies." [79].

About neuroprotective effects of cannabinoid compounds in experimental HD, three mechanism of neuroprotection have been hypothesized: CB1-dependent, CB2-dependent and CB1-/CB2-independent. The first hypothesis is corroborated by the fact that CB1 receptor is early down-regulated in ongoing disease, even in asymptomatic phases, so that CB1 receptor loss could have a role in HD pathogenesis [78].

The second hypothesis born from the evidence given by CB2 receptor localization. It was observed that it is poorly expressed in striatal parenchima under healthy condition while it is progressively over-expressed during degenerative events leading to HD. In this circumstance, CB2-activation preserve striatal neurons from inflammatory insults produced by reactive microglial cells, maybe through the release of neurotrophins, anti-inflammatory cytokines and metabolic substrates [80]. Finally, the CB1-/CB2-independent pathway, involved in the neuroprotection during experimental models of HD seems related to some cannabinoids with antioxidant properties, such as Δ^9 -THC and CBD, since their particular phenolic structures could exert a scavenger action against ROS. Parallel, there is also the assumption of an intracellular signal regulation via the expression control of antioxidant enzymes of phase II (i.e., Nrf-2/ARE signaling) [78]. On this framework, there are conflicting data and the literature about it is very wide.

Cannabinoids in Multiple Sclerosis

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system that causes inflammation, muscular weakness and a loss of motor coordination. Over time, MS patients typically become permanently disabled and, in some cases, the disease can be fatal. According to the US National Multiple Sclerosis Society, about 200 people are diagnosed

every week with the disease -- often striking those 20 to 40 years of age. Clinical and anecdotal reports of cannabinoids' ability to reduce MS-related symptoms such as pain, spasticity, depression, fatigue, and incontinence are plentiful in the scientific literature [81]. Investigators have also reported that the administration of oral THC can boost immune function in patients with MS. These results suggest pro-inflammatory disease-modifying potential of cannabinoids for MS [82].

Although cannabinoids have been used mainly to alleviate symptoms of multiple sclerosis, there is also experimental evidence to suggest that they may be immunomodulatory. Cannabinoids are believed to be antiinflammatory, mainly through activation of the CB2 receptors, which is principally located peripherally, especially on leucocytes. CB2 activation may be associated with a Th1 to Th2 shift. Consequently, there is some evidence that cannabinoids may be therapeutically useful in treating multiple sclerosis, which is generally believed to be an autoimmune condition [83].

To better understand the etiopathogenesis of MS and to find new therapeutic strategies, researchers use some models. The most used is the experimental autoimmune encephalomyelitis (EAE), which mimics the main features of human MS. Using synthetic cannabinoid agonists of CB1 and CB2 receptors, such as dexamabinol (HU210, (–)-1,1-dimethylheptyl analog of 11-hydroxy- Δ^8 -THC) and WIN 55,212-2 in EAE mice, it was demonstrated that they promote oligodendrocytes survival via CB1 and CB2 receptor-mediated effects, potentially reducing demyelination and apoptosis [84,85]. Also, these cannabinoids were able to reduce inflammation, probably by suppression of TNF- α and IL-1 β and enhances the release of antiinflammatory cytokines such as IL-10 in brain and peripheral blood [86].

Conclusion

The diverse and almost universal presence of cannabinoid receptors makes them the most versatile and encouraging therapeutic targets at present. The molecular mechanisms underlying the neuroprotectant properties of cannabinoids are quite diverse and frequently, complementary. They include some events not mediated by cannabinoid receptors [i.e. N-methyl- D -aspartate (NMDA) receptor antagonism, antioxidant properties and others that are definitively mediated by either CB1 or CB2 receptors including their capability [87] to reduce

processes such as glutamate release, calcium influx and/or inflammation [88], to stimulate γ -aminobutyric acid (GABA) action and [89] to improve blood supply to the injured brain [90]. Other additional processes also influenced by cannabinoids, such as improvement of glucose utilization, or alternatively the production of ketone bodies – which, produced by glial cells, may replace glucose as the major source of neuronal energy metabolism in ischemia [91] might be also considered.

In summary, the endocannabinoid system is an age old but recently understood regulatory physiological system that holds great promise for improvements in human quality of life. The complicated pathological complications discussed in the present review speaks a volumes about the possibility of eCBs as a viable and potential therapeutic target that if understood, manipulated and researched, holds a great promise and may be pathbreaking in the discovery of treatment of these complications. In the past, it has not received the attention that it deserves in physician and patient education, nor in research expenditures. Current research scenario although encouraging yet lot more is required to be done to bring these potential candidates to the market.

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