The Multiplicity of Action of Cannabinoids: Implications for Treating Neurodegeneration

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SUMMARY

The cannabinoid (CB) system is widespread in the central nervous system and is crucial for controlling a range of neurophysiological processes such as pain, appetite, and cognition. The endogenous CB molecules, anandamide, and 2-arachidonoyl glycerol, interact with the G-protein coupled CB receptors, CB₁ and CB₂. These receptors are also targets for the phytocannabinoids isolated from the cannabis plant and synthetic CB receptor ligands. The CB system is emerging as a key regulator of neuronal cell fate and is capable of conferring neuroprotection by the direct engagement of prosurvival pathways and the control of neurogenesis. Many neurological conditions feature a neurodegenerative component that is associated with excitotoxicity, oxidative stress, and neuroinflammation, and certain CB molecules have been demonstrated to inhibit these events to halt the progression of neurodegeneration. Such properties are attractive in the development of new strategies to treat neurodegenerative conditions of diverse etiology, such as Alzheimer's disease, multiple sclerosis, and cerebral ischemia. This article will discuss the experimental and clinical evidence supporting a potential role for CB-based therapies in the treatment of certain neurological diseases that feature a neurodegenerative component.

Introduction

The use of the *Cannabis sativa* plant as a medicinal preparation is referred to in ancient Asian pharmacopoeia but it was the Irishman Sir William B. O'Shaughnessy who conducted the first series of formal experiments into the potential medicinal use of *Cannabis sativa* and the publication of his findings in 1842 brought the use of cannabis for the treatment of pain, spasticity, and rheumatism to clinicians throughout Europe [1]. However, difficulties in obtaining consistent preparations and the availability of more effective drugs marginalized the medicinal use of cannabis. A renewed revival in the cannabinoid (CB) field occurred in the 1960s upon the identification and synthesis of the active psychotropic component of cannabis, Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) [2]. In addition to the phytocannabinoid molecules, such as Δ^9 -THC and cannabidiol (CBD), that have been extracted from *Cannabis sativa*, recent years have witnessed a marked advance in endocannabinoid biology that has propelled it to the forefront of biomedical research. The CB system is now recognized as an important physiological modulator of various central nervous system processes including pain [3,4], appetite [5,6], motor function [7,8], synaptic plasticity [9], neuroinflammation [10,11], and neural cell fate [12–14]. The current therapeutic applications

of CB-based medications, such as Dronabinol and Nabilone, include the treatment of anorexia and emesis [15]. The oromucosal spray, Sativex, which contains the phytocannabinoids, Δ^9 -THC, and cannabidiol (Figure 1), is effective in treating the spasticity and pain experienced by patients with multiple sclerosis (MS) [16], and Δ^9 -THC has been demonstrated to exert antitumoral activity in clinical studies [17]. There is also a growing interest in developing a CB-based approach to treat other disorders, which are associated with neuroinflammation and neurodegeneration. The development of such therapeutic strategies will rely on a more detailed understanding of the role of the CB system in the disease pathology in order to exploit that knowledge and circumvent the disease process.

The CB System

The endogenous CB signaling system in the brain is composed of the endocannabinoid molecules, 2-arachidonoyl glycerol (2-AG), and anandamide (AEA), which interact with the G-protein-coupled CB receptors, CB₁ and CB₂. The CB₁ receptor is abundantly expressed in the central nervous system (CNS) [18] while expression of the CB₂ receptor is mainly associated with the peripheral immune system. CB₂ receptor expression has

Figure 1 Chemical structure of cannabinoids. The chemical structure of the phytocannabinoids **(A)** Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and **(B)** cannabidiol; the endocannabinoids **(C)** anandamide and **(D)** 2-arachidonoyl glycerol (2-AG); the synthetic cannabinoids **(E)** HU-210 and **(F)** HU-211.

been observed in the CNS, albeit confined to neurones within the brainstem [19] and on microglia during neuroinflammation [20]. Endocannabinoids are synthesized on demand and travel in a retrograde manner across the postsynaptic membrane to activate presynaptic CB₁ receptors resulting in the depression of neurotransmitter release. Endocannabinoid levels are controlled by the action of two enzymes: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) which degrade AEA and 2-AG, respectively. Endocannabinoid pharmacology is constantly evolving with new cannabinimetic ligands [21] and putative CB receptors [22] being proposed. For example, novel orphan receptors such as GPR55 [23,24] and GPR18 [25] are sensitive to CBs and have been demonstrated to regulate the recruitment and activation of microglia and neuropathic pain. The TRPV1 receptor is also regulated by CBs and is involved in pain and inflammation [26]. These proteins may represent interesting targets for drug development to treat neurological conditions, which are associated with neuroinflammation and neuropathic pain.

Activation of the canonical CB receptor inhibits adenylate cyclase resulting in a decreased level of the second messenger cyclic adenosine monophosphate (cAMP). This second messenger regulates a number of intracellular signaling cascades essential to a number of cellular functions such as the regulation of cell fate [27]. CB receptor activation also couples to ion channel regulation such as inhibition of voltage-dependant Ca²⁺ channels and activation of inwardly rectifying K⁺ channels [28–30]. The modulation of voltage-dependent ion channels is thought to underlie

CB-induced depression of excitatory neurotransmission [31]. Currently, the potential neuroprotective effects of CBs in acute brain injury such as stroke and in chronic neurodegenerative diseases such as Alzheimer's disease (AD) have been attributed, in part, to their proclivity to reduce neuronal damaging events such as excessive glutamatergic transmission, prolonged Ca²⁺ influx, and oxidative stress [32]. There is now abundant experimental and clinical evidence demonstrating that the endocannabinoid system is altered in common neurodegenerative conditions and that CB molecules can confer neuroprotection through an array of mechanisms. The CB system is therefore an opportunistic target for therapeutic exploitation, especially for those diseases with a neurodegenerative component for which effective treatment is lacking.

CBs and AD

AD is an age-related neurodegenerative disease and with the demographic shift toward an increasingly aged population, an increase in the prevalence of AD is to be expected. AD is defined by the progressive deterioration of cognition and memory and is the most common form of dementia among the elderly [33]. The pathological hallmarks of AD include neurofibrillary tangles, amyloid-beta (A β) plaques, and synaptic degeneration resulting in the preferential neuronal loss in the hippocampus and surrounding areas of the cerebral cortex. This disease is also characterized by the prolonged activation of microglia in plaque-bearing

areas which give rise to an environment profuse in inflammation [34,35] and oxidative stress [36].

The high density of CB₁ receptors in the hippocampus and cerebral cortex [37] was an early indication that the endocannabinoid system might play a role in AD pathogenesis. In the AD brain, microglial CB₁ and CB₂ receptor expression is significantly increased, principally in plaque-bearing areas [38], while neuronal CB₁ receptor expression is reduced, particularly in the hippocampus and basal ganglia [38,39]. In the AD brain CB receptors are nitrosylated [38], thus affecting G protein coupling and rendering the receptors functionally impaired. An upregulation of the endocannabinoid-metabolizing enzyme, FAAH, on plaque-associated astrocytes has also been reported in the AD brain [40]. Given that AEA and, at least partially 2-AG, are metabolized by FAAH to produce arachidonic acid, the increased presence of FAAH on astrocytes links the endocannabinoid system to the destructive inflammatory process that accompanies AD. These AD-related alterations provide evidence that components of the endocannabinoid system may be critically intertwined with the progression of AD pathogenesis.

The preclinical data have highlighted some beneficial effects of CBs in inhibiting certain neuropathological features of relevance to AD [38]. Van Der Stelt and colleagues demonstrated that in an animal model of AD-like pathology, the A β -induced hippocampal degeneration, gliosis, and cognitive decline result in a concomitant increase in 2-AG [41]. The conclusions drawn from that study proposed that endocannabinoid tone may be enhanced in the diseased brain as a protective mechanism against A β -induced damage. Several studies have supported neuroprotective attributes of the endocannabinoid system against a wide range of insults, including those that play prominent roles in the AD brain, for example, excitotoxicity, inflammation, and oxidative stress. These underlying pathologies are the target of many current AD therapies, though none of the drugs used in AD patients have had any curative or lasting effect. With regards to the endocannabinoid system, its therapeutic attraction is based on the fact that it has widespread effects, in some cases mimicking the results of current drugs approved by the Food and Drug Administration (FDA), and in most cases alleviating symptoms with superior potency. For example, the drug memantine, a noncompetitive low affinity antagonist of the N-methyl D-aspartate (NMDA) receptor, acts to reduce Ca²⁺ influx and limit excitotoxicity. In a similar fashion, the synthetic CB, HU-211 (Dexanabinol) acts as a stereoselective inhibitor of NMDA receptors, and thus protects cells from NMDA-induced neurotoxicity [42,43]. Endocannabinoid-mediated neuroprotection against excitotoxicity is a widely established phenomenon, and is therapeutically beneficial given that it can be achieved by a number of different mechanisms, including inhibition of presynaptic glutamate release [44], blockage of voltage-dependent N-, P/Q-, and L-type calcium channels [45–47], and inhibition of Ca²⁺ release from ryanodine sensitive stores [48]. Also, akin to the effect of memantine, CB₁ receptor stimulation increases levels of brain-derived neurotrophic factor (BDNF) [49], a neurotrophin required for adult neurogenesis [50], that is decreased in the AD brain [51,52].

A β toxicity triggers neuroinflammatory processes, which are closely associated with the neuropathological and cognitive symptoms of AD [53]. For this reason antiinflammatory drugs, such as

nonsteroidal antiinflammatory drugs, are thought to reduce the incidence of AD [54]. Ehrhart and colleagues have reported that stimulation of CB₂ receptors suppresses microglial activation and subsequent production of TNF- α and nitric oxide [55]. Similarly, in an animal model of AD-like pathology, administration of the synthetic CB, WIN55,212-2, prevents A β -induced cognitive impairment and neuronal loss [38] while *in vitro* analysis demonstrated that the CB₁ and CB₂ receptor agonist, HU-210, prevents A β -induced increases in microglia activation and TNF- α release [38]. Thus, the upregulation of microglial CB₂ receptors observed in the AD brain [38,40] may in fact be a neuroprotective response by the endocannabinoid system to limit neuroinflammation. CB₁ receptors, which are increased on glial cells in the AD brain [38], play a role in the modulation of several inflammatory cytokines [56].

The majority of drugs currently in use for the treatment of AD, such as tacrine (Cognex), act as acetylcholine esterase (AChE) inhibitors which prevent or slow the breakdown of ACh, a neurotransmitter that is reduced in the AD brain. Eubanks and colleagues have demonstrated that the phytocannabinoid, Δ^9 -THC, has the proclivity to competitively inhibit AChE, thus increasing ACh levels [57]. Moreover, Δ^9 -THC is capable of preventing A β peptide aggregation, which may hinder plaque formation [57]. These represent additional aspects of CB action that may be beneficial in AD.

The nonpsychoactive phytocannabinoid, CBD, has several features that could be exploited for the treatment of AD, including the prevention of glutamate-induced excitotoxicity [58], reduction of proinflammatory mediators [59], and the ability to scavenge reactive oxygen species (ROS) and reduce lipid peroxidation [60]. CBD, by reducing the phosphorylation of glycogen synthase kinase-3 β , inhibits tau protein hyperphosphorylation, an additional neuropathological feature of AD [61].

Thus, manipulation of the CB system has diverse and effective consequences against a wide range of pathologies prominent in the AD brain. While the studies discussed here focus on recent preclinical data, the clinical data, albeit limited to a small number of studies, have also provided positive feedback on the usefulness of CB-based drugs in AD. Dronabinol, an oil-based solution of Δ^9 -THC, is an antiemetic and appetite-stimulator in AD patients [62], while Δ^9 -THC also reduces the agitation that is common in patients with severe AD [63]. Despite these promising outcomes, the usefulness of CB-based drugs for the treatment of AD awaits the results of rigorous clinical trials and the identification of novel molecular neurobiological affects of CBs [64].

CBs in Multiple Sclerosis

MS is an autoimmune disease that promotes demyelination of neurones and subsequent aberrant neuronal firing that contributes to spasticity and neuropathic pain. MS patients have significant neuroinflammation [65] and the disease is associated with excitotoxicity [66] and chronic neurodegeneration [67]. These pathological features of MS share similarities with other neurodegenerative conditions including AD and cerebral ischemia; disorders which may obtain benefit from compounds that target the endocannabinoid system. Indeed, there is evidence that MS patients

gain symptomatic relief from cannabis extracts [68]. Furthermore, Sativex, an oral-mucosal spray containing a 1:1 ratio of Δ^9 -THC and CBD, has antispasmodic and analgesic properties with efficacy in MS patients [69]. The neuropathic pain associated with MS is reduced by dronabinol, an oral preparation of the Δ^9 -THC analog [16,70] and a *meta*-analysis has revealed that CB-based medications are superior to placebo in the treatment of MS-related neuropathic pain [71]. The ability to modify pain may be attributed to a CB-mediated regulation of supraspinal GABAergic and glutamatergic neurones [72]. Such analgesic properties of CBs represent an additional feature of CB-based drugs that offer benefit to patients with MS.

The mechanisms underlying the efficacy of CB-based treatments in MS may be addressed in the experimental autoimmune encephalomyelitis (EAE) animal model, which displays demyelination and neurological dysfunction consistent with the human disease [73]. The neurodegeneration associated with EAE is a complex series of events initiated by neuroinflammation and the associated infiltration of immune cells into the CNS, followed by a dysfunction of neural activity and neuronal loss [74]. Changes in the endocannabinoid system are a feature of EAE, as well as human MS. In EAE, brain endocannabinoid levels are downregulated [75], which may alter the immune-regulatory function of the endocannabinoid system, while plasma endocannabinoid levels are increased in MS patients [76]. CB receptors are distributed in human immune cells including macrophages, lymphocytes, and natural killer (NK) cells [77] and mediate the effects of CBs on the activation, differentiation, and migration of these cells. Thus, the synthetic CB, HU-211, reduces clinical disease severity in an EAE model in parallel with a reduction in inflammatory cell infiltration [78]. The CB₁ and CB₂ receptor agonist, WIN55,212-2, reduces the differentiation of T cells into Th1 effector cells, thereby reducing the production of inflammatory mediators and disease severity [79]. The CB₂ receptor is notable for its role in the regulation of inflammation associated with EAE with CB₂ deficiency associated with a more pronounced disease, increased mononuclear cell infiltration, and enhanced production of proinflammatory cytokines [80]. In MS patients increased CB₂ immunoreactivity has been observed in the spinal cord [81], which may represent an attempt to reduce the neuroinflammation occurring during the disease.

In CB₁ receptor-deficient animals induced with EAE the development of neurodegeneration is more rapid [82] indicating an important role for CB₁ in the provision of neuroprotection, which may be via an inhibition of excitotoxicity and/or oxidative stress [83,84]. The neurodegenerative component of EAE has been demonstrated to involve glutamate-induced excitotoxicity, which has been verified using glutamate receptor antagonists [85]. However, adverse effects of glutamate receptor antagonists have been reported in humans [86] and this has prompted investigation into alternative approaches to reduced excitotoxicity. In this regard, upregulation of endocannabinoid tone using UCM707, an inhibitor of endocannabinoid uptake, protects neurones from excitotoxicity in parallel with a therapeutic effect in a mouse model of MS [87]. This approach may therefore augment CB activity at sites of injury without the necessity for direct CB₁ receptor activation, thereby reducing possible psychoactive side effects.

The CB System in Cerebral Ischemia

Cerebral ischemia is an acute neurodegenerative insult that may arise as a consequence of stroke, trauma, or cardiac arrest. There are mounting *in vitro* and *in vivo* data to suggest that CBs have neuroprotective effects following brain injury [88]. Indeed, the formation of endocannabinoids is enhanced after brain injury and there is evidence that these compounds reduce the secondary damage incurred after the initial injury [89–91]. Studies have shown increased AEA levels following controlled interruptions of blood flow *in vivo* [92] due to a decrease in AEA catabolism since FAAH expression and activity were found to be decreased [93]. Furthermore, AEA levels are significantly and preferentially (above other N-acyl ethanolamines) increased in middle cerebral artery occlusion (MCAO) ischemic models that include a reperfusion period compared to occlusion only [93,94]. These data have been observed in one human study where increased AEA levels were found in a patient with a hemispheric stroke [95]. Although 2-AG levels are increased following physical trauma such as concussive head injury and seizures [90,96], a reduction in 2-AG levels were observed in mice following MCAO [94,97]. Studies have demonstrated that reperfusion injury is associated with a rapid increase in CB₁ receptor expression on resident cells [98,99] while increased CB₂ receptor expression is seen on astrocytes, microglia, and infiltrating macrophages in the ischemic penumbra following transient MCAO [100]. Treatment with CB receptor agonists WIN55,212-2 and CP 55940 prior and up to 30 min postischemic insult prevents neuronal death and reduces infarct volumes in a CB₁-dependant manner [101]. These results have been supported in experiments using CB₁ receptor knockout mice which show increased mortality following MCOA, thus reinforcing a role for the CB₁ receptor in preventing ischemia-induced neuronal loss [102]. Furthermore, the nonpsychoactive phytocannabinoid, CBD, results in the dramatic reversal of brain damage in hypoxic-ischemic newborn piglets, in addition to other extracerebral benefits [103]. The control of the cerebral vasculature is an important consideration in ischemia/reperfusion injury and in this regard the CB₁ receptor antagonist, SR141716A, in combination with the CB₂ receptor agonist, O-1966, has been found to increase blood flow to the brain in an animal model of stroke [104]. The proclivity of O-1966 to attenuate neuroinflammation represents an additional beneficial effect of this molecule in cerebral ischemia [104]. In experiments where endocannabinoid catabolism is inhibited a neuroprotective effect against ischemia was observed [105]. However, the upregulation of the endocannabinoid system can manifest a dual response since some studies show that inhibition of the CB₁ receptor is neuroprotective against ischemia [106,107] while other studies report an exacerbation of brain injury following activation of the CB system [108].

Dexanabinol (HU-211), the synthetic noncompetitive NMDA antagonist, exerts long-term cerebroprotective effects in models of focal cerebral ischemia [109,110] and combines its NMDA receptor antagonistic activity with free radical-scavenging abilities to confer neuroprotection [111]. This multiplicity of action supports the potential use of dexanabinol in conditions such as stroke where oxidative stress and excitotoxicity feature. Both CBD and Δ^9 -THC are neuroprotective following MCAO [112]. The effects of CBD have been attributed to its potent antioxidant activity

and, notably, tolerance does not develop to the neuroprotective actions of CBD. Also, since the actions of CBD are CB₁ receptor-independent, and thus devoid of psychoactivity, CBD is an attractive therapeutic possibility for the treatment of cerebrovascular disorders. CBD is also a ligand at GPR55 [113] and an inhibitor of the nucleoside transporter resulting in an enhancement of adenosine-mediated antiinflammatory effects [114]. Such non-CB receptor targets and subsequent antiinflammatory actions may also be of potential benefit in the future. Although no consensus has been reached as to the exact nature of neuroprotective mechanism of endocannabinoids in ischemia, the application of CBs to the treatment of brain injury and stroke is extremely relevant and deserving of further investigations.

Parkinson's Disease

Parkinson's disease (PD) is a degenerative condition affecting dopaminergic neurotransmission in the basal ganglia resulting in hypokinesia. The disease may be precipitated by environmental factors such as pesticides and neuroleptic drugs or mutations in genes encoding several proteins (e.g., α -synuclein, parkin, PINK1). The disease is associated with the intracellular accumulation of misfolded proteins and Lewy bodies which lead to neurodegeneration. Oxidative stress, excitotoxicity, and neuroinflammation are additional features of the disease, which share commonality with other neurodegenerative conditions. Current therapeutic strategies aim to augment dopaminergic transmission in the basal ganglia through administration of dopamine precursors such as L-DOPA, however in a proportion of patients the efficacy of the treatment declines over time. The endocannabinoid system may serve as a useful target for the treatment of motor dysfunction since the endocannabinoid system is expressed in the basal ganglia where it regulates neurotransmitter release [115] and motor activity [116]. In PD patients endocannabinoid levels in the cerebrospinal fluid are increased [117] and basal ganglia CB₁ receptor mRNA is upregulated in a rodent model of PD. Despite the upregulation of the CB system that is observed at intermediate-late stages of the disease process, in the presymptomatic phase of the disease CB₁ receptors are desensitized [118] which may render the basal ganglia more vulnerable to the cytotoxic milieu of the PD brain and promote excitotoxicity due to the loss of CB₁-mediated presynaptic inhibition of glutamate release [119].

Since CB receptor agonists promote hypokinesia [116], CB₁ receptor antagonists are a preferable option for the treatment of PD in order to counter the consequences of an upregulation of the CB system that occurs at the advanced stage of the disease. Pre-clinical studies have demonstrated that the CB₁ receptor antagonist, rimonabant, reduces the hypokinesia in an animal model of PD in a manner that is particularly effective at low dose [120]. Notwithstanding the hypokinetic profile of CB agonists, which is undesirable in the treatment of PD, certain CB agonists have neuroprotective properties which would halt the neurodegenerative aspect to this disease. Δ^9 -THC and CBD have been found to protect nigrostriatal dopaminergic neurones from the neurotoxin 6-hydroxydopamine via a nonreceptor, antioxidant action [121]. The CB-based medicine, Sativex, which contains both Δ^9 -THC and

CBD, may therefore be an interesting candidate for future clinical investigation in PD.

CBs and Brain Repair: Implications for Huntington's Disease

Regardless of the diverse etiology, there are common features of neurodegenerative disorders, such as neuroinflammation and oxidative stress, which contribute to the neuronal cell loss. While CB-based drugs can target these processes to confer neuroprotection, the ability to directly evoke pathways associated with cell survival is another interesting facet of CB action. Neuronal survival is dependent upon the local concentration gradients of growth factors and neuronal viability may be enhanced by augmenting the availability of neurotrophic factors. BDNF is crucial for sustaining neuronal survival and neuronal sensitivity to BDNF is enhanced by the endocannabinoid, 2-AG, which may represent an important regulator of neural repair [122]. Also, BDNF gene transcription is upregulated by CB₁ receptor activation in striatal excitotoxic lesions to rescue striatal neurones from degeneration [123]. That study may be of particular relevance to Huntington's disease where BDNF has been implicated in the pathophysiology of that disease. However, in Huntington's disease there is a reduction in CB₁ receptor expression and since CB₁ agonists can trigger undesirable psychoactive effects, the search for alternative CB targets for neurodegenerative conditions is gaining momentum. In this regard, the CB₂ receptor may be an interesting candidate since the CB₂ receptor activation is neuroprotective in models of Huntington's disease by virtue of its ability to reduce microglial activation [124]. An additional physiological process that is crucial for sustaining neural function is the formation of new neurones by neurogenesis and in neurodegenerative conditions such as AD and Huntington's disease neurogenesis is impaired [125,126]. The age-related reduction in neurogenesis is reversed by the CB₁ and CB₂ agonist, WIN55,212-2 [10] and the CB₁ receptor has been implicated in neural precursor proliferation and neurogenesis in a model of excitotoxicity [127]. The CB₂ receptor has also been identified as a physiological regulator of neural progenitor cell proliferation [128]. CB₂ receptor agonists and the pharmacological inhibition of FAAH can stimulate neurogenesis in the adult mouse and since this proneurogenic effect was also seen in aged animals, it has been proposed that the CB system may help to counteract the decline in adult neurogenesis that occurs in aging [129]. Targeting this pathway in the future may help to replenish neurones in neurodegenerative diseases.

Both acute and chronic neurodegeneration occurs upon a platform of neuroinflammation and, as such, the antiinflammatory aspect of CB action may be useful for the treatment of a number of brain disorders. In terms of the antiinflammatory mechanisms of action, Δ^9 -THC and CBD inhibit activation of the inflammatory transcription factors, NF κ B and STAT1 in a CB receptor-independent manner [130]. The upregulation of antiinflammatory cytokines, such as IL-10, is induced by AEA via engagement of CB₂ receptor signaling [131]. Since IL-10 is a negative regulator of microglial activation, the pharmacological modulation of AEA uptake and degradation may prove useful for the treatment of diseases with a neuroinflammatory component.

Figure 2 Summary of cannabinoid targets that are relevant to the treatment of neurodegenerative disease. Cannabinoids can limit neurodegenerative processes via a direct influence on neurones to reduce glutamate release and subsequent excitotoxicity, as well as inducing neurotrophic factors and stimulating neurogenesis. Disease-specific pathology such as amyloid precursor protein (APP) processing and tau hyperphosphorylation

in Alzheimer's disease is reduced by cannabinoids. Microglial activation and the production of proinflammatory cytokines is attenuated by cannabinoids and their antioxidant properties also contribute to improving neuronal viability. CBD, cannabidiol; eCBs, endocannabinoids; ROS, reactive oxygen species.

Outlook

The CB₁ receptor is likely to have limited usefulness as a drug target due to its psychoactive activity, together with the fact that the CB₁ receptor is downregulated in certain neurodegenerative states and the important physiological role that CB₁ plays in processes such as appetite, pain, and cognition. Alternative targets that may be more fruitful include the development of CB₂ receptor ligands since this receptor is crucial in regulating neural inflammation and neurogenesis, as well as being devoid of psychoactive side effects. Also, CBD, the nonpsychotropic component of cannabis, is considered to be a promising drug for neurodegenerative disorders due to its antiinflammatory and antioxidant profile [132]. Alternatively, neuroprotection may be achieved by enhancing endogenous CB tone or via allosteric modulation of CB receptors [133,134].

In summary, the CB system exerts multiplicity of actions, which may be harnessed in the development of new therapeutic approaches to treat neurodegenerative conditions (Figure 2). The antiinflammatory, antioxidant, and proneurogenic properties of the CBs are characteristics that may be relevant to the treatment of a number of neurodegenerative conditions. The existing challenges are to develop drugs that lack psychoactive side effects and, in that regard, targeting the nonpsychotropic CB₂ receptor offers particular promise.

Conflict of Interest

The authors have no conflict of interest.

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