Endocannabinoid System in Neurodegenerative Diseases

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The altered expression of endocannabinoids and cannabinoid receptors has been observed in neurodegenerative conditions. Accordingly, it has been assumed that endocannabinoid-degradative enzymes, CB1 and CB2 receptors, and the modulation of the activity of endogenous cannabinoids represent valuable therapeutic targets in neurodegenerative diseases, as well as in other diseases such as epilepsy, stroke, inflammation, multiple sclerosis, traumatic brain injuries and psychiatric illnesses.

cannabinoids neuroprotection redox-sensitive signaling pathways

1. Introduction

Cannabis is one of the first plants that was cultivated for human use. The earliest writings about the medical uses of *Cannabis* can be found in Chinese pharmacopoeias as early as second century BCE [1]. In 1980, epidemiological studies described the potential anticonvulsant effects of marijuana extracts. Since then, a great amount of research has been conducted to better reveal the pharmacological effects of natural and synthetic cannabinoids. These studies demonstrated that they could exert many beneficial health effects. The neuroprotective potential of cannabinoids has been investigated in a wide range of brain-related diagnoses. These include brain tumors, neurodegeneration-related diseases, multiple sclerosis, neuropathic pain, and some specific forms of childhood seizures [2][3][4]. The therapeutic potential of cannabinoids is also being considered for various psychiatric diseases such as schizophrenia, anxiety, autism, addiction, and depression [5][6].

The Endocannabinoid System

The lipid endocannabinoid system (ECS) consists of G protein-coupled cannabinoid receptors (GPCRs) CB1 and CB2, endogenous cannabinoids (endocannabinoids), and enzymes involved in their synthesis and metabolism [7][8][9]. Both types of cannabinoid receptors inhibit adenylyl cyclase and protein kinase A (PKA) and modulate the activation of mitogen-activated protein kinases (MAPKs) (including extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38 kinases) via $G_{i/o}$ signaling [10]. It is considered that CB1 and CB2 receptors regulate various aspects of neuronal physiology, acting independently and/or cooperatively [7][11].

Besides CB1 and CB2 receptors, additional receptors are involved in the biological effects of cannabinoids with signaling distinct from the CB1 and CB2 receptors, including the nuclear peroxisome proliferator-activated

receptors (PPARs), transient receptor potential vanilloid type 1 (TRPV1) channel, G protein-coupled receptor 55 (GPR55) and G protein-coupled receptor 119 (GPR119), metabotropic glutamate receptors, μ- and δ-opioid receptors, and serotonin 1A receptor (5HT1A) [10][12][13][14][15][16][17][18][19][20].

The best-characterized endocannabinoids that act via the CB1 and CB2 receptors are eicosanoids *N*-arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG). These small lipid transmitters are synthesized on demand from the membrane phospholipids that contain arachidonic acid. They are produced by specific lipases as a response to increased intracellular Ca^{2+} levels, and it is generally considered that they are immediately released, without storage in the vesicles [9][10][21]. Both display a higher relative intrinsic affinity for CB1 receptors than for CB2 receptors. 2-AG is a full agonist, whereas anandamide behaves as a partial agonist of the two cannabinoid receptors [8][10][21][22].

The inactivation of cannabinoids includes cellular uptake and hydrolysis. Anandamide is degraded by fatty acid amide hydrolase (FAAH) to arachidonic acid and glycerol. Some other enzymes, such as cyclooxygenase-2 (COX2) and lipoxygenases, that are upregulated during neuroinflammation are also able to metabolize anandamide, some of them providing derivatives that may promote endocannabinoid-like effects [7][8]. The COX-2 metabolism of anandamide generates anandamide-derived prostaglandins (prostaglandin-ethanolamides or PGs-EA) that are relatively poor activators of CB1 and CB2 receptors. 12- or 15-lipoxygenases convert anandamide into 12(S)-hydroxyeicosatetraenoic acid-ethanolamine (HETE)-EA and 15(S)-HETE-EA that target CB1 receptors [23][24][25]. Several cytochrome P450 isoforms also metabolize anandamide to hydroxylated and epoxygenated metabolites. The oxidation of anandamide by human cytochrome P450 enzymes yields metabolites such as 20-hydroxyeicosatetraenoic acid ethanolamide and the 5,6-, 8,9-, 11,12-, and 14,15-epoxyeicosatrienoic acid ethanolamides. Pharmacological studies have shown that 20-hydroxyeicosatetraenoic acid ethanolamide (20-HETE-EA) and 14,15-epoxyeicosatetraenoic acid ethanolamide (14,15-EET-EA) bind to rat CB1 receptors [26], whereas the 5,6-epoxide of anandamide, 5,6-epoxyeicosatrienoic acid ethanolamide (5,6-EET-EA), is a potent and selective agonist of CB2 receptors [27]. Diacylglycerol (DAG), the product of phospholipase C (PLC), is the main precursor for 2-AG synthesis. DAG lipase (DAGL) catalyzes the hydrolysis of DAG and forms 2-AG, which is further converted into arachidonic acid and glycerol, mostly by the activity of the serine hydrolase monoacylglycerol lipase (MAGL). 2-AG may also be a substrate for COX and lipoxygenases.

In the central nervous system (CNS), endocannabinoids can be produced and degraded by both neurons and glia [9][28][29][30][31]. It has been shown that reactive microglia secrete hydrophobic anandamide in the form of extracellular vesicles, i.e., microvesicles, through the outward blebbing of the microglial plasma membrane or as exosomes formed in the endosomal system. In microvesicles, anandamide is carried on their surface and is able to stimulate CB1 receptors in target neurons [32][33]. On the other hand, adiposomes, the lipid droplets, represent an intracellular reservoir for the accumulation of taken up anandamide. These lipid droplets are spatially associated with anandamide hydrolase, and adiposome size correlates with the intensity of anandamide catabolism. Although these findings may challenge the dogma that anandamide is produced on demand, the biological context of anandamide storage needs to be addressed in further studies [34][35].

CB1 receptors are the main targets of endocannabinoids and are the most abundant GPCRs in the brain. They are primarily located at presynaptic terminals. The net result of endogenous cannabinoid signaling after the activation of presynaptic CB1 receptors is the inhibition of excitatory and inhibitory neurotransmission through the inhibition of neurotransmitter release (GABA, glutamate, dopamine, norepinephrine, serotonin, and acetylcholine) [7][36][37]. CB1 receptors located at post-synaptic sites regulate the activity of specific ion channels, of which ionotropic glutamate N-methyl-D-aspartate (NMDA) receptors have received particular attention in the context of cannabinoid-mediated and antioxidative-based neuroprotection [8][38].

CB1 receptors are abundantly expressed in most brain areas, including the prefrontal cortex, cingulate gyrus, CA3 region and dentate gyrus in the hippocampus, basal ganglia, hypothalamus, amygdala, and cerebellum, implying the important role of the ECS in cognition, motoric functions, and emotions [4][8][9][39][40]. CB1 receptors and endocannabinoids are also involved in the regulation of adult hippocampal neurogenesis and may facilitate the induction of long-term potentiation in the hippocampus [41][42][43]. Both in culture and in vivo, it was shown that anandamide may inhibit neuronal differentiation (from cortical neuron progenitors to mature neurons) via CB1 receptors, though without affecting neuronal viability [44]. The ERK-mediated phosphorylation of the transcription factor Elk is critical for the transcriptional regulation of neuronal differentiation. Anandamide attenuates the nerve growth factor (NGF)-mediated activation of the Rap1/B-Raf pathway, thereby suppressing the activation of ERK and the further phosphorylation of Elk, ultimately interfering with the differentiation program [44]. In addition to neuronal cells, the expression of CB1 receptors has been confirmed in astrocytes, oligodendrocytes, and endothelial vascular cells of the blood–brain barrier [45][46][47][48]. Outside the CNS, CB1 receptors are expressed in the peripheral and enteric nervous system [48][49][50][51]. In addition to orthosteric sites, there are one or more allosteric sites at the CB1 receptors. Ligands of these allosteric sites may modulate the activation induced by direct cannabinoid agonists and modify their effects [10].

CB2 receptors are mainly involved in immune functions and are predominantly expressed by immune cells. In physiological conditions, their expression in the brain is very low (they are detectable in brainstem neurons and the spinal cord). However, they are highly upregulated during the neuroinflammatory response that accompanies neurodegenerative diseases due to the activation and proliferation of microglial cells [52][53]. For example, in malonate-induced toxicity in rats, a marked increase in CB2 receptors in astrocytes and microglia was observed, probably as a mechanism of protection for reducing neuronal damage [54]. Similar to CB1 receptors, CB2 receptor signaling inhibits adenylyl cyclase and reduces cAMP levels and PKA activity. It has also been observed in some studies that $G\alpha_{i/o}$, likely via the Gβγ subunit, may stimulate cAMP synthesis and activate the Akt and ERK pathways, presumably by regulating various adenylyl cyclase isozymes [8][53][55][56]. The activation and increased expression of CB2 receptors have been shown in various neurodegenerative diseases, and these receptors have been intensively studied as possible pharmacological targets against neuroinflammation and neuroinflammation-related neurodegeneration [54][57][58]. The observed neuroprotective effects of CB2 receptor agonists and CB2 receptor activation are mainly related to the suppression of microglial activation, the modulation of cytokine release, and the production of reactive oxygen species (ROS) [10][38][54][59][60][61]. Inflammatory mediators, such as nitric oxide (NO), ROS, proinflammatory cytokines and chemokines, are important contributing factors in microglia-mediated neuronal death due to the induction of nitrosative and oxidative stress [62]. The stimulation of CB2

receptors suppresses microglial activation via different signaling pathways, such as the Janus kinase (JAK)/signal transducer and activator of transcription 1 (STAT1) pathway [63] and the protein kinase C (PKC) pathway [64]. Moreover, 2-AG and anandamide signaling may polarize microglia towards the M2 (reparative) phenotype [29].

2. Endocannabinoid System in Neurodegenerative Diseases

The altered expression of endocannabinoids and cannabinoid receptors has been observed in neurodegenerative conditions (**Table 1**). Accordingly, it has been assumed that endocannabinoid-degradative enzymes, CB1 and CB2 receptors, and the modulation of the activity of endogenous cannabinoids represent valuable therapeutic targets in neurodegenerative diseases, as well as in other diseases such as epilepsy, stroke, inflammation, multiple sclerosis, traumatic brain injuries and psychiatric illnesses [4][65][66][67][68].

In Huntington's disease (HD), a reduced density of CB1 receptors has been found before the onset of the first symptoms in disease mutation carriers and in symptomatic HD patients, whereby the number of CAG repeats in the *HTT* gene was negatively correlated with the CB1 receptor density in the prefrontal and premotor cortices [69][70][71][72]. In the R6/2 mouse, a well-established model of HD, the re-expression of the CB1 receptors by adeno-associated viral vector normalized otherwise reduced levels of brain-derived neurotrophic factor (BDNF) in the dorsolateral striatum and rescued striatal atrophy [69]. However, Sativex, a botanical extract with equimolar amounts of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (the two major active ingredients of marijuana) did not improve motor, cognitive and behavioral deficits or induce molecular changes in HD patients [73]. On the other hand, agonists of CB2 receptors, but not agonists of CB1 receptors, were found to protect striatal projection neurons from death in a rat model of HD induced by the intrastriatal injection of malonate, an inhibitor of the mitochondrial complex II that induces apoptosis and microglial activation. The increased expression of CB2 receptors in astrocytes and reactive microglia was observed during the progression of striatal degeneration, and CB2 receptor agonists reduced the production of tumor necrosis factor alpha (TNF-α) and gliosis but did not affect the mechanisms of antioxidative defense such as the expression of superoxide dismutase (SOD)-1 and SOD-2, altogether suggesting that targeting CB2 receptors is a promising approach against neuronal injury in diseases that are accompanied by the upregulation of CB2 receptors in glial cells [54]. On the other hand, in one study, THC exacerbated neurodegenerative changes induced by the intrastriatal administration of malonate. Surprisingly, an even more pronounced effect on malonate-induced striatal lesions was observed for SR141716, a selective CB1 antagonist, suggesting that the activation of CB1 receptors produces neuroprotective effects [74]. Importantly, in a cellular model of HD, biased signaling properties have been observed. Endocannabinoids 2-AG and anandamide displayed preference to $G\alpha_{i/o}$-dependent ERK phosphorylation that normalized the levels of CB1 receptors and improved the viability of HD cells, whereas THC preferentially activated β-arrestin 1 recruitment, further depleting the levels of CB1 receptors and cell survival. This study suggests that the enhancement of Gαi/o-biased endocannabinoid signaling is a reliable pharmacological approach in HD that should be exploited to limit the adverse on-target effects of potent synthetic cannabinoids [75]. Functional selectivity at the CB2 receptors was also demonstrated [76].

Regarding AD, the reduced expression of CB1 receptors has been observed in Alzheimer's disease (AD) brains, particularly in areas of microglial activation [77]. Alterations of CB1 receptor expression are regionally specific and dependent on the course of the disease [78]. One study showed that the overall CB1 receptor levels were unchanged in the hippocampi of AD patients, but the protein levels of the enzymes involved in the synthesis and degradation of endocannabinoids were altered: sn-1-DAGL α and β isoforms, enzymes synthesizing 2-AG, were significantly increased in Braak stage VI, serine hydrolase α/β-hydrolase domain-containing 6 expression disappeared in neurofibrillary tangle-bearing neurons, and MAGL expression was reduced in comparison with pyramidal cells without signs of neurofibrillary pathology [79]. The activity of FAAH was also reduced in the frontal cortices of AD patients [80], together with depleted levels of anandamide and its precursor 1-stearoyl, 2-docosahexaenoyl-sn-glycero-phosphoethanolamine-N-arachidonoyl in the midfrontal and temporal cortices of AD. Moreover, the levels of anandamide and its precursor were positively correlated with cognitive deficits and inversely correlated with Aβ levels [81]. In another study, the expression of CB1 receptors was reduced in post mortem cortical brain tissue but did not correlate with cognitive status and the molecular markers of the disease. However, in the same study, an increase in the expression CB2 receptors was positively correlated with the Aβ42 levels and senile plaque score [82]. Moreover, CB2 receptor agonists were efficient in promoting Aβ clearance and the reversal of cognitive deficits. They also attenuated microglial activation and the production of interleukin (IL)-1β, and they prevented the upregulation of CB2 receptors [83]. Interestingly, in an animal model of AD with CB1 receptor deficiency (obtained by breeding amyloid precursor protein (APP) Swedish mutant mice (APP23) with CB1-deficient mice), more pronounced learning impairments and memory deficits were observed together with the reduced plaque deposition [84]. AD pathology was also shown to be accompanied by increased levels of 2-AG in the plasma of AD patients [85] and the hippocampi of rodents administered with the Aβ42 peptide [86]. As VDM-11, an inhibitor of endocannabinoid cellular uptake, reverses hippocampal damage and cognitive deficits when concomitantly applied with Aβ42 at the early stages of Aβ42 treatment, it seems that an early increase in endocannabinoids serves a protective role against Aβ toxicity [86]. Increases in 2-AG may also affect the immune response and pathological hallmarks of AD. It has been shown that MAGL inhibitors (which increase 2-AG levels) reduce the proinflammatory response of microglia and astrocytes, the expression and activity of β-secretase-1 (BACE1), and the Aβ burden in the hippocampus and the temporal and parietal cortices, as well as improve cognitive impairments, in animal models of AD [87][88]. Cannabinoid-profiled compounds (endocannabinoids, FAAH inhibitors, and synthetic cannabinoids) have also demonstrated neuroprotective effects in combined high glucose and Aβ conditions [89]. They improved the viability of primary hippocampal neurons; reduced the aggregation of Aβ, ROS formation and nitrosative stress; modified the enzymatic activity of SOD, catalase and antioxidant enzymes involved in glutathione homeostasis; reduced the formation of end products of lipid peroxidation and the levels of inflammatory markers (iNOS, IL-1β, and TNF-α); prevented decreases in mitochondrial membrane potential; and stimulated Nrf2 and CREB phosphorylation. At least partially, the protective effects of anandamide and synthetic cannabinoid WIN 55,212-2 were achieved via its direct scavenging ability [89].

Elevated levels of anandamide and CB1 receptors were found in the basal ganglia and cerebrospinal fluid of patients with Parkinson's disease (PD), probably as a compensatory mechanism to counteract dopamine depletion. Of note, anandamide levels were restored in patients under chronic dopaminergic therapy [90][91], although clinical

results with CB1/CB2 receptor agonists failed to show encouraging results regarding motor disabilities [9]. However, cannabis smoking improved motor symptoms in one study, suggesting that several marijuana components with synergistic activity could be a better approach than treatment with individual cannabinoids in alleviating the motor symptoms of PD patients [92]. The activation of CB2 receptors also demonstrated great potential in PD by attenuating the inflammatory response [93]. In a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of PD, the activation of CB2 receptors prevented the degeneration of dopaminergic neurons in substantia nigra by reducing the damage of the blood–brain barrier, the infiltration of peripheral immune cells, and the expression of iNOS and pro-inflammatory cytokines after microglial activation [93].

In a transgenic G93A-SOD1 mice model of amyotrophic lateral sclerosis (ALS), increased levels of anandamide and 2-AG were found in the spinal cord, probably as a mechanism of endogenous defense as changes were observed before overt motor deficits [94]. In the human spinal cords of ALS patients, the upregulation of CB2 immunostaining was also observed post mortem, probably reflecting the activation of microglial cells [95].

Table 1. Endocannabinoid system (ECS) in neurodegenerative diseases.

Disease	ECS	Observed Change	Model	Reference
HD	Receptors	↓ CB1R	R6/2 mouse	[69]
		↓ CB1R	pre-HD mutation carriers and symptomatic HD patients	[70]
		↓ CB1R	basal ganglia of patients	[72]
		↓ CB1R	grey matter of patients	[73]
		↑ CB2R in astrocytes and reactive microglia	malonate-induced rat model	[54]
AD	EC	↓ anandamide and its precursor	midfrontal and temporal cortices of patients	[81]
		↑ 2-AG	plasma of patients	[85]
		↑ 2-AG	hippocampi of rat model	[86]
	Receptors	↓ CB1R	brains of AD patients	[77]
		alterations of CB1R expression	mouse model of AD	[78]
		unchanged levels of CB1R	hippocampi of patients	[79]
		↓ CB1R	post mortem cortical brain	[82]
		CB1R deficiency	rat model of AD	[83]

Disease	ECS	Observed Change	Model	Reference
	EC enzymes	↑ sn-1-DAGL α and β isoforms, no expression of ABHD6, ↓ MAGL	hippocampi of patients	[79]
		↓ FAAH	frontal cortices of patients	[80]
PD	EC	↑ anandamide	cerebrospinal fluid of patients	[91]
	Receptors	↑ CB1R	basal ganglia of patients	[90]
ALS	EC	↑ anandamide and 2-AG	spinal cords of SOD1 G93A mice	[94]
	Receptors	↑ CB2R	human spinal cord	[95]

↓ decreased level, expression or activity; ↑, increased level, expression or activity; ABHD6, α/β-hydrolase domain-containing 6; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; 2-AG, 2-arachidonoylglycerol; CB1R, cannabinoid receptor type 1; CBR2, cannabinoid receptor type 2; DAGL, DAG lipase; EC, endocannabinoids; ECS, endocannabinoid system; FAAH, fatty acid amide hydrolase; HD, Huntington's disease; MAGL, monoacylglycerol lipase; PD, Parkinson's disease.

receptors
e, but not
2-AG, were found in the cerebrospinal fluid of untreated patients with temporal lobe epilepsy [96], whereas increased CB1 receptor signaling efficacy (despite the low mRNA and protein expression), increased levels of anandamide, and low 2-AG levels were noticed in the hippocampi of patients with pharmacoresistant temporal lobe epilepsy [97]. Yet another study revealed the downregulation of the CB1 receptor mRNA, the decreased expression of DAGL-α, and the reduced fraction of CB1-positive glutamatergic nerve endings [98]. Several lines of evidence indicate the anticonvulsive potential of cannabinoids [1][4][99], although caution is required as the acute administration of the synthetic cannabinoid AM2201 induced epileptic seizures in freely moving mice. Seizures were mediated by CB1 receptors and related to the rapid elevation of hippocampal glutamate release [100].

Similarly, brain damage after cerebral ischemia was found to be more prominent in CB1 receptor knockout mice, suggesting the neuroprotective role of CB1 receptors [66], although the neuroprotective effects of CB1 receptor antagonist were also observed. In ischemic rats, the administration of CB1 receptor antagonist AM251 reduced CA1 injury and behavioral deficits [101]. CB1 and CB2 receptor antagonists were also able to prevent minocycline-mediated neuroprotective effects in traumatic brain injury, implying the complex regulatory effects of cannabinoids in neuroprotection [9][102].

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