CANNABINOID PHARMACOLOGY/THERAPEUTICS IN CHRONIC DEGENERATIVE DISORDERS AFFECTING THE CENTRAL NERVOUS SYSTEM

Maria S. Aymerich[1,2,3], Ester Aso[4,5], Miguel A. Abellanas[1,2], Rosa M. Tolon[6], Jose A. Ramos[5,7,8], Isidre Ferrer[4,5], Julian Romero[6], Javier Fernández-Ruiz[5,7,8]

[1]Universidad de Navarra, Facultad de Ciencias, Departamento de Bioquímica y Genética, Pamplona, Spain

[2]Universidad de Navarra, CIMA, Programa de Neurociencias, Pamplona, Spain

[3]IdiSNA, Instituto de Investigación Sanitaria de Navarra, Spain

[4]Departamento de Patología y Terapéutica experimental, Universidad de Barcelona, L'Hospitalet de Llobregat, Spain

[5]CIBERNED, Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas, Instituto de Salud Carlos III, Spain

[6]Facultad de Ciencias Experimentales, Universidad Francisco de Vitoria, Pozuelo de Alarcón, Spain

[7]Instituto Universitario de Investigación en Neuroquímica, Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Universidad Complutense, Madrid, Spain

[8]IRYCIS, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain

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Abstract

The endocannabinoid system (ECS) exerts a modulatory effect of important functions such as neurotransmission, glial activation, oxidative stress, or protein homeostasis. Dysregulation of these cellular processes is a common neuropathological hallmark in aging and in neurodegenerative diseases of the central nervous system (CNS). The broad spectrum of actions of cannabinoids allows targeting different aspects of these multifactorial diseases. In this review, we examine the therapeutic potential of the ECS for the treatment of chronic neurodegenerative diseases of the CNS focusinged on Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. First, we describe the localization of the molecular components of the ECS and how they are altered under neurodegenerative conditions, either contributing to or protecting cells from degeneration. Second, we address recent advances in the modulation of the ECS using experimental models through different strategies that includinge the direct targeting of cannabinoid receptors with agonists or antagonists, increasing the endocannabinoid tone by the inhibition of endocannabinoid hydrolysis, and activation of cannabinoid- receptor--independent effects. Pre-clinical evidence indicates that cannabinoid pharmacology is complex, but supports the therapeutic potential of targeting the endocannabinoid systemECS. Third, we review the clinical evidence and discuss the future perspectives on how to bridge human and animal studies to develop cannabinoid-based therapies for each neurodegenerative disorder. Finally, we close summarizeing the most relevant opportunities of cannabinoid pharmacology related to each disease and the multiple unexplored pathways in cannabinoid pharmacology that could be useful for the treatment of neurodegenerative diseases.

Abbreviations

Aβ: amyloid-beta

AD: Alzheimer's disease

AEA: anandamide

2-AG: 2-arachidonoylglycerol

ALS: amyotrophic lateral sclerosis

APP: amyloid precursor protein

BBB: blood–brain barrier

BDNF: brain-derived neurotrophic factor

CB_1: cannabinoid receptor type-1

CB_2: cannabinoid receptor type-2

CBD: cannabidiol

CBG: cannabigerol

CNS: central nervous system

DAGL: diacylglycerol lipase

ECS: endocannabinoid system

FAAH: fatty acid amide hydrolase

FTD: frontotemporal lobar dementia

FUS: fused in sarcoma protein

GPe: external segment of the globus pallidus

GPi: internal segment of the globus pallidus

GSK3β: glycogen synthase kinase 3β

HD: Huntington's disease

L-dopa: L-3,4-dihydroxyphenylalanine

LID: L-dopa-induced dyskinesia

LPS: lipopolysaccharide

MAGL: monoacylglycerol lipase

MPTP: 1-~~m~~Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

NAPE-PLD: N-arachidonoyl-phosphatidylethanolamine phospholipase D

NMDA: N-methyl D-aspartate

NO: nitric oxide

iNOS: inducible nitric oxide synthase

PET: positron emission tomography

PD: Parkinson~~'~~s disease

PPARγ: peroxisome proliferator-activated receptor γ

ROS: reactive oxygen species

SN: substantia nigra

SNpc: substantia nigra *pars compacta*

SNpr: substantia nigra *pars reticulata*

SOD: superoxide dismutase

STN: subthalamic nucleus

TDP-43: TAR-DNA~~-~~binding protein 43

Δ^9-THC: Δ^9-tetrahydrocannabinol

1. Common features and challenges in the cannabinoid research in neurodegenerative diseases

Neurodegenerative diseases affecting the central nervous system (CNS), such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and others, are characterized by the progressive loss of specific neuronal subpopulations~~, which~~that affect selective regions of the brain and the spinal cord ~~regions~~ and neurotransmitter systems, thereby leading to different clinical features [1]. ~~Since~~Because aging is the major risk factor for these diseases, the prevalence of ~~CNS~~ degenerative disorders of the CNS is expected to increase in the next decades [2]. Currently, there is no cure for any of these disorders. Available treatments provide transient temporary symptomatic relief, but they are poorly active in the underlying disease progression. Seeking molecules with disease-modifying activity is one of the greatest challenges demanded by patients affected by these diseases [3]. Abnormal protein accumulation, impairment of the lysosomal system, excitotoxicity, oxidative stress, and neuroinflammation are classic hallmarks of the aged brain and neurodegenerative conditions [4]. The endocannabinoid system (ECS) has the ability to modulate these common traits in neurodegeneration, thus emerging as a viable target for symptom alleviation or disease progression based on pharmacological modulation of endocannabinoid signaling [5]. Cannabinoids provide a broad-spectrum profile, which is particularly interesting when dealing with complex pathologies of multifactorial origin [6]. The pleiotropic properties of cannabinoids confer the~~m~~ cannabinoids as ~~an~~ important ~~advantage~~ molecules for the development of neuroprotective strategies. Endocannabinoid signaling involves cannabinoid receptor-dependent effects (e.g., activation of cannabinoid type-1 (CB_1) receptors to normalize glutamate homeostasis or to activate autophagy, activation of cannabinoid type-2 (CB_2) receptors and peroxisome

proliferator-activated receptor γ (PPARγ), or modulation of G-protein receptor 55 (GPR55) to reduce local inflammatory events), ~~but~~and also cannabinoid receptor-independent effects to reduce oxidative stress, all of which may ultimately promote neuron survival [7]. The key localization of ECS elements in the CNS and their alteration under pathological conditions suggest~~s~~ that this system participates in crucial processes for ~~the~~ balanc~~ing~~e neurodegeneration/neuroprotection (Fig. 1). This review ~~is~~ focuse~~d~~ on how the components of the ECS are altered in chronic degenerative diseases affecting the CNS, such as AD, PD, HD, and ALS (see footnote #1), and indicat~~ing~~es that bioactivity of endocannabinoid-based therapies is likely to vary depending on the disease type and the stage at the time of treatment. The review emphasizes on recent advances in pre-clinical evidence that provides scientific support to propose cannabinoids ~~to~~for the treatment of different neurodegenerative conditions and discusses the future perspectives of cannabinoid-based therapies for the treatment of each neurological disorder.

2. Cannabinoid pharmacology in Alzheimer~~´~~'s disease

~~Alzheimer´s disease~~AD is the most common form of dementia among the elderly, and it is defined ~~by~~as a progressive decline of cognition, memory, and other mental functions, ultimately ~~that~~ result~~ing~~s in a ~~ultimately~~ fatal outcome. The morphological hallmarks of ~~AD~~ brains affected by AD include amyloid-beta (Aβ) plaques and neurofibrillary

FOOTNOTE #1:

Other neurological disorders with degenerative components (e.g., multiple sclerosis, and spinal injury) ~~or~~ affecting the peripheral nervous system rather than the central nervous system have been reviewed in other articles within this Special Issue~~;~~ ~~so~~therefore, they ~~we~~are not addressed here.

tangles composed of hyperphosphorylated microtubule-associated tau protein, which induce neuronal death and impaired inter-neuronal communication, and these hallmarks progress from the brain stem and inner parts of the temporal lobes to the major part of the whole telencephalon [8]. In fact, most of the experimental models of AD are based on the exogenous administration or the genetic manipulation for overexpressing of Aβ and/or hyperphosphorylated tau in cell cultures or rodent models [9]. Although they have some limitations because they do not fully replicate the AD pathology, those experimental models based on Aβ and/or hyperphosphorylated tau have significantly contributed to AD research.

However, other multiple alterations converge in the pathogenesis of AD, including synaptic degeneration, mitochondrial defects, and increased production of reactive oxygen species (ROS). In addition, the inflammatory responses to protein aggregation/deposition, the altered neurotransmission, and production of other neuromodulators, together with a vascular dysfunction and impaired degradation pathways, are assumed to play crucial roles in AD progression as wellalso [10][11]. Current available therapies against AD produce mild improvement of cognitive and functional capacities [12]. These therapies act on a single target and are administered after clinical manifestations, when there is no turning back for certain pathological events. The progression from early stages of the neurodegenerative process to symptomatic stages may take decades, whereas once the dementia symptoms appear, the disease progression accelerates causing devastating effects [10]. Therefore, two of the major goals of current research in AD are to develop new tools for early diagnosis and to search for more effective treatments that are more effective aimed at curbing or retarding disease progression toward dementia by acting on multiple targets during the prodromal period of the disease.

In this context, targeting the ECS has attracted growing interest during the last decade based on the numerous findings revealing that the stimulation of ECS contributes to modulate in parallel several of the pathological processes occurring during the early stages of AD, thereby conferring cannabinoid compounds a potential utility against this neurodegenerative disease, as summarized below~~next~~.

2.1. The endocannabinoid system in Alzheimer~~'~~'s disease

Neuropathological changes in AD trigger a potent neuroinflammatory reaction in which glial cells (astrocytes and microglia) become a source of increased cytokine production [13]. In this context, the ECS becomes profoundly altered, with modifications ranging from changes in anandamide (AEA) and 2-arachidonoylglycerol (2-AG) levels~~,~~ to the expression pattern of their regulatory enzymes and of cannabinoid receptors [14].

A seminal study by Westlake et al [15] showed a significant decrease in CB_1 receptors in tissue sections from AD donors, as measured by autoradiography, probably ~~due to~~because of the neuronal loss associated ~~to~~with this disease. Further studies, however, have not confirmed these observations. For instance, no changes in CB_1 receptor levels were found by immunoblotting and receptor binding in human brain samples [16]. In addition, an *in vivo* study conducted in 11 patients with AD ~~patients~~ and 7 healthy volunteers by using the specific radiotracer [^{18}F]MK-9470 for~~CB_1 receptor~~ ~~P~~positron ~~E~~emission ~~T~~tomography (PET) of CB_1 receptors~~ radiotracer, [^{18}F]MK-9470,~~ found no significant differences in CB_1 receptor availability in any of the brain regions studied [17]. It is relevant to note that a hyperactivated state of CB_1 receptor in the early stages of AD, followed by a significant decrease as the disease progresses, has been reported, thus suggesting that CB_1 receptor might have therapeutic potential in the progression of the disease [18].

Data obtained in mouse models of AD have ~~so~~thus far not been conclusive either. Different groups have reported increases [19], decreases [20], or no changes [21] in CB_1 receptor levels in several brain areas (at the mRNA, protein, or receptor coupling efficiency) in the past few years. The current perception is that CB_1 receptors may play a role in the progression of AD, but it is difficult to establish the precise role(s) in which they might contribute. These could range from modifying amyloid processing to protect neurons in the risk of degeneration or to dampen inflammation (see below).

Perhaps, one of the most intriguing aspects of these changes is the profound alteration in the expression pattern of CB_2 receptors, ~~that~~which takes place in AD. The analysis of human AD samples by immunohistochemistry revealed the absence of signal for CB_2 receptors in ~~control~~ brains of the control group (with a limited presence in a subset of microglial cells~~,~~ such as the perivascular microglia) but an intense level of staining in AD samples [22]. Co-localization studies confirmed that CB_2 receptors were expressed in microglial cells only, located in the surrounding areas of amyloid-enriched neuritic plaques. However, questions regarding the specificity of antibodies raised against the CB_2 receptor [23] made confirmation of these data necessary. Several groups successively provided data supporting the expression of CB_2 receptors in microglial cells in the context of AD. Thus, Ramirez et al [24] reported that CB_2 receptors were present in microglial cells in human AD samples. More recently, an ~~elegant~~ classic study in which the expression of CB_2 receptors in the brains of two mouse models of AD was analyzed by immunohistochemistry and PET with the specific radiotracer [^{11}C]A836339 confirmed this observation [25]. These authors also used human samples to complete their observations that described the presence of CB_2 receptor in not only microglial cells~~,~~ but also ~~in~~ astrocytes and neurons. Interestingly, CB_2 receptor levels in microglia increased in ~~the context of~~ AD, whereas~~ile~~ those in neurons decreased ~~with~~in

the disease. These data confirmed the value of CB_2 receptors as diagnostic as well as putative therapeutic targets in AD~~,~~ and provided evidence for the expression of CB_2 receptors in neurons, a matter of intense controversy. Another recent *in vivo* study found a decrease in CB_2 receptor availability in patients with AD ~~patients~~, although this observation could be biased by the affinity of the radiotracer ~~employed~~ used toward~~s~~ CB_1 receptor and CB_2 receptor [26]. Finally, by ~~means of~~using a newly developed reporter mouse model, we have recently corroborated the selective expression of CB_2 receptor in plaque-associated microglial cells in the 5xFAD mouse model of amyloidosis [27].

Few data are currently available regarding the levels of endocannabinoids and the functional status of their regulatory enzymes in ~~the context of~~ AD. The metabolism of 2-AG and AEA has~~ve~~ been shown to be altered in AD, both in human samples as well as in mouse models of the disease, with conflicting results. Thus, ~~while~~although an increase in AEA and 2-AG levels in the 5xFAD model of AD has been reported [28], we were unable to find significant differences in the same animal model [29]. In addition, other authors have reported decreases in 2-AG levels in the AβPPswe/PS1ΔE9 mouse model of AD [19].

Regarding human samples, a significant decrease in AEA levels and its precursor NArPE, but not 2-AG, in the cortical areas of postmortem brain samples has been reported [30]. Furthermore, this decrease was correlated ~~by~~with the patients' performance in cognitive tests of psychomotor speed and linguistic ability~~,~~ but not ~~by~~with amyloid plaque density or tau hyperphosphorylation. These data may correlate with those in previous reports in which an induction of the expression of the AEA-degrading enzyme fatty acid amide hydrolase (FAAH) was found in AD samples [22]. In this study, we observed an increase in FAAH immunoreactivity in hypertrophied

astrocytes located around the foci of neuroinflammation, such as amyloid plaques. This increase was paralleled by a significant augment in FAAH enzymatic activity in samples obtained by micro-dissection of amyloid plaques. Finally, Mulder et al [31] used human AD samples to obtain data indicative of an enhanced endocannabinoid signaling, involving mainly 2-AG, around neuritic plaques. This enhancement would be in direct correlation with a loss of monoacylglycerol lipase (MAGL) enzymatic activity dueowing to impairment in its recruitment to biological membranes.

Perhaps more difficult to interpret areis data obtained from peripheral samples. The analysis of blood plasma revealed no changes in any of the endocannabinoids considered, and their levels showed no correlation with the cognitive performance in healthy individuals at risk of AD [32]. Other authors, however, have found a significant increase in 2-AG and PEA levels in the blood plasma of AD patients with AD [33], thatand this could reflect a putative protective mechanism in the development of the disease. Interestingly, another report showed that an increase in FAAH mRNA and protein in peripheral blood mononuclear cells of patients with AD was patients linked to a decrease in the methylation state of the FAAH gene promoter region [34], thus suggesting a facilitation in gene expression. Inhibition of FAAH activity may render positive anti-inflammatory effects in the context of AD.

2.2. Pre-clinical evidence for the therapeutic potential of cannabinoids in Alzheimer's disease

2.2.1. Cannabinoids and Aβ processing

A neuroprotective role for cannabinoids against Aβ has been demonstrated in several *in vitro* and *in vivo* studies. The administration of endocannabinoids such as AEA, 2-AG, and noladin ether, or the supply of endocannabinoid reuptake inhibitors, increased the

viability of neurons in culture exposed to different toxic Aβ species [35][36][37][38]. Similarly, ~~the~~ exposure to cannabidiol (CBD), possibly the most atypical cannabinoid from a mechanistic ~~point of view~~perspective [38][39]~~,~~; the synthetic CB_1 receptor agonist ACEA [40]~~,~~; the CB_2 receptor selective agonists JWH-015 and JWH-133~~,~~; or ~~to~~ the mixed CB_1/CB_2 receptor agonists Δ^9-THC, HU-210 and WIN55,212-2 [24][38][41] reduced the Aβ peptide toxicity *in vitro*. Neuroprotection against Aβ deleterious effects might underlie ~~the~~ memory improvement observed after treatment with certain cannabinoids in animal models of AD. Either the elevation of endocannabinoid~~s~~ levels [42] or the administration of synthetic selective CB_1 or CB_2 receptor~~s~~ agonists [43][44][45], or non~~-~~specific CB_1~~/~~ or CB_2 receptor agonists [24][46][47] or CBD [46], reduced memory impairment in Aβ-injected rodents. Moreover, chronic treatment with ACEA [40], JWH-133 [48][49], WIN55,212-2 [48], CBD [50][51], or with a combination of Δ^9-THC and CBD [52][53] reduced the cognitive impairment in two different transgenic mouse models of AD.

Multiple mechanisms might participate in ~~the~~ neuroprotection against Aβ mediated by cannabinoid compounds, acting in parallel or interacting within them. Apart from the capacity of cannabinoids to indirectly mitigate the harmful effects of Aβ (i.e., inflammation~~,~~ and oxidative stress), which are discussed in the next sections, a direct effect of cannabinoids on Aβ processing has also been reported. Δ^9-THC directly interacts with Aβ, thereby inhibiting its aggregation [41], and CBD induces the amyloid precursor protein (APP) ubiquitination and the consequent decrease in Aβ production ~~via~~through the activation of PPARγ [54].

CB_2 receptor agonists facilitate Aβ clearance by stimulating the phagocytic activity of macrophages [55][45] and by favoring Aβ transport through the choroid plexus [48]. Similar Aβ clearance across the blood–brain barrier (BBB) was also demonstrated for

2-AG, a synthetic CB_1/CB_2 receptor agonist, and MAGL, but not for FAAH inhibitors, in *in vitro* and *in vivo* BBB models [56]. The reduction in Aβ levels observed in AD mouse models chronically treated with CB_2 or CB_1/CB_2 receptor agonists [48][28][57] and MAGL inhibitors [28][58] could be explained by the facilitation of Aβ clearance. In line with these observations, the genetic deletion of CB_2 receptors altered the Aβ levels in two different AD models [59][60][61]. InBy contrast, the specific role of CB_1 receptors on Aβ production is stillremains a matter of debate. Whereas some authors reported that specific agonists of this receptor did not alter the Aβ production, aggregation, or clearance in two different transgenic AD models [40][62], others provided evidence about a crosstalk between CB_1 receptors and APP. On one hand, deletion of these receptors resulted in reduced APP protein levels and Aβ plaque deposition in APP23 transgenic mice [63], but not in APP/PS1 mice [64]. Furthermore, APP overexpression altered membrane localization and inhibitory signaling activity of CB_1 receptors in the hippocampus of Tg2576 mice [65]. On the other hand, the combination of Δ^9-THC and CBD, but not each cannabinoid individually, resulted in a reduction ofin soluble $A\beta_{42}$ levels, the most toxic form of the Aβ peptide. This activity was CB_2 receptor independent and might be achieved by facilitation of $A\beta_{42}$ deposition in plaques to decrease its toxicity [52][61].

2.2.2. Effects of cannabinoids on tau hyperphosphorylation

Cannabinoids are able to modulate tau hyperphosphorylation, another AD pathological hallmark of AD. Pioneering studies performed in Aβ-stimulated PC12 neuronal-like cells demonstrated that CBD, ACEA, and WIN 55,212-2, inhibited tau hyperphosphorylation by reducing the active form of glycogen synthase kinase 3β (GSK3β) by direct activation of CB_1 receptor [66][67]. In agreement with these studies,

a significant reduction ~~of~~in hyperphosphorylated tau levels was reported in the area surrounding Aβ plaques after ~~the~~ chronic treatment with ACEA in the APP/PS1 mice [40], likely through the reduction ~~of~~in GSK3β activity as ~~was~~ suggested in other studies [41]. Moreover, the same authors revealed a reduction ~~of~~in the activity of different tau kinases in APP/PS1 mice chronically treated with a specific CB_2 receptor agonist, lowering tau hyperphosphorylation in neurites closely related to Aβ deposition [49]. ~~In~~By contrast, deletion of CB_2 receptors did not modify tau hyperphosphorylation in dystrophic neurites associated ~~to~~with Aβ plaques in the APP/PS1 mouse [61]~~.~~, ~~A~~although total tau levels were significantly decreased in a different AD mouse model lacking CB_2 receptors [59]. According to the hypothesis that suggests a role for cannabinoids in tau phosphorylation, a combination of Δ^9-THC and CBD natural extracts reduced the formation of neurofibrillary tangles in parkin~~-~~ null, human tau overexpressing (PK-/-/TauVLW) mice, a model of complex frontotemporal dementia (FTD), parkinsonism, and lower motor neuron disease [70].

2.2.3. Anti-inflammatory effects of cannabinoids

It is currently accepted that the activation of the ECS is part of a neuroprotective response against different types of brain injury, including the appearance of neuritic plaques. The involvement of the ECS is partially based on its anti-inflammatory properties derived of the activation of CB_1 and CB_2 receptors [24][48]~~,~~ and also of PPARγ receptors [47][71] by endogenous ligands as well as by phyto~~-~~ and synthetic cannabinoids. As mentioned before, CB_2 receptors are upregulated in microglial cells in ~~the context of~~ AD, thus suggesting a role for them in the neuroinflammatory process triggered by amyloid deposition. This role has been described in studies performed both *in vivo* and *in vitro*, thus confirming the anti-inflammatory effects associated ~~to~~with CB_2

activation (reviewed in [72][73]). Interestingly, these effects are accompanied by improvements in behavioral performance and also by decreased deposition of amyloid plaques, probably ~~due~~owing to a CB_2-mediated decrease in cytokine secretion and enhancement of amyloid removal by increased phagocytosis.

However, recent studies suggest that the contribution of this receptor type to AD progression and to the therapeutic effects of certain ECS modulators may be more complex than initially expected. Thus, the neuroprotective effect of an MAGL inhibitor in APP transgenic mice was independent of CB_2 receptors [74]. Similar results were obtained in APP/PS1 mice treated with a combination of Δ^9-THC and CBD [61]. These results are in agreement with those suggesting a limited role for CB_2 receptors in the progression of AD-like pathology in 5xFAD [75][27] or APP/PS1 mice [61].

One of the most promising approaches for neuroprotection is the indirect enhancement of endocannabinoid~~s~~ levels through the inhibition of MAGL and FAAH [28][29] [58][75][74]. Both the pharmacological blockade of MAGL with JZL184 ~~as well as~~and its genetic inactivation~~,~~ improved behavior, decreased the density of amyloid plaques, and reduced astro- and microgliosis and the production of inflammatory cytokines [58][75]. Interestingly, none of these effects were prevented by CB_1 receptor or CB_2 receptor antagonists~~,~~ but were mediated primarily by alterations in arachidonic acid and/or prostaglandin signaling. As mentioned above, degradation of 2-AG by MAGL has been proposed as a novel pathway for prostaglandin synthesis and a new target to suppress neuroinflammation [76].

Evidence ~~points towards~~suggests a beneficial effect of FAAH inhibition in animal models of age-related neuroinflammation [29][77]. Murphy *et al* [77] demonstrated that the selective FAAH inhibitor~~,~~ URB597~~,~~ reversed the age-linked inflammation in terms of cytokine expression and preserved hippocampal long-~~-~~term potentiation in aged rats.

Pharmacological inhibition of FAAH with URB597 had a limited effect in 5xFAD mice~~,~~ in terms of cytokine expression and behavior, which contrasted with the significant changes observed after genetic inhibition [29]. Interestingly, our data are suggestive of a putative shift in the ~~endocannabinoid system~~ECS neurotransmission from a CB_1 receptor-mediated anti-inflammatory action to a pro-inflammatory one, in the context of AD and triggered by a long-term inhibition of FAAH. Paradoxically, this long-term inhibition would also be beneficial, as mice showed improvements in memory and decreased amyloid deposition. It is still unknown whether these changes involve, for instance, preservation of neuronal morphology in the hippocampus. In any case, it seems to be currently~~now~~ accepted that inhibiting FAAH activity may render positive effects, and~~,~~ in fact, mixed inhibitors for FAAH and other enzymes, i.e., acetylcholinesterase (AChE) or butyrylcholinesterase, are under study ~~in order~~ to be used as potential therapeutic tools for AD [78][79].

2.2.4. Other effects of cannabinoids

Many studies report different effects of cannabinoids with potential interest for AD. Alterations in the components of the respiratory chain located in the inner mitochondrial membrane that lead to the production of excessive ROS are described in ~~AD~~ brains affected by AD [80], with ~~the~~ subsequent oxidative damage of certain macromolecules that jeopardizes their functionality. Compounds that are able to counteract free radical damage are then assumed to confer neuroprotection, ~~that~~which bestows them potential utility against AD [81]. Among the antioxidant compounds tested in AD models, a few cannabinoids have been included. CBD was the first one to be evaluated. CBD prevented ROS production and lipid peroxidation in PC12 neuronal-like cells exposed to Aβ, reduced apoptosis, and counteracted the Aβ-induced increase in intracellular

calcium concentration [39]. CBD also reduced the levels of nitric oxide (NO)~~,~~ ~~as well as~~and the expression of the inducible NO synthase (iNOS) [67][82]. Mechanisms of action of CBD have been classically assigned to cannabinoid receptor-independent antioxidant properties, a fact derived from its particular chemical structure having two hydroxyl groups. Recent evidence relates this potential to novel non-endocannabinoid signaling mechanisms, e.g., PPAR-γ, Nrf-2 signaling, and adenosine signaling [68]. Recent studies claim for a role of CBD as a negative allosteric modulator of both CB_1 [69] and CB_2 [83] receptors. Although, it is unlikely that this capability may underlie its anti-excitotoxic, anti-inflammatory, and neuroprotective properties, which are related to elevated rather than reduced CB_1 and CB_2 receptor signaling. ~~T~~These properties may be supported by the ability of CBD to increase the activity of mitochondrial complexes in a hippocampal cell line [84], in different structures related to AD in the rat brain [85] and to rescue memory deficits in rats [86]. However, studies using the mitochondrial fraction from the pig brain cortex claim that CBD inhibits the activity of the respiratory chain [87][88].

~~Cannabinoids also exhibited antioxidant properties in *in vivo* models of AD. Thus,~~ The selective CB_2 receptor agonist JWH-133 reduced hydroxynonenal adducts, derived from lipid peroxidation, and enhanced the levels of the superoxide dismutases 1 and 2 in the area surrounding Aβ plaques in APP/PS1 mice, thus demonstrating a role for CB_2 receptors in promoting responses against oxidative stress and reducing its harmful consequences [49]. The combination of Δ^9-THC and CBD also resulted in a reduction of free radicals in a mouse model of tauopathy [70] and in the augmentation of the levels of thioredoxin 2 protein, a member of the mitochondrial antioxidant system responsible for the clearance of reactive intermediates and the repair of proteins with oxidative damage [52].

Certain cannabinoids are known to act on the same targets ~~than~~compared to the current ~~AD~~ medications for AD, i.e., AChE inhibitors and noncompetitive antagonists of the N-methyl D-aspartate (NMDA) receptor. Δ^9-THC competitively inhibits AChE increasing acetylcholine availability and prevent~~sing~~ AChE-induced Aβ aggregation [89]. CB_2 receptor agonists exhibit inhibitory effects on butyrylcholinesterase [90]. The synthetic cannabinoid HU-211 inhibits NMDA receptors, thereby protecting cells from glutamate-induced neurotoxicity [91][92][93]. CB_1 receptors mediate neuroprotection against excitotoxicity by inhibiting presynaptic glutamate release [94] and excessive calcium release [95][96][97]. In agreement with these observations, the combination of Δ^9-THC and CBD modulated the levels of certain glutamatergic and GABAergic receptors in the cortex of aged APP/PS1 mice, thus suggesting an attempt of these natural cannabinoids to reduce the imbalance of excitatory *versus* inhibitory neural activity occurring in AD [53].

Additional beneficial effects of cannabinoids in AD include their capacity to prevent Aβ-mediated lysosomal destabilization in cultured neurons, thereby reducing the apoptotic signaling [98]~~,~~; to promote neurogenesis in response to Aβ insult [82][99]~~,~~; to normalize the levels of the pre~~-~~synaptic SNAP25 protein involved in aberrant neuritic sprouting in brain areas affected by Aβ [49]~~,~~; and to induce autophagy facilitating the degradation of aberrant cellular components [70]. Moreover, a recent study revealed that the CB_1/CB_2 mixed agonist WIN 55,212-2 and the CB_2 selective agonist JWH-133 ameliorated the vascular dysfunction in a transgenic model of AD [100]. In addition, a role for CB_2 agonists in stimulating brain glucose uptake was also described in the same animal model [101].

2.3. *Therapeutic implications for a cannabinoid-based therapy for Alzheimer's disease: clinical evidence and future perspectives*

Considering the complexity of the pathological mechanisms involved in the progression of AD, compounds such as cannabinoids targeting in parallel several processes that play key roles in AD could offer a more promising therapeutic profile than treatments targeting a single causal or modifying factor. However, as described above, the potential therapeutic utility of cannabinoids in AD is mainly based on the evidence obtained using *in vitro* and *in vivo* models. Consequently, there is a need to move the evidence from the bench to the bed. Nevertheless, it is worth noting that the limited clinical information on the use of cannabinoids in patients with dementia also suggests some beneficial effects. Clinical trials in ~~AD~~ patients with AD at advanced stages who received an analog~~ue~~ of Δ^9-THC (nabilone or dronabinol) for several weeks showed a significant reduction ~~of~~in agitation and aggression refractory to antipsychotics and anxiolytics, together with weight gain in individuals previously rejecting food, although no reduction ~~of~~in other neuropsychiatric symptoms was observed. Equally important is the almost total absence of side effects observed during treatment with Δ^9-THC in these patients, and beyond a certain euphoria, drowsiness or fatigue [102][103][104][105][106][107]. Despite the limited number of subjects included in the trials and the lack of assessment of cognitive parameters and markers of neurodegeneration, which limits drawing definitive conclusions about the effectiveness of Δ^9-THC in the treatment of dementia [108], the available information derived from these studies is relevant and, together with the extensive basic evidence, provides encouragement for conducting controlled clinical trials geared to clarifying the therapeutic potential of cannabinoids in AD.

3. Cannabinoid pharmacology in Parkinson's disease

PD, the second most common neurodegenerative disease, is a motor disorder affecting 1-2% of the population aged ~~over~~more than 65 years, with an incidence that increases with age [109]. The classic motor symptoms~~,~~ rigidity, bradykinesia, and tremor, are caused by the striatal dopamine deficit generated by the specific loss of dopaminergic neurons in the substantia nigra *pars compacta* (SNpc). The SNpc, the striatum (caudate nucleus and putamen), the globus pallidus (internal and external segments, GPi and GPe, respectively), and the substantia nigra *pars reticulata* (SNpr) are subcortical structures that are part of the basal ganglia, a group of brain nuclei involved in the control of movement ~~which~~whose activity is primarily affected in PD. The most effective treatment for PD is levodopa (L-dopa), a dopamine~~-~~ replacement therapy that was identified 50 years ago [110]. However, as the disease progresses and more neurons are lost, the efficacy of L-dopa decreases and patients experience motor fluctuations and abnormal involuntary movements known as L-dopa~~-~~-induced dyskinesia~~s~~ (LID) [111]. The ~~D~~development of new non-dopaminergic drugs capable ~~to~~of attenuating~~e~~ motor symptoms without producing dyskinesia is necessary. Ultimately, disease-modifying treatments are needed to stop the neurodegenerative process. On the ~~B~~basis~~ed~~ ~~on~~of the cellular location of cannabinoid targets and the neuroprotective activities described for cannabinoids, they represent an interesting therapeutic approach for PD.

Different aspects of the disease can be reproduced in experimental animals. Models based on ~~C~~classic neurotoxin~~s based models~~, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), rotenone, paraquat, or lipopolysaccharide (LPS), reproduce the loss of dopaminergic neurons and the motor impairment, thus representing a late-stage model of the disease. Transgenic or knockout genetic models simulate better the pathogenic mechanisms of PD, but their pathological

and behaviou~~u~~ral phenotype is often quite different from that of the human condition. Similar strategies are used to generate *in vitro* cellular models [112].

3.1. The Endocannabinoid System in Parkinson's disease

In agreement with the effect of cannabimimetic drugs on motor activity, ~~the~~ different elements of the ECS are ~~very~~ abundant in the basal ganglia [113]. The high density of CB_1 receptor~~s~~ immunoreactivity in these nuclei, except for dopaminergic neurons in the SNpc, supports a role for these receptors in the regulation of basal ganglia physiology and pathology [114]. Activation of presynaptic CB_1 receptors in GABAergic and glutamatergic terminals within basal ganglia leads to presynaptic inhibition of neurotransmitter release [115]. In the striatum, the ECS interacts closely with the dopaminergic system. Activation of postsynaptic dopamine type 2 receptors stimulates AEA release that ~~retrogradely~~ activates CB_1 receptors in a retrograde manner to down-regulate glutamate neurotransmission [116][117]. ~~Even~~ Although dopaminergic neurons lack CB_1 receptors, they can be~~come~~ activated in a CB_1 receptor-dependent manner by reducing their GABAergic input, thereby favo~~u~~ring dopamine release [118][119]. Cannabinoid receptors and their endogenous ligands are modulated in animal models and patients with PD. CB_1 receptors showed no differential expression in the striatum of 6-OHDA-lesioned rats, but ~~they experienced~~ a significant increase in the receptor levels was observed in animals treated with L-dopa [120][121]. A transient increase in CB_1 receptor transcripts in the striatum of the 6-OHDA rats, ~~that~~ which was not accompanied by changes in [^{3}H]WIN-55,212-2 binding or [^{35}S]GTPγS stimulation, was described in the striatum, ~~the~~ GPe, and ~~the~~ SNpr [120][122][123]. [^{3}H]CP-55,940 binding and [^{3}H]WIN-55,212-2 activation of [^{35}S]GTPγS were up-regulated in MPTP-lesioned marmosets and returned to control levels upon L-dopa treatment [124]. Interestingly, an increase in CB_1 receptor expression was detected in the basal ganglia

of parkinsonian monkeys treated with L-dopa exclusively during the active phase of dyskinesia, CB_1 receptor transcripts returned to control levels when MPTP monkeys were ~~off~~ not administered with L-dopa [125]. Not only receptor activation but also endocannabinoid~~s~~ levels are altered in experimental models of PD. The levels of AEA, but not 2-AG, were increased in the striatum of the 6-OHDA rat [126]. MPTP-lesioned marmosets showed elevated levels of AEA in the striatum and GPe, ~~that~~and these levels ~~lowered~~ decreased to control levels with L-dopa therapy. 2-AG was increased in the striatum and substantia nigra (SN) but decreased in the GPe~~,~~; these changes returned to control levels with acute L-dopa therapy but persisted when LID was present [127]. Changes in the ~~E~~expression ~~changes in the~~ levels of AEA synthesizing/degrading enzymes in the GPe of MPTP monkeys suggest a role for this endocannabinoid as a compensatory mechanism to counteract the dopamine deficit [125]. Changes in the expression of 2-AG synthesizing/degrading enzymes during the active phase of dyskinesia suggest~~s~~ that this endocannabinoid may play a role in LID [125].

~~The s~~Studies carried out with human samples from ~~PD~~ patients with PD are difficult to interpret because patients are under L-dopa treatment, and most of them do not mention the presence of LID. Therefore, it is not possible to determine whether the observed changes are due to the disease itself, due to the dyskinetic status, or due to the chronic dopaminergic therapy. Analysis of CB_1 receptor transcripts in the postmortem tissue from L-dopa~~-~~treated ~~PD~~ patients with PD showed a down~~-~~regulation restricted to the anterior-dorsal region of the putamen and to the GPe, thus suggesting that their expression might be modulated heterogeneously in the putamen [128]. A similar study showed an up~~-~~regulation of CB_1 receptor transcripts in the putamen [129]. The small piece of tissue comprising different regions of the putamen might account for the different observations. The binding of [^{3}H]CP-55,940 was increased in the caudate

nucleus and putamen, and the stimulation of [^{35}S]GTPγS by [^{3}H]WIN-55,212-2 was high~~er~~ in the caudate nucleus, putamen, GPe, and SN of ~~PD~~ patients with PD [124]. An interesting study measured CB_1 receptor binding *in vivo* by PET in different groups of ~~PD~~ patients with PD using the selective radioligand [^{18}F]MK-9470 [130]. An increase in CB_1 receptor availability was displayed in the putamen and a decrease in the SN of ~~PD~~ patients with PD with regard~~spect~~ to controls. In this case, no regional differences were detected between patients with or without LID [130]. Analysis of AEA levels in the cerebrospinal fluid in ~~PD~~ patients with PD showed that newly diagnosed ~~PD~~ subjects with PD and those undergoing a complete L-dopa washout presented higher AEA levels, ~~that~~and these levels were restored to control levels in patients under chronic dopaminergic therapy [131]. Therefore, data obtained from ~~PD~~ patients with PD and animal models point toward~~s~~ profound rearrangements of the ECS in the basal ganglia after dopamine depletion and with dopamine replacement therapy.

The presence of CB_2 receptors has been demonstrated in activated microglia of the diseased brain [132], thus suggesting that CB_2 receptors are up-regulated as part of the activation process. Albeit some limitations, there is evidence of CB_2 receptor expression in striatal fibers and in the SN of rats [133]~~,~~ and in the GPe and GPi of primates [134][135]. There is no consensus regarding the cellular localization of CB_2 receptors in the human brain of ~~PD~~ patients with PD. A predominant expression of CB_2 receptors has been reported in activated microglia and ~~in~~ dopaminergic neurons of ~~the~~ SN [136][137]. However, Navarrete et al. (2018) reported a major localization of CB_2 receptors in activated astrocytes [129].

Neuroinflammation is a classical neuropathological hallmark of patients with PD [139][140] and of animal models of the disease. Intrastriatal administration of LPS, 6-OHDA, or rotenone induced an increase in CB_2 receptor mRNA levels that correlated

with microglial cell activation [141][142]. In the acute MPTP mouse model, CB_2 receptor was upregulated in microglial cells of the midbrain but not in the striatum [143]. Similar to these results, CB_2 receptor transcripts were upregulated in ~~the~~ SN and downregulated in the putamen of parkinsonian patients [129].

These data highlight the potential role played by the ECS in PD pathophysiology and LID~~,~~ and provide~~s~~ an excellent opportunity to develop new therapeutic strategies directed specifically toward~~s~~ different aspects of the disease. Neuronal cannabinoid receptors modulate the main neurotransmitter systems in basal ganglia and offer a target that might influence motor and non~~-~~motor symptoms of PD or counteract LID. The ability of CB_2 receptors to modulate the immune response places them as an interesting therapeutic target for neuroprotection.

3.2. Pre~~-~~clinical evidence for the therapeutic potential of cannabinoids in PD

Animal studies suggest that cannabinoids improve motor symptoms of PD and LID and that they ~~are~~exert neuroprotective effects ~~by~~through cannabinoid receptor-dependent and -independent mechanisms. ~~Since~~Because blockade of CB_1 receptors facilitates dopamine type 2 receptor-mediated facilitation of movement [116], CB_1 receptor~~s~~ antagonists would enhance dopaminergic transmission. Furthermore, one of the classical effects of direct activation of CB_1 receptors in rodents is the cannabinoid tetrad, ~~that~~ includinge~~s~~ catalepsy and hypolocomotion [144], which supports the use of CB_1 receptor antagonists for akinesia. ~~In~~With ~~this~~ regard to this, motor behavior in different 6-OHDA rat models was improved by the CB_1 receptor antagonists rimonabant, AM251, and the phytocannabinoid Δ^9-tetrahydrocannabivarin (Δ^9-THCV) at low doses [145][146][147]. Rimonabant as monotherapy ameliorated parkinsonian symptoms in MPTP primates and reduced LID without compromising L-dopa efficacy [127],

although a lack of beneficial effect has also been reported in this animal model [148]. Paradoxically, CB_1 receptor agonists improve motor impairment. Administration of either~~,~~ the non~~-~~selective cannabinoid receptor agonist CP 55,940 or AM404 to enhance AEA availability~~,~~ into the denervated striatum of 6-OHDA rats had anti-parkinsonian properties [149][150]. Δ^9-THC had anti-parkinsonian properties in MPTP-lesioned marmosets, although it induced side effects [151]. From a theoretical ~~point of view~~perspective, the anti-parkinsonian effect of both~~,~~ CB_1 receptor activation ~~or~~and blockade~~,~~ could be explained depending on which nuclei of the basal ganglia ~~is~~are being primarily targeted by the treatment [152]. The different status of the ECS in the basal ganglia under parkinsonian conditions, dose, gender, trial design, or the extent of the dopaminergic lesion might explain the different efficacy of agonists or antagonists [145][146][151]. The specific localization of CB_1 receptors at glutamatergic or GABAergic terminals of neurons in different basal ganglia nuclei [153] and alteration of these pools of receptors under pathological conditions might account for such effects.

Promising data arise from pharmacological studies targeting CB_2 receptors. In the 6-OHDA rat model, which has a lower inflammatory response ~~compared to~~than other PD models, a mild improvement in dopamine levels was detected after the administration of the CB_2 receptor agonist HU-308 [154]. Treatment of the acute MPTP mouse model with WIN 55,212-2 ~~prior~~before the neurotoxin injection protected dopamine neurons from degeneration in a CB_2 receptor-dependent manner, probably through the inhibition of microglial activation. In fact, all CB_2 receptor knockout mice died after MPTP administration, thus suggesting that they are critical for protection against the neurotoxin [143]. Similar results were obtained with a lower dose of WIN 55,212-2 and with the CB_2 receptor selective agonists JWH-133 and AM1241 [155][156]. Striatal LPS injection induced a mild dopaminergic neurodegeneration and a prominent pro-

inflammatory response. The CB_2 receptor selective agonist~~,~~ HU-308~~,~~ and the CB_2 receptor agonist activity of the phytocannabinoid Δ^9-THCV protected dopaminergic neurons and decreased the expression of the microglial activation markers CD68 and iNOS in the striatum [137][147]. Interestingly, dopamine neurons in the CB_2 receptor knockout mice showed a high~~er~~ vulnerability to LPS and a high~~er~~ degree of macrophage infiltration and astrogliosis in the SN [147][137]. In the rotenone rat model, pre-treatment of rats with β-caryophyllene, a phytocannabinoid and selective agonist of CB_2 receptor, prevented neurodegeneration and showed anti-inflammatory and antioxidant properties [157].

Biological actions of endocannabinoids are terminated by enzymatic hydrolysis. In the CNS, the MAGL is the main 2-AG~~-~~-inactivating enzyme and AEA is hydroly~~z~~s~~e~~d by the FAAH [158][159]. Therefore, rather than direct stimulation of cannabinoid receptors with exogenous ligands, an interesting approach is to increase the levels of the endocannabinoids, 2-AG or AEA, by inhibiting their degradation. MAGL inhibition with JZL184 increased 2-AG levels in the brain, improved motor behavio~~u~~r, and ~~it was~~exerted neuroprotective effects in the chronic MPTP mouse model [160]. *In vitro* studies showed that the neuroprotective effect of JZL184 was mediated by CB_2 and not by CB_1 receptors [161]. ~~In~~By contrast, FAAH inhibition with URB597 increased AEA levels in the brain and improved motor behavio~~u~~r~~,~~ but lacked neuroprotective activity [162]. Both, CB_1 and CB_2 receptors~~,~~ were involved in the symptomatic relief exerted by URB597, thus suggesting that it was mediated by neuronal CB_2 receptors probably through CB_1/CB_2 receptor heteromers [162]. The efficacy of dopamine type 2 receptor agonists to improve motor behavior was enhanced by the co-administration of URB597 [163].

Phytocannabinoids have cannabinoid receptor-independent anti-parkinsonian properties. Δ^9-THC and CBD restored dopamine levels in the 6-OHDA rat model in a CB_1 receptor-independent manner [120], presumably by acting through the same mechanisms (e.g., PPAR-γ, Nrf-2 signaling, thus improving mitochondrial function), ~~which~~and these mechanisms have been described for AD in the previous subsection (see 2.2.4.). However, a lack of neuroprotective activity was described for CBD in the chronic MPTP mouse model [164]. The phytocannabinoid Δ^9-THCV, with its antioxidant properties and the ability to activate CB_2 and to block CB_1 receptors, presents an interesting pharmacological profile for PD. It protected dopaminergic neurons in the 6-OHDA and in the LPS mice models [147]. An interesting group of cannabinoids are those that bind and activate PPARs [165], a type of intracellular receptors involved in the control of neuroinflammatory responses [166]. AEA is among the lipids that are considered to be an endogenous ligand for PPARs [167]. Some quinone derivatives of cannabigerol (CBG) such as VCE-003.2 act~~behave~~ as PPARγ activators and attenuate~~d~~ the loss of dopaminergic neurons in the LPS mouse model by decreasing the inflammatory response [168]. However, VCE-003.2 failed to protect dopaminergic neurons in the 6-OHDA mouse model, probably ~~due to~~because of the poor inflammatory response of the model [168].

3.3. Clinical evidence for the therapeutic potential of cannabinoids in PD and future perspectives.

Clinical trials to test the beneficial effect of cannabinoids in different aspects of PD do not show consistent results. Nabilone, a non-selective CB_1 receptor and CB_2 receptor agonist, improved LID [169]. Oral administration of a cannabis extract to ~~PD~~ patients with PD in a randomized, placebo-controlled, crossover study concluded that it did not

produce any pro- or anti-parkinsonian effect [170]. ~~In~~By contrast, an open-label observational study showed that smoked cannabis improved motor symptoms of PD such as bradykinesia, tremor, and rigidity and non-motor symptoms of the disease such as sleep and pain [171]. However, a single dose of smoked marijuana failed to improve tremor, thus suggesting that the anxiolytic action might benefit some ~~tremorous~~ patients with tremor when anxiety is an important triggering factor [172]. A subjective improvement in motor symptoms, namely, bradykinesia, rigidity, and tremor, and alleviation of LID was reported ~~by~~in ~~PD~~ patients with PD ~~that~~who smoked cannabis [173]. However, a different study reported that the main benefit was observed in sleep rather than in motor symptoms [174]. A retrospective study collecting subjective impressions of ~~PD~~ patients with PD under medical cannabis suggests an improvement in the initial stages of treatment without major adverse effects [175]. The different outcome of studies using plant extracts could be related to the administration route~~,~~ ~~since~~because cannabinoids are lipid-~~ ~~~~soluble compounds~~.~~;~~ hence, oral administration results in lower peak concentrations in plasma than ~~following~~ through inhalation. The Δ^9-THC content and the Δ^9-THC:CBD ratio are other parameters ~~that need~~ to be ~~taken into account~~considered.

These results indicate that targeting the ECS might be useful in the treatment of PD symptoms or dyskinesias. Further clinical studies involving larg~~er~~ samples of patients, placebo groups, appropriate molecular targets, and objective outcome measures are necessary to clarify the effectiveness of cannabinoid-based therapies.

The potential role played by the ECS in PD provides an excellent opportunity to develop new therapeutic strategies aimed at different aspects of the disease. Although an enormous effort has been made in ~~the~~ understanding ~~of~~ the elements of the ECS ~~has been done~~, further studies are necessary to unravel the functional significance of the

system under physiological and pathological conditions. The complex interplay between the main neurotransmitter systems in the basal ganglia and the modulatory role of the ECS, mainly through CB_1 receptors, might provide the base for the development of non-dopaminergic therapies or alleviation of LID. Among the different cannabinoid targets, stimulation of CB_2 receptors, either directly or by increasing endogenous cannabinoids, might offer an interesting disease-modifying alternative and a non-dopaminergic therapy for the disease.

The inconsistent effect of some cannabinoid receptor ligands could be attributed to their functional selectivity to induce specific conformational changes in the receptors modulating different intracellular signalling pathways [176][177]. Furthermore, cannabinoid receptors can form heteromers with other G-protein-coupledGPCR receptors generating new signalling entities that contribute to the heterogeneity of their responses [178][179]. The use of CB_1 receptor antagonistsm has been successfully investigated in preclinical models, but the only clinical trial using rimonabant for the hypokinetic symptoms in PD failed [180]. However, this trial recruited PD patients with PD thatwho were all well responded well to L-dopa, and it is possible that rimonabant could be a better option for those patients thatwho do not respond to classic dopaminergic replacement therapy (approximately 30%). While an attempt to directly target CB_1 receptors seems an improbable clinical approach for PD, manipulation of endogenous levels of AEA and 2-AG or compounds targeting different receptors may be a promising strategy. Further research is needed to define the multiple opportunities for manipulating this system in movement disorders.

4. Cannabinoid pharmacology in Huntington's disease

The key clinical symptoms in ~~Huntington´s disease (~~HD~~)~~ are choreic movements, which are produced by the degeneration of striatal medium-sized spiny neurons projecting to the GPe and SN [181]. The disease is also accompanied by behavioral disturbances and dementia, which are caused by the deterioration of specific neurons located in cortical structures [182]. These two neuronal subpopulations are the most vulnerable cells affected in this genetic pathology~~,~~ and the first to deteriorate [181][182][183]. However, the disease may ultimately affects other neuronal subpopulations in different CNS structures such as the cerebellum [183]. From a molecular ~~point of view~~perspective, HD is an inherited disorder caused by mutations in the gene encoding the regulatory protein huntingtin. The mutation consists in an excessive number of CAG repeats in the first exon, ~~that~~and this leads to a polyglutamine trait in the amino terminal end, thus causing a variety of anomalies in its cellular function [184]. HD is the most prevalent polyglutamine disorder, which also includes other diseases such as autosomal dominant hereditary ataxias [185]. The key neuropathological feature in HD is the formation of inclusions of the mutant huntingtin, with ubiquitin and other proteins. These inclusion bodies are located predominantly in the cell nucleus producing a transcriptional dysregulation of key genes like *BDNF* [186]. With lower frequency, huntingtin inclusions are also found in the cytosol and in the neurites, thereby ~~explaining~~ pointing out the damage observed in mitochondria and ~~in the~~ cytoskeleton, respectively [184]. The disease can be recapitulated in laboratory animals, including predominantly mice (e.g., R6/1, R6/2, HD94, and YAC128) ~~but~~and also other vertebrates (e.g., zebrafish) or invertebrates (*Drosophila*~~,~~ and *Caenorhabditis*~~.~~ *elegans*) by means of transgenes containing the human mutant huntingtin, and also in cells transfected with these mutant forms. Additional models may be generated by intrastriatal or systemic administration of excitotoxins or mitochondrial toxins (e.g., inhibitors of mitochondrial complex II)

Con formato: Fuente: Cursiva

(see [187] for a review on experimental models). Pharmacological therapies for ~~HD~~ patients with HD are extremely limited and circumscribed to the treatment of choreic movements. Currently, the only agent licensed is the inhibitor of the vesicular monoamine transporter-1 tetrabenazine (Xenazine®) [188]. Some antioxidants, minocycline, histone deacetylase inhibitors, and unsaturated fatty acids have been or are being investigated at the clinical level [188][189]. Cannabinoids were included in the list of neuroprotective agents investigated for HD early in the 2000s [190], although they had already been investigated as symptom-relieving agents [191]. In both cases, the research reached the clinical scenario [192][193][194][195][196][197].

4.1. The endocannabinoid system in Huntington's disease

Numerous changes in the endocannabinoid elements, affecting mainly CB_1 and CB_2 receptors and the hydrolyzing enzymes, have been described in brain samples from ~~HD~~ patients with HD and animal models. A key observation in *postmortem* tissues derived from ~~HD~~ patients with HD [198] and in different transgenic animal models [199][200][201][202][203] was the early defects in striatal CB_1 receptor signaling with a progressive loss of these receptors, which was evident even ~~prior to~~before neuronal death and the occurrence of choreic symptoms. An early stimulation of the CB_1 receptors located in striatal projecting neurons dampened their impairment, thus improving their capacity to inhibit the excitotoxic events that initiate the damage and to regulate growth factor generation that promotes striatal neuron survival [204].

Down-regulation of CB_1 receptors might be caused by a loss-of-function of the mutant huntingtin in its capacity to sequestrate the gene silencing factor REST to the cytoplasm, which facilitates its translocation to the nucleus and the inhibition of different genes including *BDNF* and *Cnr1* [205]. Other studies described equivalent effects exerted

through the inhibition of the ability of the mutant huntingtin to regulate other transcriptional modulators such as CREB-binding protein/CREB or NFκB-p65/Re1A acting at the promoter ~~for~~of the CB_1 receptor gene [206]. Despite the relationship between the reduction ~~of~~in CB_1 receptors and the mutant huntingtin, an early impairment in CB_1 receptor coupling to G proteins was observed days before the onset of the striatal degeneration in an experimental model generated by neurotoxin administration, the rat lesioned with the irreversible mitochondrial complex II inhibitor 3-nitropropionate [207]. Further studies conducted in R6/2 transgenic mice described that, ~~within the basal ganglia,~~ the loss of CB_1 receptors within the basal ganglia was evident in striatal projecting neurons, but it was preserved in corticostriatal neurons. The relationship between CB_1 receptor expression and neuronal vulnerability suggests that this receptor pool constitutes a promising target for neuroprotective therapeutic strategies [208][209]. These observations modified the initial idea that the potential benefits of CB_1 receptor activation are restricted at early stages of the disease~~,~~ and provided the basis for a therapeutic intervention at intermediate and advanced stages of the neurodegenerative process [210][209]. Although this question needs to be investigated, a recent study has demonstrated that the activation of corticostriatal CB_1 receptors protects striatal neurons projecting to the SN, but not those projecting to the GPe, against different insults [211].

The expression of CB_2 receptors is also altered in ~~HD~~ patients with HD and animal models. In rats lesioned with malonate, a reversible complex II inhibitor applied directly into the striatum [212]~~,~~; ~~in~~ genetic mouse models~~,~~ [213][214]~~,~~; and ~~in~~ *postmortem* tissue from ~~HD~~ patients with HD [213], CB_2 receptors were overexpressed in activated astrocytes and microglial cells recruited to the lesioned site [212][213][214]. One study conducted with human HD tissue~~s~~ samples failed to detect CB_2 receptor expression in

astrocytes and microglial cells but located this receptor in endothelial cells [215]. Alteration ~~of~~in cannabinoid receptors in HD shows consistent results ~~within~~among different experimental models, neurotoxin-based or transgenic model, and human samples. The deficit of CB_1 receptors clearly represents an alteration that contributes to HD progression by promoting excitotoxic damage and growth factor deficiency. CB_2 receptor expression increases during the progression of the disease, and it appears to be more of an endogenous protective response.

Endocannabinoid~~s~~ levels were also markedly reduced in the brain in experimental models of HD [216][217]. ~~In~~By contrast, the R6/2 transgenic mouse model presented an increase in FAAH levels [205][218]. Recent studies in patients with HD identi~~f~~fied an increase in endocannabinoid levels in the blood due to a reduction in FAAH activity [219], thus suggesting that changes related to FAAH levels and activity in human patients may be different ~~comparing patients with~~from those in animal models. A reduction in the level of this enzyme in patients with HD may be interpreted as an endogenous protective response to promote elevated AEA levels. The elevation of FAAH levels found in R6/2 mice may be part of the pathogenesis supporting the interest of exploring the possibilities of therapies based on FAAH inhibition for HD [205][218].

4.2. Pre-clinical evidence for the therapeutic potential of cannabinoids in Huntington's disease

The positive results obtained in a broad spectrum of animal models of HD confirmed the benefits of specific cannabinoids against different cytotoxic stimuli reproduced in the experimental models [220][14]. The cannabinoid receptor agonist WIN 55,212,2 protected striatal neurons in a rat model that relies on quinolinate-induced excitotoxic

damage [204]. CB_1 receptor activation with Δ^9-THC in the genetic model of the disease~~,~~ R6/2 mice~~,~~ attenuated striatal neuron loss, whereas striatal degeneration was aggravated in R6/2 mice with a genetic deficiency in CB_1 receptors [205]. The genetic rescue of CB_1 receptors using viral approaches recovered striatal synapses, although it was ineffective for the motor impairment [221]. The genetic ablation of the CB_1 receptor in other HD murine transgenic model or following 3-nitropropionate intoxication yielded equivalent results [222].

Cannabinoids that activate the CB_2 receptors selectively are also effective in HD, acting preferentially on inflammatory events and microglial activation in rats lesioned with malonate [212]~~,~~ in R6/2 mice [213] and following the excitotoxic lesion with quinolinate in mice [213]. The treatment of R6/1 transgenic mice with low doses of the non~~-~~selective synthetic agonist WIN_55,212-2 prevented the development of motor deficits and preserved striatal projecting neurons, although the study did not specified whether these effects were CB_1 and/or CB_2 receptor~~-~~ _ ~~mediated~~dependent [223]. However, administration of the non~~-~~selective cannabinoid agonists either HU-210 or Δ^9-THC to R6/1 mice lacked beneficial effects [224], whereas the FAAH inhibitor URB597 did not restore motor impairment but improved CB_1 striatal expression [224]. Differences in doses or agonists might account for such differences.

Antioxidant non~~-~~psychoactive phytocannabinoids CBD and CBG have also been investigated in experimental models of HD, ~~even~~ although their effects are independent of CB_1 and CB_2 receptors. CBD was neuroprotective in rats intoxicated with 3-nitropropionate, a model characterized by mitochondrial damage, oxidative stress, and calpain activation [225]. ~~In~~By contrast, it was inactive in malonate-lesioned rats, a HD model with a pro-inflammatory component [212]. CBG was neuroprotective in the R6/2 and ~~in~~ the 3-nitropropionate-lesioned mice [226]. The effect of CBD and CBG might be

mediated by the activation of non-endocannabinoid targets such as PPARs or by the other mechanisms indicated before for CBD (see subsection 2.2.4). The quinone derivative of CBG VCE-003.2, which activates PPARγ improved neuronal survival against the neurotoxicity caused by the mutant huntingtin and quinolinate *in vitro*, and against quinolinate and 3-nitropropionate *in vivo* [227]. Based on these broad-spectrum effects of cannabinoids in HD in experimental models, a combination of CBD with Δ^9-THC, as in the cannabinoid-based medicine Sativex®, was studied in animal models of HD [210]. This combination preserved striatal neurons in the neurotoxin-induced models, the malonate-lesioned mouse [228], and the 3-nitropropionate-lesioned rat [229]. In R6/2 mice, only Δ^9-THC in the form of botanical extract showed a beneficial effect [230].

4.3. Clinical evidence for the therapeutic potential of cannabinoids in Huntington's disease and future perspectives

The first clinical trials with cannabinoids in HD were conducted in the 1990s and examined whether CBD [192][231] or the Δ^9-THC synthetic analog nabilone [193] may improve choreic movements. However, an aggravation of these movements was reported [192][231][193]. Nabilone was beneficial on chorea and ~~on~~ behavioral disturbances in a case report study [194] and in a pilot clinical study [195]. Recently, a clinical study investigated the effect of different cannabinoid formulations, Sativex®, nabilone, or dronabinol on dystonia, a frequent symptom in HD [232], and patients experienced motor improvements mainly in dystonia and presented less irritability and apathy [197]. These clinical studies conducted with cannabinoids were focused on symptom relief.

~~As~~With regard~~s~~ to neuroprotectant effects, the positive results obtained in experimental animals with the combination of CBD and Δ^9-THC supported to test whether Sativex® may serve as a disease-modifying therapy for ~~HD~~ patients with HD [196]. The trial was conducted in Spain and was the first trial designed to test a neuroprotective strategy. Although Sativex® was safe and well-tolerated in ~~HD~~ patients with HD, unfortunately, it failed to provide evidence that it may slow down disease progression in HD [196]. Such failure may be related to the relatively short time, 12 weeks, for the active treatment and an unexpected prolonged placebo effect [196], thus suggesting the need ~~of~~for additional clinical testing using longer periods of treatments.

Therefore, the major challenges for cannabinoid-based therapies in HD are to find the appropriate cannabinoid formulations and to implement clinical trial designs to correlate the benefits observed in the pre-clinical models with a positive effect in ~~HD~~ patients with HD. A formulation with a single cannabinoid with a broad-spectrum profile might render a positive outcome, but a formulation based on the combination of cannabinoids with different activities would be better. In fact, this was the reason to select Sativex® [196]. To test disease-modifying therapies, a new trial design~~,~~ ~~using~~with long~~er~~ periods for the active treatment *versus* placebo~~,~~ would be necessary to reveal a neuroprotective effect in ~~HD~~ patients with HD treated with Sativex® or similar preparations [196].

5. Cannabinoid pharmacology in Amyotrophic Lateral Sclerosis

~~Amyotrophic lateral sclerosis (~~ALS~~)~~ is a progressive neurodegenerative disease predominantly affecting the upper and lower motor neurons leading to muscle denervation, atrophy, and paralysis [233]. The most abundant form of the disease is sporadic [234]. Approximately, 20% of patients present a hereditary form of ALS, which is associated with mutations in genes encoding for the key antioxidant enzyme

superoxide dismutase-1 (SOD-1), and the proteins involved in pre-mRNA splicing, transport, and stability of TAR-DNA--binding protein-43 (TDP-43) or FUS (fused in sarcoma) protein [233][235]. More recently, a CCGGGG hexanucleotide expansion was described in the *C9orf72* gene, which represents most of the cases of familial ALS [236]. It encodes a protein involved in intracellular trafficking in neurons, and other cell functions not completely understood [237]. Familial and sporadic forms of ALS are clinically and histopathologically indistinguishable, sharing pathogenic events and therapeutic intervention. In the case of some ALS-related genes, *TARDBP* (encoding TDP-43), *FUS*, or *C9orf72*, the disease can be accompanied by features of frontotemporal dementia (FTD), which supports the idea that, rather than being one disorder, ALS belongs to a broad spectrum of disorders ranging from motor to cognitive deficits [238]. As in other neurodegenerative disorders, the damage of upper and lower motor neurons occurs by the combination of excitotoxicity, chronic inflammation, oxidative stress, protein aggregation, and other cytotoxic events [239][240][235]. A characteristic feature in ALS pathogenesis is the extreme vulnerability of the axonal transport of proteins or cell organelles duowing to their excessive axonal length of motor neurons [241]. Experimental models for the study of ALS include predominantly transgenic mice overexpressing mutated forms of the different ALS-related genes (e.g., *SOD-1*, *TARDBP*, and *C9orf72*) [242]. The disease still lacks an effective treatment for symptoms and/or disease progression. For a long time, the antiexcitotoxic agent riluzole (Rilutek®) was the only approved drug [243]. More recently, the antioxidant agent edavarone (Radicava®) and the tyrosine kinase inhibitor masitinib [244] have been approved (or designed as orphan drugs) for the treatment of ALS patients with ALS. Solid evidence derived from studies describing the changes in specific elements of the ECS in the spinal cord, brainstem, and motor cortex, the CNS areas more affected in

~~ALS~~ patients with ALS and in animal models, placed cannabinoids as a possible and ~~promising~~ potential disease-modifying therapy in ALS [245][246].

5.1. The endocannabinoid system in Amyotrophic Lateral Sclerosis

The levels of the endocannabinoids AEA and 2-AG are elevated in the spinal cord of SOD-1 mutant mice [247][248]. This was paralleled by an increase in the expression of NAPE-PLD, but no changes were observed in DAGL~~,~~ nor in FAAH and MAGL [249]. ~~The i~~Increased ~~2-AG~~ levels of 2-AG in the spinal cord of these mice ha~~s~~ves been interpreted as an endogenous protective response, fuel~~l~~ing the idea that inhibiting endocannabinoid-~~–~~inactivating enzymes may be neuroprotective in ALS [250]. CB_2 receptors experienced an important up-regulatory response in the spinal cord of SOD-1 mutant [251][249], TDP-43 transgenic [252] mice, in an ALS-related canine neurodegenerative pathology [253] and in ~~ALS~~ patients with ALS [254][255]. This up-regulation appears to occur predominantly in astrocytes recruited at lesioned sites in mutant SOD-1 mice (unpublished results), dogs with degenerative myelopathy [253], and *postmortem* primary motor cortex samples from ~~ALS~~ patients with ALS [255]. CB_2 receptor expression was up-regulated in activated microglia in spinal grey and white matter areas in TDP-43 transgenic mice [252] and in *postmortem* spinal cord samples from ~~ALS~~ patients with ALS [254]. ~~-~~These observations suggest that beneficial effects may be obtained by selectively targeting this receptor in the control of astrocyte support or microglial toxicity for motor neurons. Changes in the expression of CB_1 receptors in animal models are inconclusive. A study reported down-regulatory responses in the spinal cord of SOD-1 mutant mice, even at early pre-symptomatic phases [256], thus suggesting that it may predispose motor neurons to excitotoxic events, but these observations were not validated in the same mutant mice [249]. No changes in CB_1

receptor~~s~~ expression were reported in the TDP-43 transgenic mice [252]. In the spinal cord of ~~ALS~~ patients with ALS, CB_1 receptors appear to be reduced [257].

5.2. Pre~~-~~clinical and clinical evidence for the therapeutic potential of cannabinoids in Amyotrophic Lateral Sclerosis

Most ~~of~~ pharmacological studies on the ~~with~~use of cannabinoids in experimental ALS were conducted in the classic transgenic mouse that overexpresses a mutated form (G93A) of SOD-1 despite mutations in this enzyme ~~only~~ represent~~s~~ing~~s~~ only a small percentage of ALS cases. The model was developed in the 1990s and was used to investigate the neuroprotective effects of Δ^9-THC [258], cannabinol (CBN) [259], WIN 55,212-2 [248], and the selective CB_2 agonist AM1241 [260][251], in all cases with beneficial effects. Similar findings were obtained from double mutants generated by crossing mutant SOD-1 mice with mice deficient in endocannabinoid genes~~,~~ FAAH or CB_1 knockout mice [248]. These results ~~not only~~ reinforced not only the interest in ~~of~~using CB_1 receptor agonists~~,~~ but also the elevation of endocannabinoid levels with FAAH inhibitors. Inhibition of MAGL in the same mutant SOD-1 mouse model delayed disease onset and progression~~,~~ and improved animal survival, probably through the reduction in pro~~-~~inflammatory cytokines and the elevation of BDNF in the spinal cord [250]. These effects were also reproduced *in vitro* [250]. Recent studies have extended the cannabinoid pharmacology to the new transgenic mouse model of TDP-43 (A315T). Activation of CB_2 receptors improved motor behavior, preserved spinal motor neurons, and attenuated glial reactivity [261]. CB_1 receptor activation also decreased glial reactivity but to a lower extent [261].

Clinical evidence for the use of cannabinoids in ALS is scarce.~~-~~ The first studies were exclusively observational, based on subjective impressions of ~~ALS~~ patients with ALS

who self-medicated with cannabis, and the results suggested a mild improvement for different symptoms [262]. A randomized, double-blind, crossover trial conducted with oral Δ^9-THC showed that, although the drug it was well tolerated in patients, it failed to decrease the frequency and intensity of cramps [263][264]. No clinical studies have tried been attempted to investigate the potential of cannabinoids as disease-modifying therapies. There is an urgent need for additional clinical investigations in ALS, and cannabinoids might represent an interesting therapeutic approach [245].

5.3. Therapeutic implications for a cannabinoid-based therapy for Amyotrophic Lateral Sclerosis

The rResearch in cannabinoid-based neuroprotective therapies in ALS has been circumscribed to the pre-clinical level supporting the relevance of CB_2 receptor activation on astrocyte trophic support, microglial reactivity, and neuroinflammation. It also involves certain CB_1 receptor-mediated effects that might contribute to attenuate excitotoxic damage [265]. Cannabinoids with antioxidant properties (e.g., Δ^9-THC, CBN) that haveexerting a cannabinoid receptor-independent mechanism of action (perhaps related to PPAR-γ signalling) offer and interesting therapeutic alternative, but pre-clinical studies are needed before reaching the clinic [265]. In this context, the potential of a Sativex-like combination of botanical extracts enriched in Δ^9-THC and CBD was investigated in post-symptomatic SOD-1 mutant mice [249]. However, this combination provided a poor neurological recovery and no changes in animal survival [249], thus suggesting the need for additional cannabinoid combinations that demonstrate to be effective in preclinical models and that may be translated to the clinical scenario.

6. Conclusions and future perspectives

Cannabinoids are compounds with a broad spectrum of effects, which makes them suitable to target the multiple pathological features that characterize neurodegenerative diseases (Fig. 2). ~~Currently, compounds with multiple targets or combinations of cannabinoids with different activities are being investigated~~. Pre-clinical studies provide evidence to support the potential of cannabinoid pharmacology for the treatment of these conditions. Each neurodegenerative disease has specific alterations of the ECS~~,~~ that will provide specific substrates for a cannabinoid-based therapy. ~~In~~With ~~this~~ regard to this, an interesting experimental therapy for AD would be a 1:1 combination of Δ^9-THC:CBD because of the synergy existing between the mechanisms of action ~~of~~for each natural cannabinoid. The administration of both compounds was more effective than each single cannabinoid in reducing the cognitive decline and certain pathological processes. Moreover, available clinical data about the chronic use of a combination of Δ^9-THC and CBD for other indications suggest~~s~~ that it might result in a safe and well-tolerated treatment for ~~AD~~ patients with AD ~~with~~and a virtual absence of the side effects commonly associated with the psychotropic properties of Δ^9-THC ~~due~~owing to the capacity of CBD to counteract them. Interesting pre-clinical alternatives for the treatment of PD would be targeting CB_2 receptors, as well as the modulation of endocannabinoid levels through the inhibition of their catabolic enzymes MAGL, which is neuroprotective, and FAAH. The phytocannabinoid Δ^9-THCV with its particular profile has emerged as a valuable alternative, ~~that~~which needs to be further ~~explored~~investigated. On the ~~B~~basis~~ed~~ ~~on~~of the promising data on experimental models of HD, activation of CB_1 and CB_2 receptors would be the targets of choice for cannabinoid-based therapies, whereas cannabinoids targeting both receptors and also PPARγ would be the best option in ALS. ~~Different strategies have been tested, directly~~

~~targeting cannabinoid receptors with agonists or antagonists, or indirect modulation of the endocannabinoid signaling with inhibitors of endocannabinoid degradation or activation of cannabinoid receptor independent effects.~~ In fact, further research is needed to ~~explore~~ investigate one of the most interesting aspects of cannabinoid pharmacology, their neuroprotective profile, probably ~~due~~owing to their pleiotropic activity. The profound rearrangements ~~suffered~~ experienced by the ECS during the time course of neurodegenerative diseases are specific for each disease and may vary through the different stages of the degenerative process. ~~Since~~ Because ECS changes are not homogeneous along the disease course and affect neuronal subsets differentially, ~~the~~ similar therapeutic effects might be observed with drugs producing opposing actions or the same compound might produce both, thus amelioration or worsening of symptoms. An additional level of complexity is attributed to the functional selectivity of cannabinoids [177]. Different receptor agonists induce specific changes in receptor conformation, thereby activating different signaling pathways. Therefore, each class of cannabinoid receptor ligand needs to be evaluated separately for therapeutic efficacy. An important consideration that ~~has not been~~requires an in-de~~e~~p~~th~~~~ly explored~~investigation is the ability of cannabinoid receptors to form heteromers with other receptors generating unique signaling units that cannot be achieved by the individual receptors [153]. These heteromers contribute to the heterogeneity of cannabinoid receptor signaling and provide novel pharmacological targets. PPARγ is one of the most relevant targets for CBD and other cannabinoids and a key element ~~in~~for ~~their~~exerting anti-inflammatory and neuroprotective properties [68]. The recent formulation of CBD as Epidiolex® (GW Pharmaceuticals, UK), which was approved by the Food and Drug Administration~~gency~~ for the treatment of infantile refractory

epileptic syndromes, may facilitate ~~its~~the use of this cannabinoid in clinical trials for neurodegenerative disorders.

Consequently, further research is needed to identify the precise formulation for each type of pathology~~,~~ and each subset of patients ~~and~~as well as for ~~to~~ achievinge a neuroprotective effect. New clinical studies involving large~~r~~ samples of patients, placebo groups, appropriate molecular targets, and objective outcome measures are necessary to clarify the effectiveness of cannabinoid-based therapies.

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Declaration of authors' competing interests

The ~~A~~authors declare they have no~~t any~~ potential conflict of interest in relation ~~with~~to this submission.

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Figure legends

Figure 1: Versatility of the endocannabinoid system (ECS) elements to counteract the effects of aging and neurodegeneration. The ~~endocannabinoid system (~~ECS~~)~~ modulates common traits of neurodegeneration counteracting neuronal death, oxidative stress, neuroinflammation, or abnormal protein accumulation. The key location of the different ECS elements within the brain enables modulation of crucial processes for the correct balance between neuron survival and degeneration. Neurons express preferentially CB_1 receptors involved in the regulation of neurotransmitter release. During the degenerative process, these receptors experience important alterations that may contribute to neuronal death. Resting microglia express low levels of CB_2 receptors, ~~that~~and the levels were ~~became~~ up~~-~~regulated under pathological conditions. Targeting these receptors modulates neuroinflammatory responses. Astrocytes express low levels of CB_1 receptors. Upon activation, they may modify the expression of either CB_1 or CB_2 receptor~~ expression~~. The different cell types have the machinery for endocannabinoid biosynthesis, 2-arachidonoylglycerol (2-AG), or anandamide (AEA), thus contributing to the endocannabinoid tone of the brain. The specific contribution of each cell type may ~~be~~ vary under different pathological conditions.

Figure 2: Broad~~-~~spectrum profile of cannabinoids for the treatment of different neuropathological traits of neurodegenerative diseases. ~~A b~~Beneficial effects of cannabinoid-based therapies ~~were described~~determined ~~in~~from animal models of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Modulation in microglial immune responses showed a therapeutic response in AD, PD, HD, and ALS models. The antioxidant properties of cannabinoids were beneficial in animal models of AD and HD. In models

of AD, targeting the endocannabinoid system successfully improved synaptic plasticity and prevented Aβ aggregation and toxicity. Glutamatergic excitotoxicity was reversed by cannabinoid treatment in animal models of AD and HD. Endocannabinoid signaling modulation provides neuroprotection and disease modification in experimental models of PD, HD, and ALS.