Endocannabinoids and Neurodegenerative Disorders: Parkinson's Disease, Huntington's Chorea, Alzheimer's Disease, and Others

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Contents

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R.G. Pertwee (ed.), *Endocannabinoids*, Handbook of Experimental Pharmacology 231, DOI 10.1007/978-3-319-20825-1_8

Abstract

This review focuses on the role of the endocannabinoid signaling system in controlling neuronal survival, an extremely important issue to be considered when developing new therapies for neurodegenerative disorders. First, we will describe the cellular and molecular mechanisms, and the signaling pathways, underlying these neuroprotective properties, including the control of glutamate homeostasis, calcium influx, the toxicity of reactive oxygen species, glial activation and other inflammatory events; and the induction of autophagy. We will then concentrate on the preclinical studies and the few clinical trials that have been carried out targeting endocannabinoid signaling in three important chronic progressive neurodegenerative disorders (Parkinson's disease, Huntington's chorea, and Alzheimer's disease), as well as in other less well-studied disorders. We will end by offering some ideas and proposals for future research that should be carried out to optimize endocannabinoid-based treatments for these disorders. Such studies will strengthen the possibility that these therapies will be investigated in the clinical scenario and licensed for their use in specific disorders.

Keywords

Alzheimer's disease • Cannabinoids • Endocannabinoids • Huntington's disease • Neurodegeneration • Neuroprotection • Parkinson's disease

Abbreviations

2-AG	2-Arachidonoyl-glycerol
3NP	3-Nitropropionate
$5HT_{1A}$	Serotonin 1A receptor type
AD	Alzheimer's disease
AEA	Anandamide
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BACE1	β-site amyloid precursor protein cleaving enzyme 1
BBB	Blood brain barrier
CAG	Cytosine-adenine-guanine
CB	Cannabinoid
CB_1	Cannabinoid receptor type 1
CB_2,	Cannabinoid receptor type 2
CBD	Cannabidiol
CBN	Cannabinol
CNS	Central Nervous System
COX-2	Cyclooxygenase-2
DAGL	Diacylglycerol lipase
eCB	Endocannabinoid
FAAH	Fatty acid amide hydrolase
HD	Huntington's disease

HU-211	Dexanabinol
IL-10	Interleukin-10
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MAGL	Monoacylglycerol lipase
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NADPH	Nicotinamide adenine dinucleotide phosphate
NMDA	N-methyl-D-aspartate
PD	Parkinson's disease
PPAR	Peroxisome proliferator-activated receptor
ROS	Reactive oxygen species
SCA	Spinocerebellar ataxia
TNF-α	Tumor necrosis factor-α
TRPV1	Transient receptor potential vanilloid type 1
Δ^9-THC	Δ^9-tetrahydrocannabinol
Δ^9-THCV	Δ^9-tetrahydrocannabivarin

1 Compounds Targeting Endocannabinoids as Neuroprotective Agents

The homeostastic regulation of cells is one of the key functions assigned to the endocannabinoid (eCB) system, and it extends to the decision of cells to die or survive in certain unfavorable conditions. This influence of eCBs on death/survival explains the notable cytoprotective properties exhibited by compounds that target specific elements in the eCB system in distinct pathological conditions (Fernández-Ruiz et al. 2010, 2014). These properties are especially relevant in the central nervous system (CNS), in which neuron loss is extremely difficult to overcome given that neurons are post-mitotic cells incapable of replicating their DNA and dividing. Lost neurons may be replaced by new neurons, although orchestrating the generation of these neurons from neural cell progenitors in the adult brain is still limited by our lack of understanding (Ziemka-Nałęcz and Zalewska 2012). These limitations make the preservation of the original neurons generated during brain development or naturally replaced during the lifetime of the individual, a key objective to ensure the correct functioning of the different brain structures. Numerous compounds have been investigated to achieve such preservation and to facilitate the development of novel neuroprotective therapies for neurodegenerative disorders (e.g., antioxidants, anti-inflammatory or anti-excitotoxic agents, inhibitors of apoptosis, enhancers of autophagy, neurotrophic factors, etc.. . .), although most have failed to reproduce in humans the positive effects seen in experimental models (Athauda and Foltynie 2014; Berk et al. 2014; Sampaio et al. 2014).

In the past 10–15 years, the capacity of compounds targeting the eCB system to protect neurons and some glial cell sub-populations (e.g., astrocytes, oligodendrocytes, and their precursor cells) against different types of cytotoxic insult has been

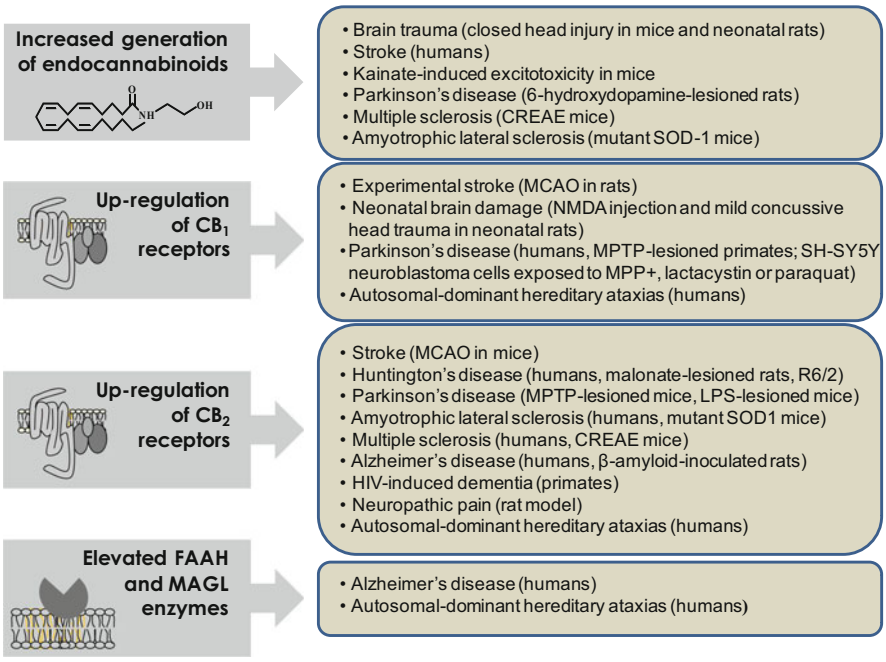

Fig. 1 Alterations to eCB ligands, their receptors, and enzymes in neurodegenerative disorders

investigated by different research groups (Fernández-Ruiz et al. 2014). These studies concentrated on identifying the targets within the eCB system, such as the cannabinoid (CB) receptors or eCB enzymes that can be pharmacologically activated or inhibited, provoking neuroprotection in experimental models of the most prevalent neurodegenerative disorders (Fernández-Ruiz et al. 2010, 2014). These exhaustive studies have placed the eCB system in a promising position, since the results they have generated indicate that specific CBs or other compounds (alone or in combination) may serve as therapies for neurodegenerative disorders that modify disease progression (Fernández-Ruiz et al. 2010). These therapies might provide notable advantages over other agents with proposed neuroprotective activity, for example, by mimicking the endogenous protective response of this signaling system to stimuli that damage the brain (Fernández-Ruiz et al. 2010; Pacher and Mechoulam 2011). In other words, the well-defined alterations to eCB ligands, their receptors, and/or their signaling pathways evident in neurodegenerative disorders (see Fig. 1) may reflect an endogenous response of this system to combat the brain damage caused by inflammatory, excitotoxic, infectious, traumatic, or oxidative insults, and this response may be replicated by administering compounds that interact with the eCB system, producing beneficial results (Fernández-Ruiz et al. 2014). Indeed, the elevation of eCBs that is typically associated with neurodegenerative conditions can be further enhanced with inhibitors of their inactivation (e.g., UCM707: Marsicano et al. 2003), as well as by treatment with eCBs (Panikashvili et al. 2001), and this enhancement is expected to

be neuroprotective. However, it is also possible that the efficacy of compounds acting on the eCB system may be due to the ability of these compounds to correct any potential dysregulation of eCB signals that might be instrumental in the pathogenesis of these disorders (Fagan and Campbell 2014). Indeed, far from being mutually exclusive, both types of responses may occur concomitantly: the mimicking of endogenous protection and the correction of dysregulated signals.

The second singular feature of CBs as neuroprotectants is their broad-spectrum activity as opposed to a greater potency. Indeed, their potency is relatively similar to those neuroprotective agents studied more frequently: N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists (dizocilpine); calcium channel blockers (nimodipine); antioxidants (coenzyme Q10, *N*-acetylcysteine); and anti-inflammatory compounds (minocycline). However, their advantage is that they combine all these properties in a single molecule or in a mixture of two or more CBs. This is extremely important in neurodegenerative disorders as neuronal damage also results from the concerted influence of different cytotoxic events: energy failure, excitotoxicity, mitochondrial dysfunction, failures in proteostasis, inflammation, and oxidative stress. Accordingly, it appears difficult to effectively control brain damage with compounds or strategies that affect only one of these cytotoxic events. Thus, a reliable therapy is likely to require the use of a broad-spectrum strategy, employing "multi-target" drugs or the combination of different therapeutic agents (Geldenhuys and Van der Schyf 2013). Compounds acting on the eCB system may display such broad-spectrum activity as they can influence different elements within the eCB signaling system, for example, the type 1 (CB_1) and type 2 (CB_2) cannabinoid receptor, or fatty acid amide hydrolase (FAAH), and these elements might fulfill specific roles in the neuroprotective responses (Fernández-Ruiz et al. 2014). In addition to the possibility of combining compounds with such profiles, novel neuroprotective targets within the eCB system or in its vicinity are being identified. For example, activation of the GPR55 orphan receptor was recently found to be beneficial against excitotoxic insults in an in vitro model of cultured rat hippocampal slices (Kallendrusch et al. 2013). CBs can also act on other non-eCB system targets that might play key roles in controlling neuronal homeostasis and survival, and, hence, a well-demonstrated neuroprotective potential, such as: (1) the nuclear receptors of the peroxisome proliferator-activated receptor (PPAR) family (Fidaleo et al. 2014); (2) transcription factors like NrF-2, NFκB (Iuvone et al. 2009; Fernández-Ruiz et al. 2013); (3) the serotonin 1A receptor type ($5HT_{1A}$: Pazos et al. 2013); and (4) components of the adenosine signaling pathway (Castillo et al. 2010).

A last advantageous feature of compounds that act on the eCB system compared to other neuroprotectant agents is the key location of the molecular targets in the different cell substrates in the CNS (e.g., neurons, astrocytes, resting and reactive microglia, perivascular microglial cells, oligodendrocytes and oligodendrocyte precursor cells, and neural progenitor cells) and even in key CNS structures [e.g., the blood–brain barrier (BBB)]. These specific locations enable such compounds to exert selective control over the specific functions fulfilled by these cells in degeneration, protection, and/or repair (Fernández-Ruiz et al. 2014). This is particularly relevant to the CB receptors, for example, CB_1 receptors that are involved in

controlling excitotoxic damage are mainly located in neurons and, particularly, in glutamatergic neurons. As indicated in Fig. 1, a few studies have demonstrated that the CB_1 receptor is upregulated in chronic neurodegenerative conditions (Lastres-Becker et al. 2001; Rodríguez-Cueto et al. 2014a). However, CB_1 receptors are not generally a target for neuroprotection, precisely due to the progressive loss, in neurodegenerative disorders, of specific groups of neurons in which CB_1 receptors are expressed, thereby provoking a premature and rapid reduction in the availability of these receptors. In contrast, CB_2 receptors are generally expressed weakly in the healthy brain, but they are dramatically upregulated in glial elements in conditions of neurodegeneration in reactive microglia and activated astrocytes (Fernández-Ruiz et al. 2007, 2010), making them a particularly interesting and promising target from a therapeutic point of view. An additional and interesting discovery, in line with the idea that eCB elements may be located in structures crucial for maintaining the integrity of the CNS, is the association of CB receptors with preserving the integrity and function of the BBB (Vendel and de Lange 2014). This barrier is essential for neuroprotection, and recent studies demonstrated that it is under the control of both CB_1 and CB_2 receptor-mediated signals (Fujii et al. 2014), which maintain the integrity of tight junctions, inhibit leukocyte infiltration, and facilitate β-amyloid clearance (Vendel and de Lange 2014).

In this article, we will review the information that supports the promising therapeutic potential of compounds acting on the eCB system for preserving neurons and glial cells in conditions of brain damage. This article will be divided into three parts. First, we will review the different cellular and molecular mechanisms underlying the neuroprotective effects derived from the pharmacological manipulation of key elements of the eCB signaling system (e.g., the CB receptors) or of additional targets indirectly related to this signaling system (e.g., PPARs, transcription factors). Second, we will concentrate on three important chronic neurodegenerative disorders in which the neuroprotective effects of CBs have been studied in most depth, Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD), as well as on a few less well-studied disorders like autosomal-dominant hereditary ataxias, Down's syndrome, and prion-related disorders. Lastly, we will conclude with some ideas about the steps that should be taken to extrapolate these findings, mainly obtained in preclinical models, to the clinical arena.

2 Mechanisms Involved in the Neuroprotection Afforded by Compounds That Target the eCB System

As mentioned above (Sect. 1), compounds that target the eCB system display a wide range of effects when compared to other neuroprotectants, which may be important in neurodegenerative disorders where nerve cell damage is the consequence of a combination of cytotoxic events. To oppose such a "collaborative strategy" for killing neurons, any attempt to provide neuroprotection should be based on the idea of using broad-spectrum compounds or combinations of different therapeutic agents (Geldenhuys and Van der Schyf 2013), a profile that CBs fit

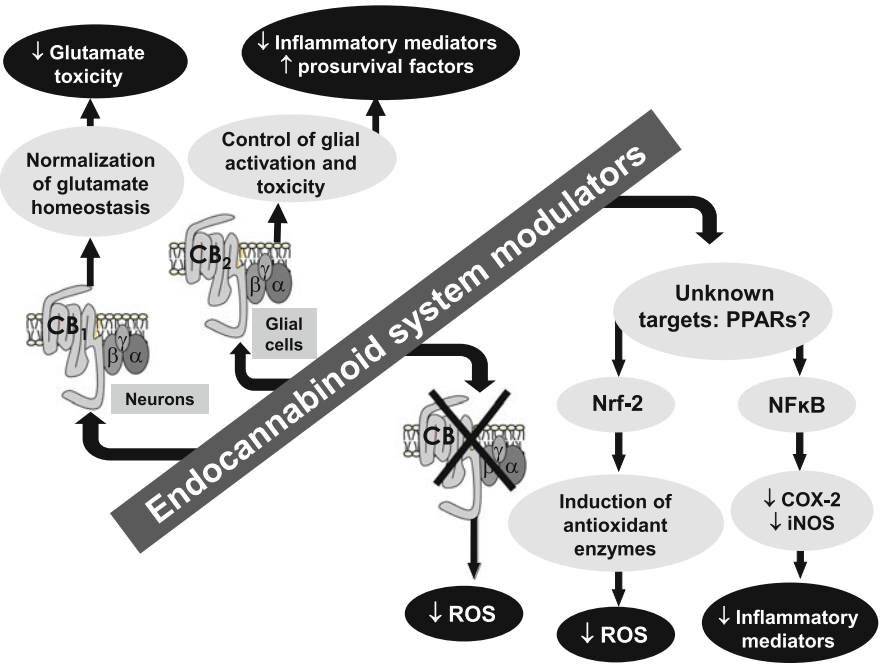

Fig. 2 Molecular and cellular mechanisms proposed for the neuroprotective effects of compounds that act on the eCB system

perfectly. Their wide range of effects are likely to be beneficial because the neuroprotective mechanisms they target are quite diverse and frequently complementary (see Fig. 2). They include not only the activation of CB_1 and/or CB_2 receptors but also they extend to CB receptor-independent mechanisms, such as the blockade of NMDA receptors, or the activation of nuclear receptors of the PPAR family, NFκB and/or Nrf-2 signaling (Fernández-Ruiz et al. 2010; Iuvone et al. 2009; Fidaleo et al. 2014).

2.1 The Effects Mediated by CB_1 Receptors

The participation of eCBs and their receptors in a retrograde signaling system in glutamatergic synapses (Ohno-Shosaku and Kano 2014) enables the eCB system to be pharmacologically targeted for diseases characterized by abnormal glutamate homeostasis, such as neurodegenerative disorders. Thus, compounds that can normalize glutamate homeostasis by targeting the CB_1 receptor (see Fig. 2) act as anti-excitotoxic agents (Fernández-Ruiz et al. 2010), although such effects may also be elicited by cannabinoids that do not activate the CB_1 receptor. One example of such a compound is dexanabinol (HU-211), which is the inactive enantiomer of HU-210, a potent CB_1/CB_2 receptor agonist (Shohami and Mechoulam 2000). HU-211 does not bind to CB receptors, but it affords neuroprotection by blocking

NMDA receptors (Nadler et al. 1993). The anti-glutamatergic properties of HU-211 have been investigated extensively in preclinical models, yet such benefits have not been demonstrated in patients (Klein and Newton 2007).

The anti-excitotoxic effects mediated by CB_1 receptors are apparently exerted at two neuronal sites: (1) through presynaptic CB_1 receptors in glutamatergic terminals where CBs would reduce excess glutamate release and (2) through postsynaptic CB_1 receptors on neurons containing NMDA receptors, in which CBs may reduce the excessive intracellular levels of calcium by closing voltage-dependent calcium channels, thereby dampening the over-activation of calcium-dependent destructive pathways. All this information has been obtained in numerous studies conducted in vitro on cultured neurons (Shen and Thayer 1998; Abood et al. 2001) or on rat brain slices (Hampson et al. 1998), as well as in vivo using rodent models of ischemic damage (Nagayama et al. 1999) or following the induction of excitotoxicity (van der Stelt et al. 2001; Marsicano et al. 2003). In all cases, the participation of CB_1 receptors was demonstrated with CB_1 receptor antagonists or using mice genetically deficient in CB_1 receptors (Fernández-Ruiz et al. 2005, 2010).

Another neuroprotective effect mediated by CB_1 receptors is improvement of the blood supply to the injured brain, which is particularly relevant to stroke or traumatic injuries (Fernández-Ruiz et al. 2005). This effect would be exerted through CB_1 receptors located in the brain microvasculature, which would reduce the generation of endothelin-1 and other endothelium-derived mediators (Mechoulam et al. 2002). In ischemic conditions, it is these factors that cause vasoconstriction and that limit the blood supply to the injured area, thereby aggravating brain damage. This effect was reversed by rimonabant, supporting the contribution of CB_1 receptors (Chen et al. 2000), although more recent evidence also suggests the involvement of CB_2 receptors (Choi et al. 2013).

2.2 The Effects Mediated by CB_2 Receptors

Based on their key location in glial elements, CB_2 receptors may be activated to control the influence of glial cells on neuronal homeostasis and survival, particularly when they become reactive (Fernández-Ruiz et al. 2007, 2010). Although CB_2 receptors are the main elements contributing to this control, we cannot rule out a neuroprotective effect of CB_1 receptors that involves glia (Chung et al. 2011). This may be particularly relevant to the regulation of astrocyte activity in conditions of brain damage, which could be affected exclusively by the activation of CB_2 receptors, or might involve CB_1 receptors, either alone or in conjunction with CB_2 receptors (Fernández-Ruiz et al. 2007, 2010; Stella 2010). Irrespective of the CB receptor type involved, the benefits that CBs may provide appear to be associated with the trophic role exerted by these glial cells, including improvements in the supply of metabolic substrates to neurons (lactate or ketone bodies: Duarte et al. 2012). They could also enhance the generation of neurotrophins or anti-inflammatory mediators that could potentially rescue damaged neurons (e.g.,

interleukin-10 [IL-10], and of IL-1 receptor antagonists, or pro-survival factors like transforming growth factor-β [TGF-β]: Smith et al. 2000; Molina-Holgado et al. 2003). Finally, CBs could also inhibit the production of chemokines by astrocytes (e.g., fractalkine), an effect that would be predominantly mediated by the activation of CB_2 receptors (Sheng et al. 2009). CB_2 receptors have also been identified in oligodendrocytes and their precursor cells (Gómez et al. 2010, 2011), in which they play a role in key functions of these glial cells, which are also crucial for neurons.

In contrast to astrocytes, microglial cells are greatly affected by CB_2 receptors in the CNS, particularly when these cells are activated. This has been studied intensively over the past 10 years after microglial cells surrounding senile plaques were seen to be immunostained for CB_2 receptors in postmortem AD brains (Benito et al. 2003). Indeed, CB_2 receptors appear to play an important role in the proliferation and migration of these cells at lesion sites (Walter et al. 2003; Carrier et al. 2004). In addition, the activation of CB_2 receptors dampens the generation of a variety of neurotoxic factors by microglial cells (Fernández-Ruiz et al. 2007, 2010), for example, tumor necrosis factor-α (TNF-α), a major contributor to the pathophysiology of brain injury (Stella 2010). Activation of CB_2 receptors apparently inhibits the production of TNF-α by inhibiting NFκB (see Fig. 2: Oh et al. 2010), a transcription factor that plays a key role in the regulation of pro-inflammatory responses. However, the inhibition of NFκB by CBs that do not activate the CB_2 receptor leads to an anti-inflammatory scenario too (e.g., cannabidiol [CBD] or HU-211: Kozela et al. 2010; Shohami and Mechoulam 2000). This may be achieved by activating the nuclear receptors of the PPAR family (Fidaleo et al. 2014) that regulate NFκB signaling (Stahel et al. 2008). Therefore, CBs may control inflammatory responses by working through two well-differentiated molecular mechanisms, consistent with the idea that their principal added value is their broad-spectrum profile.

Recent studies have also shown the CB_2 receptor to be present in certain neuronal subpopulations in the CNS (Lanciego et al. 2011; Rodríguez-Cueto et al. 2014a; García et al. 2015), supporting a possible role of this receptor in synaptic activity, although this has not yet been conclusively demonstrated. There is no evidence that the activation of these "neuronal CB_2 receptors" may be neuroprotective, although they may serve as a potential biomarker for neuronal loss in specific neurodegenerative disorders like PD (García et al. 2015) or spinocerebellar ataxias (SCAs: Rodríguez-Cueto et al. 2014a).

Therefore, the presence of CB_2 receptors in reactive microglia, activated astrocytes, oligodendrocytes, and in some neuronal subpopulations places these receptors in a promising position for their use as a target for neuroprotection (Fernández-Ruiz et al. 2010). Such pharmacological manipulations may be the best way to reproduce the endogenous response provoked by these receptors, which are upregulated in activated astrocytes and reactive microglia in response to inflammatory, excitotoxic, and traumatic insults, such as those that occur in neurodegenerative disorders (see Fig. 2). In addition, those CBs that selectively target the CB_2 receptor do not provoke the psychotropic side effects elicited by CBs

that activate the CB_1 receptor, indicating that they may be safe and well tolerated in clinical applications.

2.3 Effects Not Mediated by CB_1 or CB_2 Receptors

The neuroprotection provided by CBs includes some responses that are not mediated by CB_1 or CB_2 receptors (Fernández-Ruiz et al. 2010, 2013). For example, the antioxidant properties of phytocannabinoids and some synthetic CBs have been found not to depend on CB_1 receptor activation (Marsicano et al. 2002). An interesting compound with such a CB_1/CB_2 receptor-independent antioxidant profile is CBD, although a relatively similar antioxidant activity has also been found with other structurally similar compounds, such as Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabinol (CBN), nabilone, and HU-211 (Marsicano et al. 2002). This potential has been frequently related to the ability of CBD to act as a scavenger of reactive oxygen species (ROS) rather than to its capability to activate intracellular targets and specific signaling pathways. Indeed, CBD has a poor affinity for the CB_1 and CB_2 receptors (Fernández-Ruiz et al. 2013), although CBD does display certain activity as a CB_1/CB_2 antagonist in vitro (Pertwee 2008), and it can activate CB_2 receptors in the immature brain in conditions of neonatal ischemia (Castillo et al. 2010). A priori, this lack of CBD activity at the classic CB receptors would suggest that this phytocannabinoid does not control excitotoxicity by directly activating CB_1 receptors or by reducing microglial toxicity via direct CB_2 receptor activation. However, CBD is no less active against the brain damage produced by altered glutamate homeostasis than CBs that do target the CB_1 receptor (El-Remessy et al. 2003) or those targeting the CB_2 receptor against local inflammatory events (Ruiz-Valdepeñas et al. 2011). It is possible that these anti-glutamatergic and anti-inflammatory effects of CBD may be mediated indirectly by cannabinoid receptors, especially given the capability of CBD to inhibit the inactivation of eCBs (e.g., by inhibiting the FAAH enzyme [Leweke et al. 2012] or the eCB transporter [Bisogno et al. 2001]). Such effects may enhance the action of eCBs at CB_1 and CB_2 receptors (Fernández-Ruiz et al. 2013) and also at other receptors that may be activated by eCBs, such as transient receptor potential vanilloid type 1 (TRPV1) receptors (Bisogno et al. 2001) or nuclear PPAR receptors (Fidaleo et al. 2014). In fact, PPAR receptors, as well as other unknown intracellular targets, have recently been proposed to mediate the antioxidant and anti-inflammatory actions of CBD, Δ^9-THC, and other CBs (Iuvone et al. 2009; Fernández-Ruiz et al. 2013; see Fig. 2). These CBs could regulate the intracellular pathways that control endogenous antioxidant defenses, in particular the signaling triggered by Nrf-2 (Fernández-Ruiz et al. 2013; see Fig. 2). This transcription factor plays a major role in controlling antioxidant response elements located in genes encoding different phase II antioxidant enzymes, and it was recently linked to the activity of certain CBs in an experimental model of the infarcted heart, although a major role for CB_2 receptors was proposed in these effects (Wang et al. 2014). Recent studies proved that the eCB anandamide (AEA), which given its eicosanoid

structure is not a ROS scavenger, can nevertheless reduce oxidative stress through a mechanism that might involve CB_1 receptors (e.g., a reduction in Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-2: Jia et al. 2014). Thus, together these data implicate the two classic cannabinoid receptors in the control of oxidative stress, a process frequently regarded as being CB receptor-independent.

CBD is also anti-inflammatory, reducing microglial cell migration (Walter et al. 2003) and the pro-inflammatory mediators they produce (Esposito et al. 2007) to a similar extent as CBs that target the CB_2 receptor. However, its effects are likely to be associated with its ability to bind and activate the nuclear receptors of the PPAR family, in particular PPAR-γ (Esposito et al. 2011), and to the regulation of their downstream signals, including the NFκB signaling that controls several genes encoding pro-inflammatory enzymes (e.g., inducible nitric oxide synthase [iNOS], cyclooxygenase-2 [COX-2], metalloproteases) and cytokines (e.g., IL-1β: see Fig. 2; Esposito et al. 2006a, 2007). These PPAR-mediated anti-inflammatory effects are also elicited by other CBs, although with some differences. For example, the activation of PPAR-γ receptors by Δ^9-THC protected differentiated SH-SY5Y neuroblastoma cells exposed to relevant parkinsonian toxins (e.g., MPP+, lactacystin, paraquat), whereas other antioxidant CBs did not (e.g., CBD, nabilone: Carroll et al. 2012).

2.4 eCB-Derived Molecules May Enhance Neurotoxicity

Despite the well-demonstrated neuroprotective properties of certain CBs that directly or indirectly target the eCB system, there is evidence that some CBs may also enhance brain damage in certain circumstances (Fowler et al. 2010). Such an enhancement has been found to be produced by the two major eCBs, each of which may help generate new lipid mediators via COX-2 metabolism (e.g., prostaglandin-glyceryl-esters, prostamides), which may be toxic to neurons (Sang et al. 2007; Valdeolivas et al. 2013). When such a detrimental enhancement of brain damage occurs, inhibiting eCB synthesis, for example, with diacylglycerol lipase (DAGL) inhibitors, would be neuroprotective as it would reduce the availability of eCBs for COX-2 metabolism, and indeed, such benefits have been attributed to COX-2 inhibitors (Valdeolivas et al. 2013). In contrast, inhibiting eCB hydrolysis by monoacylglycerol lipase (MAGL) aggravated brain damage by augmenting the eCBs available (Valdeolivas et al. 2013). In other circumstances, toxicity may derive from the excess arachidonic acid generated through eCB hydrolysis (by MAGL or FAAH) and its oxygenation to prostaglandins by COX-2 promoting inflammatory damage. In this case, inhibitors of FAAH and MAGL may be neuroprotective due to mechanisms independent of CB_1 and CB_2 receptors (Nomura et al. 2011; Piro et al. 2012). Significantly, MAGL-deficient mice were less vulnerable to the induction of experimental parkinsonism than wild-type animals (Nomura et al. 2011). These mechanisms are all described in Fig. 3.

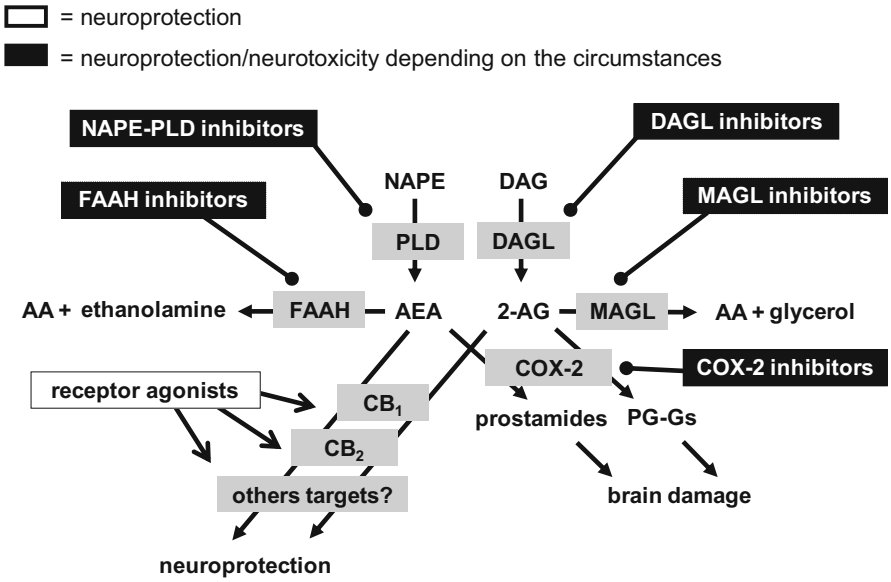

Fig. 3 Dual effects of some compounds acting on the eCB system in relation to the metabolism of the two major eCB ligands. Open rectangle = neuroprotection. Filled rectangle = neuroprotection/neurotoxicity depending on the circumstances

3 Cannabinoids in HD

HD is a chronic progressive disorder caused by an excessive number of repeat citosine-adenine-guanine (CAG) triplets in the gene encoding the regulatory protein huntingtin, and the potential use of CBs as a novel neuroprotective treatment in HD has been investigated intensively (see Fig. 4 for details: Sagredo et al. 2012). These studies have been predominantly carried out in preclinical models of HD in vivo, for example, in a rat model that relies on quinolinate-induced excitotoxic damage, in which compounds targeting the CB_1 receptor preserved striatal neurons (Pintor et al. 2006). The relevance of CB_1 receptors in HD was also demonstrated in the R6/2 mutant mouse model of the disease in which CB_1 receptor activation again preserved striatal neurons from death, whereas striatal damage was aggravated in double mutants: CB_1 receptor-deficient R6/2 mutant mice (Blázquez et al. 2011). It is noteworthy, however, that early defects have been found in CB_1 receptor signaling, and that there is a progressive loss of these receptors prior to neuronal death and the onset of choreic symptoms (Glass et al. 2000; Lastres-Becker et al. 2002). Although it is possible that early stimulation of CB_1 receptors may dampen their impairment, thereby maintaining their capacity to inhibit the excitotoxic events that initiate the damage to striatal neurons (Pintor et al. 2006), such an approach is unlikely to work at later symptomatic stages that are

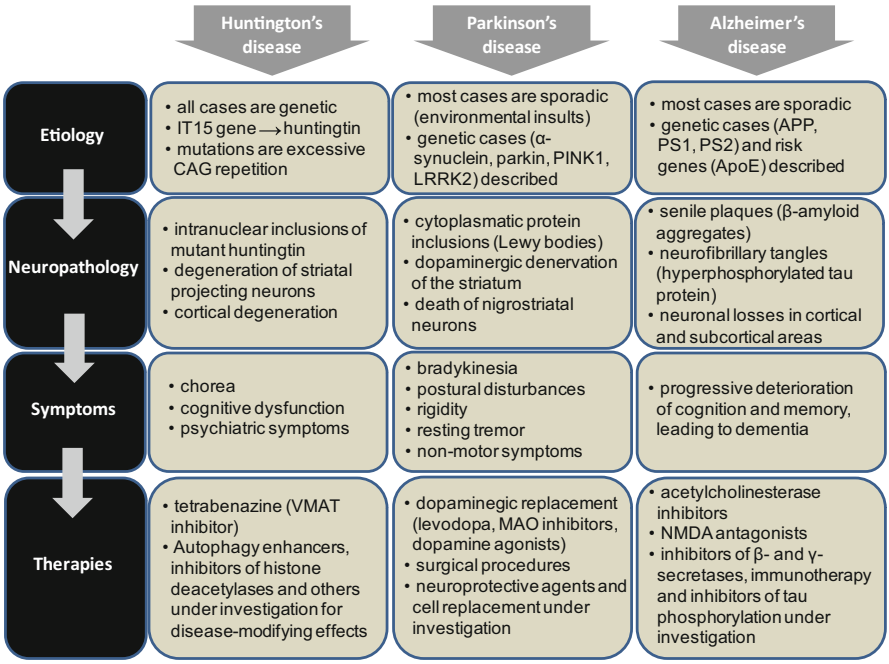

Fig. 4 Clinical, neuropathological, and pharmacological aspects of HD, PD, and AD

characterized by an important loss of CB_1 receptor-containing striatal neurons (Fernández-Ruiz et al. 2014). However, it was recently demonstrated unequivocally that CB_1 receptor-dependent neuroprotective activity in HD is predominantly derived from a restricted population of these receptors on cortical glutamatergic neurons that project to the striatum and that are preserved during the progression of HD, rather than from the CB_1 receptors located on striatal projection GABAergic neurons that are progressively lost during disease progression (Chiarlone et al. 2014). This is highly relevant as it supports the putative efficacy of treatments targeting CB_1 receptors irrespective of their loss as HD progresses.

Compounds that selectively activate the CB_2 receptor also appear to be effective in HD, preferentially ameliorating the inflammatory events and microglial activation that occurs after the striatum is damaged with malonate (a complex II inhibitor) in rats (Sagredo et al. 2009), in R6/2 mice (Palazuelos et al. 2009), and following the excitotoxicity induced by striatal lesion with quinolinate in mice (Palazuelos et al. 2009). As mentioned above, these benefits may be facilitated by overexpression of the CB_2 receptor in the striatal parenchyma, an effect that was first detected when striatal damage was provoked in rats with malonate (Sagredo et al. 2009) and subsequently, in R6/2 mice (Palazuelos et al. 2009) and other genetic mouse models of HD (Bouchard et al. 2012), as well as in postmortem tissues from HD patients (Palazuelos et al. 2009). This upregulation appears to occur in astrocytes (Sagredo et al. 2009), although no CB_2 receptor expression was

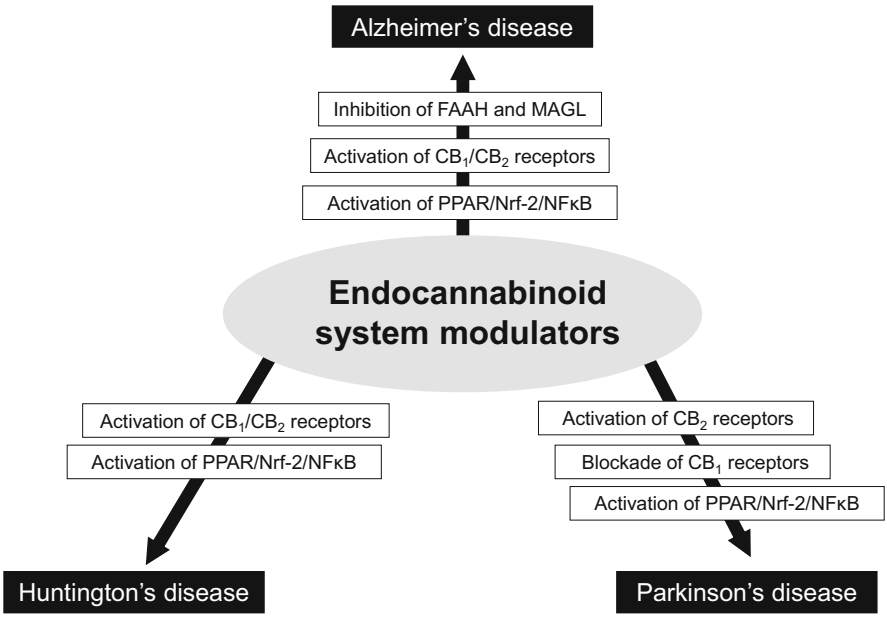

Fig. 5 Pharmacological targets and cannabinoid combinations that appear to be most adequate for clinical evaluation as neuroprotective therapies in HD, PD, and AD

found in these glial cells in human HD tissues (Dowie et al. 2014), and particularly in reactive microglia (Fernández-Ruiz et al. 2007, 2010). Hence, targeting CB_2 receptors in these glial cells may enhance the positive responses and/or reduce the negative influences exerted by these cells on striatal neurons (Sagredo et al. 2009; Palazuelos et al. 2009).

CBD has also been investigated in experimental models of HD, even though its effects are independent of CB_1/CB_2 receptors. CBD was very active in animal models characterized by mitochondrial damage, oxidative stress, and calpain activation, such as rats intoxicated with the complex II inhibitor 3-nitropropionate (3NP; Sagredo et al. 2007), yet it was inactive in pro-inflammatory models like malonate lesioned rats (Sagredo et al. 2009). The efficacy of CBD in 3NP-lesioned rats was independent of CB_1, TRPV1, and adenosine receptors (Sagredo et al. 2007), yet possibly related to the activation of PPARs (although this was not investigated). However, these nuclear receptors have been found to participate in the beneficial effects induced in 3-NP-lesioned and R6/2 mice by cannabigerol, another plant-derived CB that does not bind to CB_1/CB_2 receptors (Valdeolivas et al. 2014). CBD combined with Δ^9-THC, as in the cannabinoid-based medicine Sativex®, has also been studied in animal models of HD given the wide spectrum of pharmacological actions produced by this combination (see Fig. 5). This combination preserved striatal neurons in malonate lesioned mice (Valdeolivas et al. 2012) and in 3-NP lesioned rats (Sagredo et al. 2011), but not in R6/2 mice (unpublished results) in which the presence of CBD may possibly limit the benefits produced by

Δ^9-THC alone (Blázquez et al. 2011). We also participated in a clinical trial carried out on HD patients in Spain to determine the potential of Sativex® as a disease-modifying therapy. This was the first clinical trial aimed at validating a CB-based neuroprotective therapy in HD, as previous clinical studies focused only on the alleviation of symptoms (e.g., chorea: reviewed in Fernández-Ruiz et al. 2014). This clinical trial successfully demonstrated that Sativex® was safe and well tolerated in HD patients, as previously found in controls, yet unfortunately, it failed to provide any evidence that it may slow down disease progression in HD (García-Caldentey et al. 2015).

4 Cannabinoids in PD

Compounds acting on the eCB system are being studied to establish whether they could be used to develop disease-modifying therapies for PD (García-Arencibia et al. 2009), the most important neurodegenerative disorder affecting the basal ganglia (see Fig. 4 for details). As for HD, the different lines of research with CBs have been prompted by the changes in the eCB signaling system found in this disease in basal ganglia, as detected in animal models (Lastres-Becker et al. 2001; Gubellini et al. 2002; Price et al. 2009; García et al. 2011) or postmortem tissues (Lastres-Becker et al. 2001) and in biological fluids (Pisani et al. 2005) from PD patients. These changes include: (1) the upregulation of CB_1 receptors in striatal neurons under the control of dopaminergic neurons that degenerate in PD, as observed in postmortem tissue from patients and in different experimental models of the disease (García-Arencibia et al. 2009); (2) the elevation of CB_2 receptors in glia recruited to the lesion sites of mice suffering nigrostriatal neural damage caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Price et al. 2009) or lipopolysaccharide (LPS) (García et al. 2011); and (3) the loss of neuronal CB_2 receptors in postmortem tissues of PD patients due to the degeneration of nigrostriatal dopaminergic neurons (García et al. 2015).

Most pharmacological studies performed with CBs in experimental models of PD have concentrated on antioxidant plant-derived CBs, given that oxidative stress is a major hallmark in the pathogenesis of PD. These studies include the assessment of Δ^9-THC (Lastres-Becker et al. 2005), CBD (Lastres-Becker et al. 2005; García-Arencibia et al. 2007; García et al. 2011), and Δ^9-tetrahydrocannabivarin (Δ^9-THCV) (García et al. 2011) in rats carrying 6-hydroxydopamine lesions, a model in which the death of dopaminergic neurons is related to mitochondrial dysfunction and oxidative damage. Neuroprotection has also been provided by synthetic CBs like the AEA analogue AM404 (García-Arencibia et al. 2007) or the CB_1/CB_2 receptor agonist CP55,940 (Jiménez-Del-Rio et al. 2008), again acting through CB receptor-independent mechanisms. In contrast, CBs that selectively target the CB_2 receptor were active in MPTP-lesioned mice, a model with a modest glial response (Price et al. 2009), as well as in a more pro-inflammatory model generated by lesions with LPS (García et al. 2011), although they were inactive in 6-hydroxydopamine lesioned rats (García-Arencibia et al. 2007). In addition, CB_2 receptor-knockout mice were more susceptible to LPS than 6-hydroxydopamine

(García et al. 2011), although overexpression of CB_2 receptors in mice was recently shown to protect against 6-hydroxydopamine (Ternianov et al. 2012).

CBs selectively targeting CB_1 receptors have also been studied but with controversial results. No effects were observed in 6-hydroxydopamine lesioned rats (García-Arencibia et al. 2007), while nigrostriatal dopaminergic neurons were preserved in MPTP lesioned mice through an effect that surprisingly involves the inhibition of microglial activation (Chung et al. 2011). Nevertheless, a neuroprotective strategy based on targeting CB_1 receptors might have some disadvantages in PD, since the hypokinetic effects associated with the activation of this receptor may worsen specific parkinsonian symptoms, such as bradykinesia (García-Arencibia et al. 2009). In contrast, blockade of CB_1 receptors reduces parkinsonian akinesia (Fernández-Ruiz 2009). Therefore, it would seem that a future CB-based neuroprotective therapy for PD would have to be based on an adequate combination of compounds to ensure: (1) the antioxidant activity that would be exerted by CB receptor-independent mechanisms, possibly involving activation of the nuclear PPAR receptor family whose activators are also beneficial in experimental parkinsonism (e.g., thiazolidinedione as a PPAR-γ agonist: Carta and Simuni 2014); (2) CB_2 receptor activation and the control of inflammatory events; and (3) the blockade of CB_1 receptors to improve akinesia and reduce motor inhibition. The phytocannabinoid Δ^9-THCV has such a profile, making it an interesting compound to be used therapeutically in PD, alone or in combination with CBD (see Fig. 5), and highlighting the need for a formulation that can be further evaluated in patients.

5 Cannabinoids in AD

AD is the most prevalent chronic progressive neurodegenerative disorder (see Fig. 4 for details), and it is being intensively investigated to determine the benefits of potential CB-based therapies against β-amyloid toxicity, tau protein hyperphosphorylation, and other cytotoxic processes associated with this disease (Karl et al. 2012). As in other disorders, numerous studies have characterized the changes experienced by specific elements of the eCB signaling system during the progression of this disease, particularly in the two most affected brain structures: the hippocampus and cerebral cortex. These studies revealed: (1) an increase in 2-arachidonoylglycerol (2-AG) levels in association with β-amyloid protein-induced hippocampal degeneration and gliosis (Van Der Stelt et al. 2006); (2) a significant upregulation of CB_2 receptors in microglial cells surrounding the β-amyloid plaques (Benito et al. 2003; Ramírez et al. 2005); (3) a reduction in CB_1 receptors associated with neuronal loss, particularly in the hippocampus and basal ganglia (Westlake et al. 1994; Ramírez et al. 2005); and (4) an elevation of the FAAH enzyme in astrocytes associated with senile plaques, thereby enhancing eCB hydrolysis, elevating arachidonic acid levels, and contributing to the destructive inflammatory process that accompanies AD (Benito et al. 2003). These alterations have been interpreted in two ways. On the one hand, the loss of neuronal CB_1

receptors and the elevation of FAAH may contribute to the progression of AD pathogenesis by enhancing the vulnerability of specific groups of cortical and subcortical neurons to different neurotoxic stimuli (D'Addario et al. 2012; Manuel et al. 2014). On the other hand, the increase in 2-AG and the upregulation of microglial CB_2 receptors may protect against β-amyloid-induced neuroinflammation and neuronal injury (Benito et al. 2003; Ramírez et al. 2005).

A neuroprotective therapy for AD based on compounds that act on the eCB system may be effective in reducing classic neurotoxic events, such as excessive glutamatergic transmission, prolonged calcium influx, oxidative stress, and inflammation (Gowran et al. 2011; Karl et al. 2012), although it may also cause more specific effects on the processing, aggregation, and clearance of β-amyloid protein (Tolón et al. 2009; Martín-Moreno et al. 2012; Scuderi et al. 2014). One example of a drug which acts classically through CB_1 and CB_2 receptors and also through mechanisms independent of CB receptors is Δ^9-THC (Gowran et al. 2011). Thus, this compound can prevent β-amyloid protein aggregation and thereby hinder plaque formation by inhibiting acetylcholinesterase activity (Eubanks et al. 2006). Studies on mice bearing five amyloid-related mutations (5xFAD) demonstrated that Δ^9-THC decreases the density of neuritic plaques by increasing the expression of neprilysin, an enzyme in the β-amyloid degradation cascade, but not by inhibiting the expression of the β-site amyloid precursor protein cleaving enzyme 1 (BACE1: Chen et al. 2013). Importantly, this beneficial effect of Δ^9-THC was not reversed by COX-2 inhibition, in contrast to other damaging effects linked to the administration of this phytocannabinoid that were effectively reduced after pharmacological or genetic blockade of COX-2 (such as the impairment of hippocampal long-term synaptic plasticity, and of spatial working and fear memories, and the decrease in dendritic spine density of hippocampal neurons, all induced by Δ^9-THC: Chen et al. 2013). These observations pave the way for the development of novel therapies in which Δ^9-THC might be combined with COX-2 inhibitors, thereby preserving the putative beneficial effects of this CB while avoiding its deleterious ones.

CBD has also been studied extensively in AD, both in vitro (Iuvone et al. 2004) and in vivo (Esposito et al. 2006b, 2007), revealing a notable capacity to: (1) reduce the levels of ROS and the magnitude of lipid peroxidation; (2) prevent glutamate-induced toxicity, as well as β-amyloid-induced glial activation and pro-inflammatory responses; and (3) inhibit β-amyloid-induced tau protein hyperphosphorylation by glycogen synthase kinase-3β. These effects may be at least partially related to the activation of PPAR nuclear receptors (Fakhfouri et al. 2012; Scuderi et al. 2014), whose classic activators are also active in experimental models of this disease (e.g., pioglitazone: Yamanaka et al. 2012). Synthetic compounds targeting CB_1 and/or CB_2 receptors also effectively improve cognitive impairment, preserving neuronal cells, and preventing β-amyloid protein-induced microglial activation and the generation of pro-inflammatory mediators, as well as removing pathological deposits in different in vivo and in vitro models of AD (Ramírez et al. 2005; Tolón et al. 2009; Fakhfouri et al. 2012; Aso et al. 2012, 2013). The benefits of Δ^9-THC, CBD, and synthetic agonists of CB receptors in

preclinical models of AD support the interest that has developed in carrying out clinical studies directed at investigating whether the recently licensed phytocannabinoid-based medicine Sativex® could be a novel disease-modifying therapy for AD patients (see Fig. 5). In fact, a Sativex®-like phytocannabinoid combination was recently evaluated in a preclinical model of an AD-related disorder (frontotemporal dementia), producing a decrease in gliosis and oxidative stress, an improvement in chaperone function, a reduction in the severity of the tau and β-amyloid pathology, and the induction of autophagy (Casarejos et al. 2013).

Some recent studies have also highlighted the interest in preventing eCB inactivation in AD (see Fig. 5). For example, the development of amyloid pathology in PS1/APP$^+$ mice increased the brain levels of monoacylglycerols, *N*-acylethanolamines, free fatty acids, eicosanoids, and other lipid species, as well as the levels of some cytokines (IL1β, IL6, and TNF-α: Piro et al. 2012). Blocking MAGL with JZL184, or genetic inactivation of MAGL, improved behavioral (spatial learning and memory) parameters, decreased the density of amyloid plaques, and reduced astro- and microgliosis, as well as the production of inflammatory cytokines. Interestingly, none of these effects were prevented by CB_1 or CB_2 antagonists, suggesting that they were effects mediated primarily by alterations in arachidonic acid and/or prostaglandin signaling. In addition, the treatment of 5xFAD mice with JZL184 markedly decreased the appearance of neuritic plaques by inhibiting BACE1 expression (Chen et al. 2012). Furthermore, these changes also affected the gliotic process, with decreases in GFAP+ and CD11b+ cells in the cortex and hippocampus of JZL184-treated mice. An impact of the treatment on synaptic function was also evident, with a preservation of dendritic spine density, and a prevention of the amyloid-linked decrease in the expression of glutamate receptor subunits and of PSD-95 (a marker of post-synaptic integrity). These changes had a behavioral correlate in terms of the improved performance of JZL184-treated mice in the Morris water maze test. Finally, the anti-inflammatory effects linked to MAGL inhibition were not mediated by CB_1 or CB_2 receptors, which is consistent with previous studies (Piro et al. 2012), suggesting that other targets of 2-AG may be involved in these effects (e.g., PPAR).

The contribution of FAAH to amyloid pathology could be more complex. As mentioned above, we found that FAAH expression and activity is enhanced in the brains of AD patients (Benito et al. 2003), which is consistent with the recent observation of a significant decrease in AEA levels in the absence of changes in 2-AG in the postmortem human cortex (Jung et al. 2012). Moreover, we have recently found that the effects resulting from a reduction of FAAH activity are not the same when this reduction is induced by genetic manipulation as when it is induced by pharmacological inhibition (Benito et al. 2012; Vázquez et al. 2015). This is best appreciated by comparing the effects of URB597, a FAAH inhibitor, with the genetic ablation of FAAH. Since both manipulations significantly affect the inflammatory milieu in vitro (primary astrocytes) and in vivo (5xFAD mice), the long-term inhibition of FAAH would appear to be associated with the development of a pro-inflammatory phenotype. However, this situation may provide beneficial effects at the behavioral level in vivo (improved memory in the Morris water

maze) as well as in terms of decreased neuritic plaque density and gliosis. Although still preliminary, these data support the idea that targeting eCB degradation may be an attractive therapeutic strategy for AD, a strategy that certainly deserves more attention in the near future.

6 Cannabinoids in Other Less Well-Studied Chronic Neurodegenerative Disorders

Cannabinoid-based therapies may also be useful for other chronic neurodegenerative disorders in which CBs have been less well studied due to the lower incidence of these disorders or the lack of useful preclinical models. Such disorders include autosomal-dominant hereditary SCAs, Down's syndrome, and prion-related disorders. SCAs are a family of chronic progressive neurodegenerative diseases characterized by a loss of balance and motor coordination due to degeneration in the cerebellum, and a loss of its afferent and efferent connections (Rossi et al. 2014). They are rare diseases, although the most prevalent are all polyglutaminopathies like HD. Only very recently has interest been shown in the eCB system in relation to SCAs, and all the available data come from the analysis of postmortem cerebellar tissues from SCA patients (Rodríguez-Cueto et al. 2014a, b). These data include the notably higher presence of CB_1 and CB_2 receptors in the granular layer, in Purkinje cells, in dentate gyrus neurons, and in the white matter of the cerebellum of patients (Rodríguez-Cueto et al. 2014a). These CB_2 receptors appear to be located in Purkinje neurons, as well as in glial elements in the granular layer and the white matter of SCA patients (Rodríguez-Cueto et al. 2014a), a similar profile to that found for FAAH and MAGL (Rodríguez-Cueto et al. 2014b).

Down's syndrome is sometimes referred to as a human model of AD-like β-amyloid deposition. In postmortem human samples, immunohistochemical analysis produced similar findings to those obtained from postmortem tissues of AD patients (Benito et al. 2003; Núñez et al. 2008). Thus, in Down's syndrome, the expression of both CB_2 receptors and FAAH is greater than normal in β-amyloid plaque-associated microglia and astroglia, respectively (Núñez et al. 2008), suggesting that their induction may contribute to, or be a result of, β-amyloid deposition and subsequent plaque formation. This issue has not been investigated at the pharmacological level, in part due to the lack of useful models that reproduce this disease in laboratory animals.

Prion diseases are transmissible neurodegenerative disorders characterized by the accumulation of the protease-resistant prion protein in the CNS (Takada and Geschwind 2013). CBs have also been investigated in prion disease studies, and in a prion mouse model, in which brain levels of 2-AG but not of AEA were found to be elevated (Petrosino et al. 2011). CB_2 receptor expression was also upregulated in this model, with no changes in other cannabinoid receptors, consistent with the fact that microglial cell activation is a common feature of prion diseases (Petrosino et al. 2011). All these alterations were already evident in early stages of the disease, prior to the appearance of the major clinical symptoms (Petrosino et al. 2011). It has

also been found that CBD is effective at inhibiting the accumulation of protease-resistant prion protein in mouse and sheep scrapie infected cells in vitro, an effect that AEA, Δ^9-THC, and methanandamide did not reproduce (Dirikoc et al. 2007). In addition, treatment of scrapie infected mice with CBD also limited the cerebral accumulation of protease-resistant prion protein, significantly increasing the survival of infected mice (Dirikoc et al. 2007). The benefits of CBD were more closely related to the reduction in the cytotoxic events elicited by prion infection (e.g., microglial cell migration), than to any direct interaction of CBD with the prion protein that may alter its stabilization, sub-cellular localization, or the formation of aggregates (Dirikoc et al. 2007).

7 Concluding Remarks and Future Perspectives

Because of the nature of their pharmacological properties, compounds acting on the eCB system are potentially useful and clinically promising neuroprotectants. In this article, we have reviewed the cellular and molecular mechanisms that might be involved in these neuroprotective effects, putting emphasis on those mediated by the activation of CB_1 receptors (e.g., the reduction of excitotoxic stimuli induced either by inhibiting glutamate release or by reducing NMDA receptor-mediated calcium influx) and/or by the activation of CB_2 receptors (e.g., the decrease of local inflammatory events derived from the activation of glial elements). We have also considered the neuroprotective effects apparently mediated by CB receptor-independent mechanisms (e.g., the reduction of oxidative injury by scavenging ROS or by inducing antioxidant defenses), again emphasizing the contribution of alternative intracellular targets in these effects, such as PPARs or transcription factors. Through one or more of these processes, compounds acting on the eCB system may delay/arrest the progression of neurodegeneration in chronic diseases affecting cognitive processes like AD or motor control or performance like PD and HD. We have reviewed the knowledge accumulated over the years regarding these three disorders, as well as the incipient knowledge being generated for a few less well-studied disorders (SCAs, Down's syndrome-related dementia, and prion disorders). It is important to note that most of the studies carried out with CB-based therapies in these diseases have been preclinical. Even so, some of them have provided enough solid evidence to justify the study of these molecules or their combinations in clinical investigations. In this regard, we have proposed some ideas about the route(s) that should be followed to extend this research into the clinical area.

Acknowledgements This work was supported by grants from CIBERNED (CB06/05/0089), MINECO (SAF2012/39173), and CAM (S2011/BMD-2308).

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