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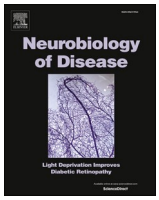

# An enquiry to the role of CB1 receptors in neurodegeneration

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ABSTRACT

Neurodegenerative disorders are debilitating conditions that impair patient quality of life and that represent heavy social-economic burdens to society. Whereas the root of some of these brain illnesses lies in autosomal inheritance, the origin of most of these neuropathologies is scantly understood. Similarly, the cellular and molecular substrates explaining the progressive loss of brain functions remains to be fully described too. Indeed, the study of brain neurodegeneration has resulted in a complex picture, composed of a myriad of altered processes that include broken brain bioenergetics, widespread neuroinflammation and aberrant activity of signaling pathways. In this context, several lines of research have shown that the endocannabinoid system (ECS) and its main signaling hub, the type-1 cannabinoid (CB1) receptor are altered in diverse neurodegenerative disorders. However, some of these data are conflictive or poorly described. In this review, we summarize the findings about the alterations in ECS and CB1 receptors signaling in three representative brain illnesses, the Alzheimer's, Parkinson's and Huntington's diseases, and we discuss the relevance of these studies in understanding neurodegeneration development and progression, with a special focus on astrocyte function. Noteworthy, the analysis of ECS defects in neurodegeneration warrant much more studies, as our conceptual understanding of ECS function has evolved quickly in the last years, which now include glia cells and the subcellular-specific CB1 receptors signaling as critical players of brain functions.

## 1. (Endo)Cannabinoid signaling in the brain

For centuries, the *Cannabis sativa* plant has been used for different purposes, such as for providing fibers, food, and oil, for recreational and religious purposes, but most interestingly it has been intensely used as a medicine (Bonini et al., 2018). The main psychoactive component of cannabis $\Delta^9$-tetrahydrocannabinol (THC) is responsible for the psychotropic effects associated with cannabis consumption. However, THC also seems to be involved in the potential therapeutic effects of cannabis use (Baker et al., 2003; Dos Santos et al., 2021; Fraguas-Sánchez and Torres-Suárez, 2018). Interestingly, THC possesses several pro-therapeutic effects, for example it can reduce nociception (i.e., reduce pain sensation), stimulate the appetite, diminish nausea/vomits or act as anticonvulsant (Baker et al., 2003; Dos Santos et al., 2021; Fraguas-Sánchez and Torres-Suárez, 2018). These THC-mediated effects might support its therapeutical use for the treatment of many pathologies including epilepsy, neuropathic pain, cancer and neurodegenerative disorders (Baker et al., 2003; Gordon and Devinsky, 2001; Pacher et al., 2006; Walsh et al., 2003). However, THC consumption is accompanied by impairment of diverse brain functions, such as catalepsy or acute impairment of attention, learning and memory (Stella, 2023). Remarkably, these negative effects are enhanced when consuming *Cannabis* that contains higher amounts of THC. Of note, the potential therapeutic or toxic effects of THC consumption might also depend on the presence of other cannabinoids compounds contained in *Cannabis sativa*, which are so far less studied (Dos Santos et al., 2021; Stella, 2023). Therefore, to better understand both the positive and negative effects of THC, several studies over the past decades have focused on determining the cellular and molecular mechanisms that underline the various effects of THC on bodily functions.

The isolation of THC from *Cannabis sativa* (Gaoni and Mechoulam, 1964; Wollner et al., 1942) pave the way to the discovery of the endocannabinoid system (ECS), a complex endogenous modulatory signaling system that is targeted by both endogenous and exogenous cannabinoids (Martinez Ramirez et al., 2023; Zou and Kumar, 2018). Remarkably, the ECS is largely distributed in diverse tissues, including the brain

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(Martinez Ramirez et al., 2023), muscle, adipose tissue or reproductive organs (Kamnate et al., 2022; Kano et al., 2009; Mendizabal-Zubiaga et al., 2016; Pagano Zottola et al., 2022; Rossato et al., 2005), and it is involved in distinct physiological functions such as whole-body energy handling and storage, cardiac function, pain control and reproduction, amongst many others (Busquets-García et al., 2022; Fonseca and Rebelo, 2022; O'Keefe et al., 2014; Piazza et al., 2017; Sierra et al., 2018; Woodhams et al., 2015). The ECS is composed the G-protein coupled receptors (GPCRs) type-1 and type-2 cannabinoid receptors (CB1 and CB2 receptors, respectively), by their endogenous lipid ligands anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), the so-called endocannabinoids (eCBs), and by the enzymes responsible for eCBs synthesis and degradation. Interestingly, a wide range of enzymes participates in the biosynthesis and degradation of eCBs. These include N-acyl-phosphatidylethanolamine-specific phospholipase D (NAPE-PLD), α/β-hydrolase domain type-4 (Abdh4), glycerophosphodiesterase-1 (GDE1), protein tyrosine phosphatase N22 (PTPN22) for AEA biosynthesis, and diacylglycerol lipase-α or -β (DAGLα and DAGLβ) for 2-AG biosynthesis. In the other hand, eCBs degradation also is carried out by specific enzymes, with fatty acid amide hydrolase-1 (FAAH) being responsible for AEA degradation, while monoacylglycerol lipase (MAGL), α/β-Hydrolase Domain Containing Protein 6 and 12 (ABDH6 and 12), and FAAH-1 are involved in 2-AG degradation (Cristino et al., 2020; Iannotti et al., 2016; Martinez Ramirez et al., 2023; Zou and Kumar, 2018). Notably, and in contrast to conventional vesicle-stored neurotransmitters, eCBs are generally believed to be synthetized and released on demand. The production of eCBs is controlled via intracellular calcium increases, caused by activation of specific GPCRs or secondary to plasma membrane depolarization in excitable cells, which stimulates the enzymes involved in eCBs synthesis, resulting in their mobilization to activate cannabinoid receptors (Cristino et al., 2020; Iannotti et al., 2016; Piomelli, 2003). In the central nervous system, the ECS governs key brain functions, such as emotional regulation, feeding behaviors and cognition via the CB1 receptors signaling (Busquets-Garcia et al., 2018; Busquets-García et al., 2022; Piazza et al., 2017). Noteworthy, these receptors are expressed across the entire brain parenchyma (Kano et al., 2009), and in diverse brain cell-types, such as neurons, microglia, oligodendrocytes and astrocytes (Eraso-Pichot et al., 2023; Marinelli et al., 2023; Martinez Ramirez et al., 2023; Molina-Holgado et al., 2023). However, the CB1 receptor-mediated intracellular signaling differs between specific brain cells. For instance, neuronal CB1 receptors are typically coupled to $G_i/G_o$ proteins, that in turn inhibit adenylyl cyclase (AC) and specific voltage-dependent calcium channels. In parallel, CB1 receptor signaling activates mitogen-activated protein kinases (MAPKs) and rectifying potassium channels (Alger, 2002; Araque et al., 2017; Howlett, 2002). Ultimately, these signaling cascades inhibit synaptic function and reduce neurotransmitter release (Araque et al., 2017). Conversely, astroglial CB1 receptors have been suggested to couple to $G_{q/11}$, and their engagement triggers intracellular calcium increases, which in turn modulates the astrocyte control of synaptic function (Han et al., 2012; Martín et al., 2015; Navarrete and Araque, 2008, 2010; Robin et al., 2018; Serrat et al., 2021).

Remarkably, CB1 receptors can be functionally associated to mitochondrial membranes (mtCB1 receptor) (Benard et al., 2012; Hebert-Chatelain et al., 2014, 2016; Jimenez-Blasco et al., 2020; Koch et al., 2015; Mendizabal-Zubiaga et al., 2016; Pagano Zottola et al., 2022; Soria-Gomez et al., 2021), thus defying the dogma of strict plasma membrane localization of most of GPCRs. Importantly, pharmacological mtCB1 receptors activation inhibits mitochondrial functions and determines diverse negative effects associated to cannabinoid exposure, such as catalepsy (Soria-Gomez et al., 2021), impaired cognitive performance (Hebert-Chatelain et al., 2016) and diminished social interaction (Jimenez-Blasco et al., 2020). In particular, it has been observed that activation of mtCB1 receptors by either endogenous or exogenous cannabinoids inhibits mitochondrial respiration and energy production. This phenomenon involves intra-mitochondrial $G_{i/o}$ protein signaling and inhibition of soluble adenylyl cyclase (sAC). This causes a reduction in cyclic AMP levels and protein kinase A activity, which in turn reduces the phosphorylation of specific subunits of the mitochondrial complex I (such as NDUFS2 and NDUFS4). Ultimately, this reduces complex activity and stability and causes a decrease in mitochondrial respiration (Benard et al., 2012; Hebert-Chatelain et al., 2016; Jimenez-Blasco et al., 2020; Soria-Gomez et al., 2021). Noteworthy, mtCB1 receptors are not found only in neurons (Benard et al., 2012; Hebert-Chatelain et al., 2014; Koch et al., 2015; Soria-Gomez et al., 2021), but also in astrocytes (Gutiérrez-Rodríguez et al., 2018; Jimenez-Blasco et al., 2020; Serrat et al., 2021), where they diminish glycolytic activity, causing an inhibition of lactate production, that impairs social behavior after 24 h of cannabinoids exposure (Jimenez-Blasco et al., 2020). Moreover, mtCB1 receptors also control the endoplasmic reticulum-mitochondria calcium transfer to modulate astrocyte-mediated control of synaptic activity (Serrat et al., 2021). Overall, CB1 receptors exert a complex modulatory function, involving cell-type specific and subcellular compartmentalized signaling, which ultimately control brain function and behavior (Busquets-Garcia et al., 2018; Busquets-García et al., 2022; Martinez Ramirez et al., 2023) (Fig. 1).

Significantly, altered CB1 receptors signaling has been observed in diverse neurodegenerative disorders that affect both the central and peripheral nervous system (Cristino et al., 2020; Paes-Colli et al., 2022; Vasincu et al., 2022). Importantly, CB1 receptors are not the only cannabinoid-related elements linked to neurodegenerative conditions. For instance, (endo)cannabinoids can activate also CB2 receptors or other targets (e.g., transient receptor potential channels), and all these processes might play roles in neurodegenerative disorders (Agarwal et al., 2017; Cristino et al., 2020; Hong et al., 2020; Vasincu et al., 2022). Nevertheless, CB1 receptors are the main studied elements of the ECS in the context of neurodegeneration and will be the focus of the present review article. Moreover, many reviews have addressed the role of CB1 receptors in neurodegenerative disorders without dealing in depth with the potential roles of specific cell-types or implicitly focusing on neuronal mechanisms (Basavarajappa et al., 2017; Cristino et al., 2020; Vasincu et al., 2022). Therefore, in the context of the present special issue, this article will specifically focus on the impact of astroglial CB1 receptors signaling on the pathogenesis of certain neurodegenerative diseases. For this purpose, we will focus on three common and well-studied neurodegenerative disorders that affect the central nervous system: Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD).

## 2. Altered ECS signaling in AD

AD is a highly prevalent neurodegenerative disease, affecting millions of people worldwide. Its incidence is expected to grow during the coming years, mostly due to the prolonged lifespan (GBD 2016 Dementia Collaborators, 2019; Knopman et al., 2021). AD is also the most common form of dementia, and is characterized by cognitive decline, as well as functional impairment in daily living activities (Alzheimer's disease facts and figures, 2023.; Knopman et al., 2021). At the histopathological level, the hallmarks of AD are cerebral atrophy, the extracellular accumulation of amyloid-β peptide (Aβ) in plaques, and the intracellular accumulation of neurofibrillary tangles of hyperphosphorylated tau protein. In addition, some other pathological hallmarks appear during the progression of the disease, such as brain inflammation, oxidative stress, metabolic failure, excitotoxicity and neurodegeneration (Heneka et al., 2015; Knopman et al., 2021). Since AD discovery (Hippius and Neundörfer, 2003), much effort has been devoted to identifying the molecular mechanisms explaining the pathogenesis and development of the disease, in order to improve both the diagnosis and therapy. Importantly, few treatments exist and most of them do not target the progression of the disease. Furthermore, several strategies to stop AD progression have failed in the clinical stages or present a low efficacy (Asher and Priefer, 2022; Fillit and Green, 2021).

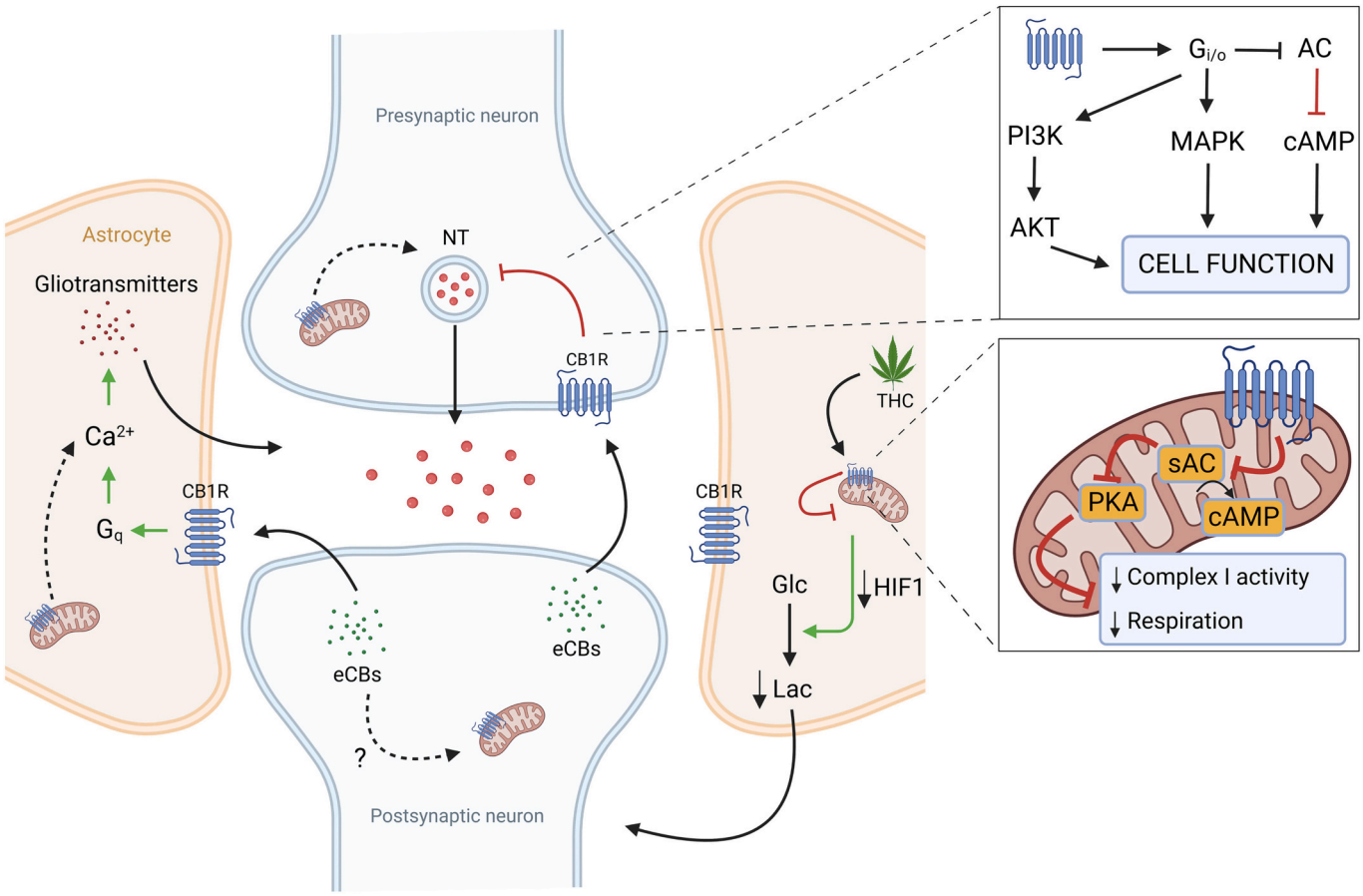


**Fig. 1.** Cellular and subcellular CB1 receptor signaling in astrocytes and neurons.
During neurotransmission, activation of postsynaptic neurons by neurotransmitters (NT) released by presynaptic neurons, causes an increase in endocannabinoids (eCBs) synthesis and release. The binding of eCBs to plasma membrane CB1 receptors in presynaptic neurons, activate $G_{i/o}$ protein signaling cascade that blocks the neurotransmitter release. In particular, CB1-dependent signaling in neurons result in reduction of adenylate cyclase (AC) activity, decreased cyclic AMP (cAMP) levels and activation of different kinases, as for example mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt). Importantly, CB1 receptors are also present in astrocytes, and their activation triggers $G_q$ protein signaling and causes a $Ca^{2+}$ level increase and promotes the release of gliotransmitters. Remarkably, CB1 receptors are also found in subcellular compartments, such as the mitochondria (mtCB1). Engagement of mtCB1 receptors pool inhibits the soluble AC (sAC) and diminishes the cAMP and PKA activity, thereby reducing complex I activity and mitochondrial respiration. This phenomenon reduces neuronal energy availability and impairs NT release. Interestingly, astroglial mtCB1 receptors activation diminishes mitochondria respiration, but also decrease HIF1 levels which impairs the glycolytic activity and reduce the lactate production.

As stated above, during AD progression, alterations in multiple and diverse biological systems have been discovered. Interestingly, one of the systems that seems to be altered is the ECS and consequently the CB1 receptor-dependent signaling. Some components of the ECS have been found to be altered in AD patients, including the enzymes that metabolize eCBs (Berry et al., 2020). For instance, whereas cortical AEA levels are decreased in AD patients and these inversely correlate with $A\beta_{42}$ levels and cognitive symptoms (Jung et al., 2012), in the hippocampus the activity of 2-AG degrading enzymes is increased (Mulder et al., 2011), which might promote aberrant 2-AG levels and CB1 receptor activity.

Regarding animal studies, several different mouse models of AD exist, each one recapitulating specific aspects of the disease (Götz et al., 2018; Mckean et al., 2021). These mutant mouse models usually consist in the overexpression of different mutated forms of the human amyloid beta precursor protein (APP) often in combination with overexpression of human mutated forms of the Presenilin 1 (PS1) protein, which is the enzyme responsible of APP cleaving and thus Aβ production. Overexpression of these mutated proteins induces more Aβ production and aggregation and is able to recapitulate some disease features. However, different mutations will differently affect the disease progression and the age of the mice is key to compare between different disease models. Interestingly, some of these AD models have shown some alterations of ECS members. In particular, the 5xFAD AD mouse model, which overexpress both human APP carrying three Familial AD (FAD) mutations and human PS1 harboring two FAD mutations, showed increased hippocampal levels of the 2-AG producing enzyme DAGLα (Medina-Vera et al., 2020). Conversely, in the APP/PS1 mouse model, which also overexpresses the two human proteins harboring one mutation each, the mRNA level of DAGLα mRNA was reduced in the prefrontal cortex and cerebellum of pre symptomatic male mice (Vidal-Palencia et al., 2022). These contradictory results may be explained by the differences between the brain areas analyzed, the mouse models used or the stage of the disease. Also, it is important to take into account the possible sexual dimorphism observed both in AD and responses to cannabinoids. For instance, both women and female mice display increased pathological AD hallmarks (Fisher et al., 2018; Jiao et al., 2016) as well as increased sensitivity to some THC-induced effects (Blanton et al., 2021; Calakos et al., 2017; Rubino and Parolaro, 2011) although CB1 availability seems to be reduced (Laurikainen et al., 2019), which add another degree of complexity in the interpretation of these results (Vidal-Palencia et al., 2022).

Studies addressing the expression of CB1 receptor and its downstream signaling in AD patients are also not conclusive. Some studies

point to a reduction in the expression and signaling of CB1 receptors in the cortex of symptomatic AD patients (Ramírez et al., 2005; Solas et al., 2013), although others did not found differences in these parameters in the cortex and hippocampus (Ahmad et al., 2014; Lee et al., 2010; Mulder et al., 2011). Interestingly, some studies have found increased CB1 expression and/or activity in some brain areas only during early stages of the disease (Farkas et al., 2012; Manuel et al., 2014) (Table 1). In AD mouse models, the CB1 receptor expression or signaling were found to be altered in a region-specific fashion, depending on the mouse model used and the stage of the disease (Bedse et al., 2014; González de San et al., 2021; Kalifa et al., 2011; Maccarrone et al., 2018; Medina-Vera et al., 2020; Takkinen et al., 2018; Vidal-Palencia et al., 2022) (Table 2). Importantly, most of these works addressed the expression of CB1 receptors without dissecting the expression in different brain cell types. However, recently it has been shown that CB1 is upregulated in reactive microglia in 5xFAD AD model (Terradillos et al., 2023), which might partially explain the differences in CB1 receptor expression in AD mouse models.

The alterations at the levels of ECS components, specially CB1 receptors, suggested that the ECS might represent a potential target in the treatment of AD (Abate et al., 2021; Páez and Campillo, 2019; Talarico et al., 2019). Of note, the deletion of CB1 receptors in different AD mouse models results in further impairment of cognitive functions (Aso et al., 2018; Stumm et al., 2013), thus suggesting a protective role of the ECS in the development of AD-like symptoms in mouse models. In this context, the targeting of CB1 receptors with exogenous cannabinoids might be a promising therapeutical avenue to slow down AD progression. For instance, exposure to THC is able to significantly reduce brain inflammation in the APP/PS1 mice (Aso et al., 2015), and chronic treatment with a mix of the phytocannabinoids THC and cannabidiol (CBD) improves the memory impairment in advanced stages of AD pathology in mice (Aso et al., 2016). Remarkably, THC treatment was able to decrease amyloid plaques level in the 5xFAD APP mouse model by increasing Aβ degradation via neprilysin activity (Chen et al., 2013). Similarly, synthetic CB1 receptor agonists have also been found to modify AD progression. Chronic administration of arachidonyl-2-chloroethylamide (ACEA) in the AβPP(swe)/PS1(1dE9) transgenic mice, either at the pre-symptomatic or early symptomatic stages, improve mice cognitive impairment (Aso et al., 2012). Moreover, ACEA treatment can prevent the cognitive impairment induced by hippocampal infusion of $A\beta_{(25–35)}$ (Patricio-Martínez et al., 2019). Finally, increasing the eCBs tone via pharmacological or genetic inhibition of eCBs degrading enzymes has also been shown to be a promising therapy for AD (Abate et al., 2021; Chen et al., 2012; Piro et al., 2012; Ruiz-Pérez et al., 2021), thus confirming the beneficial effects of modulating the ECS in AD. Nevertheless, the role of CB1 receptor signaling as potential therapeutic treatment for AD warrant further studies, especially its associated cellular and molecular mechanisms. In this context, the neuroinflammation and excitotoxicity observed in AD (Talarico et al., 2019), are two well-known processes targeted by CB1 receptors in neurons and other cell types (Aso and Ferrer, 2014; De Meij et al., 2021; Eraso-Pichot et al., 2023). Thus, further studies in this area might deliver interesting data.

Finally, several studies have established that metabolic alterations are part of the AD pathology. For instance, many investigations have demonstrated a reduction in brain glucose uptake in specific brain areas, both in patients and mouse models (Demetrius and Driver, 2013; Ferreira et al., 2010; Mosconi et al., 2009; Weise et al., 2018). Interestingly, astrocytes have a prominent role in the control of brain glucose consumption (Beard et al., 2021; Bélanger et al., 2011; Weber and Barros, 2015), and some studies have already suggested that astrocyte malfunction might be the main factor explaining the reduced brain glucose metabolism in AD (Newington et al., 2013; Zulfiqar et al., 2019). As an example, astrocytic glucose transporter GLUT1 is reduced both in AD brains and in cultured astrocytes from arcAβ mice (Merlini et al., 2011; Simpson et al., 1994), which might reduce the brain glucose uptake capacity. Accordingly, (mt)CB1 receptors modulate the energy metabolism of several different cells (Benard et al., 2012; Dando et al., 2013;

**Table 1**
Alterations in CB1 receptor expression in AD patients.

| Disease stage | Brain Area analyzed | Technique | Finding | Reference |
|---|---|---|---|---|
| Clinically defined AD patients | Frontal cortex | WIN55-mediated $^{35}$S-GTPγS binding | Increased G-protein coupling. | Ramírez et al., 2005 |
| | | Western blot | Decreased CB1 receptor protein levels | |
| Late stages | Cortical areas | Western blot | No differences in CB1 receptor protein levels or availability | (Lee et al., 2010) |
| | | $^{3}$H-SR141716A autoradiography | | |
| Braak III/IV and VI | Hippocampus | Western blot | No differences in CB1 receptor protein levels | (Mulder et al., 2011) |
| Braak I to Braak VI | Prefrontal cortex | $^{125}$I-SD-7015 autoradiography | Increased CB1 receptor availability | (Farkas et al., 2012) |
| Braak V/VI | Frontal cortex | Western Blot | Decreased CB1 receptor protein levels | (Solas et al., 2013) |
| Mild to moderate | Cortex, insula, cingulum, striatum | PET +$^{18}$F-MK-9740 radioligand | No difference in CB1 receptor availability | (Ahmad et al., 2014) |
| Three disease groups grouped by disease progression | Frontal cortex, hippocampus, Enthorinal cortex, amygdala, basal forebrain, striatum | WIN55-mediated $^{35}$S-GTPγS binding | Increased G-protein coupling in the hilus of the dentate gyrus at early disease stages. | (Manuel et al., 2014) |
| | | | Decreased G-protein coupling in the lateral nucleus of the amygdala at early disease stages. | |
| | | | Decreased G-protein coupling in different hippocampal areas at later disease stages. Increased CB1 receptor availability in Striatum and Pyramidal Subiculum at early stages | |
| | | $^{3}$H-CP55,940 autoradiography | Increased CB1 receptor availability stages in the frontal cortex at mid diseases | |
| | | | Decreased CB1 receptor availability in Hippocampus at late disease stages. | |

**Table 2**
Alterations in CB1 receptor expression in animal models of AD.

| Mouse model | Brain Area analyzed | Technique | Finding | Reference |
|---|---|---|---|---|
| APPswe/PS1ΔE9, symptomatic | Hippocampal areas | Immunohistochemistry | Decreased neuronal CB1 protein levels | (Kalifa et al., 2011) |
| 3xTg-AD, symptomatic | Prefrontal cortex, prelimbic cortex, dorsal and ventral hippocampus, basolateral amygdala, | In situ hybridization | Increased CB1 receptor mRNA level in prefrontal cortex, dorsal hippocampus and basolateral amygdala<br>Decreased CB1 receptor mRNA levels in ventral Hippocampus | (Bedse et al., 2014) |
| 3xTg-AD | Multiple brain regions | Immunostaining, immunofluorescence<br>WIN55-mediated $^{35}$S-GTPγS binding | Decreased CB1 receptor protein levels in dorsal Hippocampus and Basolateral Amygdala<br>Decreased G-protein coupling in Posterior Amygdala and Cortical layer VI | (González de San et al., 2021) |
| Tg2576 mice, presymptomatic | Hippocampus | Western blot,<br>Electrophysiological recordings | No differences in CB1 receptor protein level but altered membrane localization and function | (Maccarrone et al., 2018) |
| APP/PS1–21 | Multiple brain regions | PET +$^{18}$F-FMPEP-d2 radioligand,<br>Western blotting | Decreased CB1 receptor availability in multiple regions.<br>No differences in CB1 receptor protein in multiple areas analyzed. | (Takkinen et al., 2018) |
| 5xFAD, symptomatic | Hippocampus | Western Blot | Decreased CB1 receptor protein levels<br>Decreased CB1 receptor mRNA levels in Prefrontal Cortex and Hippocampus in male mice. | (Medina-Vera et al., 2020) |
| APP/PS1, presymptomatic | Multiple brain regions | Quantitative Real-Time PCR | Increased CB1 receptor mRNA levels in hypothalamus of male mice<br>Increased CB1 receptor mRNA levels olfactory bulb, prefrontal cortex and hypothalamus of female mice | (Vidal-Palencia et al., 2022) |

Hebert-Chatelain et al., 2014; Oláh et al., 2020; Pagano Zottola et al., 2022), and in particular, their persistent activation reduces both mitochondrial and glycolytic activity of astrocytes (Jimenez-Blasco et al., 2020). Currently, it is not known if the AD neuropathology alters mtCB1 receptors signaling in astrocytes. Similarly, further studies will be necessaries to determine if astroglial CB1 receptors participate in the effects of cannabinoids in AD. Importantly, the outcome of astrocytic (mt)CB1 activation might also vary depending on multiple factors, such as disease progression, symptomatology severity or differences across individuals. Noteworthy, other functions that are altered in AD astrocytes, such as glutamate uptake, $Ca^{2+}$ homeostasis or cholesterol synthesis (Lee et al., 2022), will be interesting to explore in relation with the activity of CB1 receptors.

## 3. PD and ECS: a complex and incomplete picture

PD is the second most common neurodegenerative disorder, characterized by bradykinesia, loss of motor control and non-motor symptoms (e.g., cognitive decline, mood disorders, and others). The main neuropathologic hallmark of PD are the loss of dopaminergic neurons in the substantia nigra and a widespread accumulation of α-synuclein in different brain areas (Parkinson, 2002; Poewe et al., 2017). Currently, the underpinnings that explain the development and progression of this debilitating disorder are scantly known. Interestingly, energy metabolism deficits have been proposed to participate in the development and/or progression of PD (Poewe et al., 2017). Despite the availability of effective therapies to reduce symptom progression, none of the current strategies promotes PD full remission (Poewe et al., 2017). Unfortunately, the chronic use of levodopa, the most effective anti-parkinsonism drug, causes dyskinesia and dystonia (Thanvi and Lo, 2004). This issue fueled the search for therapeutical targets capable of curing the disease, with minimum side effects. In this context, the CB1 receptors activity have been explored in PD, as the substantia nigra is one of the brain areas in which the CB1 receptors are highly expressed (Kano et al., 2009). Moreover, exposure to THC alters motor activity (Stella, 2023), which might suggest that targeting the ECS system can alleviate the PD motor symptoms or the levodopa side effects. In this rationale, exposure to THC or its related synthetic analog nabilone, reduce the dyskinesia induced by chronic levodopa therapy in PD patients (Sieradzan et al., 2001), thus suggesting that the ECS might be a therapeutic target for motor symptoms correction in PD and during chronic antiparkinsonian medication. However, the ECS involvement in PD pathogenesis and development is complex.

The quantification of CB1 receptor levels in PD patients and rodent models resulted in a complex pattern. The mRNA levels of CB1 receptors are decreased in PD patients post mortem samples, specifically in the caudate nucleus, anterior dorsal putamen and external segment of the globus pallidus (Hurley et al., 2003). Similarly, CB1 receptor mRNA levels are reduced in the striatum of rats with parkinsonism-like symptoms induced by reserpine, a blocker of the vesicular monoamine transporters (Silverdale et al., 2001). Conversely, a time-dependent change in CB1 receptor mRNA levels was observed in mice carrying the deletion of either PARK1, PARK2 and PARK6 genes (García-Arencibia et al., 2009), which are associated to hereditary PD pathogenesis in humans (Poewe et al., 2017). In particular, the levels of CB1 transcript in the caudate-putamen were decreased in the early phases of the disease, while increased at later stages (García-Arencibia et al., 2009) in all mouse models studied. On the other hand, in vivo determination of CB1 receptor availability in PD patients, as measured by PET and the radioligand [$^{18}$F] MK-9470, showed altered CB1 receptor availability in a region specific manner, with increased availability in nigrostriatal, mesolimbic, and mesocortical dopaminergic projection areas, while

decreased availability was found in the substantia nigra (Van Laere et al., 2012). In rats, the injection of the neurotoxic compound 6-hydroxydopamine (6-OHDA) results in the loss of dopaminergic and noradrenergic neurons, thus producing a PD-like rat model (Simola et al., 2007). The injection of 6-OHDA in the terminals (striatum) of the nigrostriatal pathway decreased CB1 receptor expression in the substantia nigra pars reticulata in rats (Walsh et al., 2010). Similarly, intrastriatal injection of 6-OHDA in rats resulted in decreased expression of CB1 receptors in internal globus pallidus and substantia nigra pars reticulata (Chaves-Kirsten et al., 2013). Conversely, intracerebroventricular injection of 6-OHDA result in increased CB1 receptors levels in the substantia nigra as measured by autoradiography in rat brain slices (González et al., 2006). These contradictory finding between PD patients and rodent models (summarized in Tables 3 and 4) can be ascribed to the poor capacity of rodent models to mimic the complex human PD neuropathology, but also is important to note that divergences might be explained by the different approaches used to induce 6-OHDA lesions (i.e., different injection sites), thus it is not clear if the result observed in rats are due differences in the spatial and temporal development of the lesions and appearance of PD-like symptoms in rats. Worthy of note, D2 dopamine receptors (D2R) form heterodimers with CB1 receptors (Kearn et al., 2005; Khan and Lee, 2014), a phenomenon that alters the signaling properties of both receptors (Bagher et al., 2016, 2017). In particular, whereas activation of each receptor alone activates a $G_i$ signaling, the simultaneous activation of both CB1 and D2 receptors triggers a $G_s$ signaling (Bagher et al., 2016, 2017). Furthermore, CB1 and D2 receptors also control the expression of each other (Blume et al., 2013). Thus, potential alterations in CB1 receptor expression might not only alter the ECS signaling in a region-specific manner in PD, but also it might modify the D2R-dependent signaling and impact PD pathology, a complex possibility that warrant further studies to fully elucidate the (patho)physiological role of this CB1 and DR2 heterodimerization.

Intriguingly, the levels of AEA are elevated in PD patients (Pisani et al., 2005, 2010). Similarly, the AEA levels in the Striatum are increased in the reserpine rat models (Gubellini et al., 2002), while the levels of 2-AG in the Globus Pallidus are elevated in the 6-OHDA rat model (Di Marzo et al., 2000). The induction of PD-like symptoms in non-human primates with the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) resulted in region-specific changes, with increased 2-AG and AEA levels in the striatum, while only 2-AG levels were found to be increased in the substantia nigra (van der Stelt et al., 2005). Whether these eCB changes are part of PD neuropathology or just a secondary effect of the pharmacological lesions remains to be elucidated. In this context, the exogenous application of 2-AG, or its indirect increase via pharmacological inhibition of its degradation, protects mouse neurons from the neurodegenerative insult induced by systemic neurotoxin MPTP delivery (Fernández-Suárez et al., 2014; Mounsey et al., 2015). Nevertheless, further studies will be necessary to understand the exact nature of such eCBs changes observed in PD patients and animal models.

Overall, the involvement of ECS signaling in PD is very likely, but its mechanisms and consequences are not clear. The study of ECS components, specifically the CB1 receptors and eCBs enzymatic machinery, in different brain cell types such as neurons, astrocytes and microglia might help to disentangle the conflictive results observed so far. Furthermore, the subcellular compartmentalization of CB1 receptor signaling warrant an special focus, as this particular characteristic enable the multimodal control of behavior via independent pools of this receptor (plasma membrane and mitochondria) in the striatonigral circuit (Soria-Gomez et al., 2021). In this context, mitochondrial dysfunction is proposed to be a key determinant of PD pathogenesis (Poewe et al., 2017), thus mtCB1 receptors signaling and its control of mitochondrial function become an interesting area to be explore in PD. The engagement of mtCB1 receptors inhibits mitochondrial function and negatively impact on brain bioenergetics (Benard et al., 2012; Hebert-Chatelain et al., 2014; Jimenez-Blasco et al., 2020), thus it might be possible that aberrant mtCB1 signaling participates in the mitochondrial dysfunction observed in PD. Further studies will be necessary to explore this intriguing possibility.

## 4. Impaired CB1 receptor signaling in HD neuropathology

HD is a neurodegenerative disorder, which, in contrast to AD and PD (Knopman et al., 2021; Poewe et al., 2017), is caused by specific genetic alterations. Indeed, HD is the result of autosomal dominant mutation of the huntingtin gene (*HTT)* with the emergence of aberrant CAG trinucleotide repeats, that are variable in length (Bates, 2005; Bates et al., 2015). This results in the expression of a mutant huntingtin protein containing several long polyglutamine repeats, thus creating a neurotoxic protein prone to fragmentation and accumulation, which induces synaptic dysfunctions. Ultimately, the neuronal malfunction leads to motor dysfunction, cognitive impairment, neuropsychiatric symptoms (e.g., obsessive compulsive behavior, apathy) and ultimately death (Bates et al., 2015). Currently, most of the HD therapies are palliative and target the motor dysfunctions (Vasincu et al., 2022), without addressing the pathology itself.

Despite being HD a disorder that affect the whole brain structure, the striatum is particularly sensitive to the neurotoxic damage induced by mutant huntingtin, which is reflected in the striatal atrophy observed in HD patients (Bates et al., 2015). In the striatum, CB1 receptors are densely expressed in dopaminergic medium spiny neurons and control motor behaviors (Martín et al., 2008). Thus, an ECS malfunction might be involved in the HD development and progression. In this context, the level of eCB has been measured in HD mouse models R6/2 and R6/1 which express the exon 1 of human huntingtin gene (Li et al., 2005), but the resulting data is conflicting. Whereas 2-AG levels were reported to be decreased in the cortex in presymptomatic R6/2 HD mice (Bisogno et al., 2008), other group using the R6/1 mice model found that 2-AG level were increased in the cortex, with a parallel decrease in the AEA levels in the hippocampus (Dowie et al., 2009). In the symptomatic R6/2 mice, 2-AG levels were reduced both in the striatum and cortex, while AEA was reduced in the striatum but increased in the cortex (Bisogno et al., 2008). Conversely, whole brain 2-AG levels were found to be increased in the R6/2 mice (Bari et al., 2013) (Table 6). This conflictive results might be explained by differences in symptom progression in the R6/2

**Table 3**
Alterations in eCBs level, CB1 receptor expression in PD patients.

| Disease stage | Sample analyzed | Technique | Finding | Reference |
|---|---|---|---|---|
| Late stage | Caudate nucleus, anterior dorsal putamen, external segment of globus pallidus | Reverse transcription polymerase chain reaction (RT-PCR) | Decreased levels of CB1 receptors mRNA | Hurley et al., 2003 |
| Mix of early, medium and late stages | Substantia nigra and dopaminergic projection areas | PET $+^{18}$F-MK-9470 radioligand and MRI | Increased CB1 receptor availability in nigrostriatal, mesolimbic, and mesocortical dopaminergic projection areas, while decreased availability in the substantia nigra | Van Laere et al., 2012 |
| Mix of early, medium and late stages | Cerebrospinal fluid | Liquid chromatography (LC) with fluorimetric detection | Increased levels of AEA, independent of disease stage, but higher levels were observed on patients without treatment | Pisani et al., 2005, 2010 |

**Table 4**
Alterations in eCBs level, CB1 receptor expression in animal models of PD.

| Rodent model | Brain area analyzed | Technique | Finding | Reference |
|---|---|---|---|---|
| Rats treated with reserpine | Striatum | In situ hybridization | Decreased levels of CB1 receptors mRNA | Silverdale et al., 2001 |
| Rats treated with reserpine | Basal ganglia | Isotope dilution Gas chromatography-Mass Spectroscopy (GC–MS) | Increased levels of 2-AG in the Globus Pallidus | Di Marzo et al., 2000; |
| Rats injected with 6-OHDA on nigrostriatal pathway terminals | Substantia nigra | Immunohistochemistry | Decreased CB1 receptor protein in Substantia nigra pars reticulata | Walsh et al., 2010 |
| Rats injected with 6-OHDA, intrastriatal | Basal ganglia | Immunohistochemistry<br>Western blot | Decreased CB1 receptor protein in the internal Gobus Pallidus and Substantia Nigra Pars Reticulata. | Chaves-Kirsten et al., 2013 |
| Rats injected with 6-OHDA, Intra-cerebroventricular | Basal ganglia | Autoradiography | Increased CB1 receptor level in substantia nigra | González et al., 2006 |
| Rats injected with 6-OHDA, on Substantia Nigra | Striatum | GC–MS | Increased levels of AEA in the Striatum | Gubellini et al., 2002 |
| PARK1, PARK2 and PARK6 KO mice | Caudate-putamen | *????* | Time dependent changes in CB1 receptors mRNA level: decreased at early disease stages, while increased in later disease stages | García-Arencibia et al., 2009 |
| Marmosets treated with MPTP | Basal ganglia | Isotope dilution atmospheric pressure chemical ionization LC- MS (LC-APCI-MS) | Increased levels of 2-AG in Striatum, Substantia Nigra. Increased levels of AEA on Striatum | van der Stelt et al., 2005 |

and R6/1 mice models and their different efficiency in transgene expression, whose is higher level in R6/2 mice (75%) than R6/1 mice (31%) (Li et al., 2005). Alternatively, the results might be explained also by differences in sample extraction and processing. This inconclusive eCBs data might cast doubt about the potential role of the ECS in HD neuropathology, however the study of CB1 receptors expression has been more consistent. The in vivo determination of CB1 receptor availability with PET and a specific radioligand, have shown an extensive decrease in brain CB1 receptors in early symptomatic HD patients (Ceccarini et al., 2019; Glass et al., 2000; Laere et al., 2010), with a further level decay in intermediate HD (Glass et al., 2000). The analysis of post mortem samples from HD patients has also shown a decrease in the CB1 receptor availability (Glass et al., 1993) (Table 5). Similarly, specific sections of the basal ganglia in HD genetic mouse models present a reduction in CB1 receptor mRNA levels (Denovan-Wright and Robertson, 2000; Dowie et al., 2009; Lastres-Becker et al., 2002), protein levels (Dowie et al., 2009), G-protein coupling (Lastres-Becker et al., 2002) and CB1 receptor availability (Dowie et al., 2009; Lastres-Becker et al., 2002; Ooms et al., 2014) (see Table 6 for details). Similar results have been observed in rodent treated with 3-nitropropionic acid (3-NP) (Lastres-Becker et al., 2004), a neurotoxin that inhibits mitochondrial complex II activity and cause a specific striatal degeneration and HD-like symptoms (Brouillet, 2014; Túnez et al., 2010). Specifically, rats treated with 3-NP presented a reduction in CB1 receptor G-protein coupling before the onset of HD-like symptoms, but without changes in mRNA levels. However, upon striatal degeneration, a marked reduction in both the G-protein coupling and mRNA levels was observed (Lastres-Becker et al., 2004). Interestingly, in vitro analysis using immortalized striatal neuroblasts suggest that mutant huntingtin downregulate CB1 receptor expression via repressor element 1 silencing transcription factor (REST) (Blázquez et al., 2011), thus suggesting that CB1 receptors reduction is part of the mechanisms of HD neuropathology. In this rationale, CB1 receptor deletion in R6/2 HD mouse model aggravates the symptomatology (Blázquez et al., 2011), and similar results were observed for CB1 deletion in the N171-82Q mouse model (Mievis et al., 2011), which expresses the N-terminally truncated human huntingtin cDNA. Noteworthy, specific deletion of CB1 receptors in glutamatergic corticostriatal terminals worsen the striatal neurodegeneration in the R2/6 HD mouse model (Chiarlone et al., 2014), indicating that this cellular pool of CB1 receptors participates in the progression of HD neuropathology. This observation underlines the neuroprotective role exerted by CB1 receptors, whose activity minimizes the excitotoxic damage induced by the neurotoxin quinolinate in vivo (Chiarlone et al., 2014). Importantly, widespread excitotoxic damage induced by glutamate and aberrant NMDAR function is observed during HD (Kaplan and Stockwell, 2012), suggesting that the loss of CB1 receptors in glutamatergic corticostriatal terminals might increase the susceptibility to excitotoxic damage during HD progression. Overall, these results suggest that the ECS signaling is altered in HD, especially at the level of CB1 receptors.

Thus, could the stimulation of CB1 receptors improve HD symptomatology? This idea has been explored using exogenous cannabinoids both in animal models and humans. In the R6/2 HD mouse model, THC exposure causes a reduction of HD-like symptomatology (Blázquez et al., 2011). In clinical trials, mixed results have been observed with Nabiximol (a mix of THC + cannabidiol (CBD) at ~1:1 ratio). Whereas in a first clinical trial this cannabinoid mix did not improve patients motor symptoms (López-Sendón Moreno et al., 2016), a following clinical trial showed that Nabiximol treatment improves patients motor symptoms, specially dystonia (Saft et al., 2018). Of note the presence of CBD in Nabiximol make difficult to determine if the main effect of this drug is due solely to THC, and potentially, CB1 receptor engagement, as it is suggested that CBD antagonizes CB1 receptors and that CBD can bind to

**Table 5**
Alterations in eCBs level, CB1 receptor expression in HD patients.

| Disease stage | Brain area analyzed | Technique | Finding | Reference |
|---|---|---|---|---|
| Presymptomatic | Whole brain | PET $+^{18}$F-MK-9470 radioligand | Decrease CB1 receptors availability in prefrontal cortex | Ceccarini et al., 2019 |
| Shoulson–Fahn stage I (early symptomatic) | Whole brain | PET $+^{18}$F-MK-9470 radioligand and MRI | Decrease CB1 receptor availability in the gray matter of the cerebrum, cerebellum, and brain stem | Laere et al., 2010 |
| HD grade 0 to 3 (presymptomatic, intermediate, advanced) | Multiple brain regions | $^{3}$H-CP55,940 autoradiography | Decreased CB1 receptor availability in Caudate Nucleus, Putamen and Globus Pallidus across all grades. Decrease magnitude correlated with grade severity | Glass et al., 2000 |
| HD grade 1 and 3 | Substantia Nigra | $^{3}$H-CP55,940 autoradiography | Decrease CB1 receptors availability in Substantia Nigra Pars Reticulata | Glass et al., 1993 |

**Table 6**
Alterations in eCBs level, CB1 receptor expression in animal models of HD.

| Rodent model | Brain area analyzed | Technique | Finding | Reference |
|---|---|---|---|---|
| R6/1 mouse, presymptomatic | Cortex and Hippocampus | LC-MS | Increased 2-AG levels in the Cortex, while decreased AEA levels in the Hippocampus | Dowie et al., 2009) |
| R6/2 mouse, presymptomatic | Whole brain | LC-MS | Increased 2-AG levels | Bari et al., 2013 |
| R6/2 mouse, presymptomatic | Cortex | LC-APCI–MS | Decreased 2-AG levels | Bisogno et al., 2008 |
| R6/2 mouse, symptomatic | Striatum, Cortex and Hippocampus | LC-APCI–MS | Decreased 2-AG levels in Striatum and Cortex.<br>Reduced AEA levels in the Hippocampus, but increased in the Cortex | Bisogno et al., 2008 |
| R6/2 mouse, presymptomatic | Striatum, Cortex and Hippocampus | In situ hybridization<br>Northern blot<br>Immunohistochemistry | Decreased CB1 receptor mRNA levels in lateral Striatum, and in some neurons in Cortex and Hippocampus | Denovan-Wright and Robertson, 2000 |
| R6/1 mouse | Basal Ganglia | In situ hybridization<br>$^{3}$H-CP55,940 autoradiography | Decreased CB1 receptor mRNA levels in the striatum.<br>Decreased CB1 receptor protein level in Substantia Nigra<br>Decreased CB1 receptor availability in all Basal Ganglia | Dowie et al., 2009 |
| R6/2 mouse, Presymptomatic and symptomatic | Whole brain | PET +$^{18}$F-MK-9470 radioligand<br>In situ hybridization | Decreased CB1 receptor availability in caudate-putamen and globus pallidus in all stages. Further decrease on hippocampus, caudate-putamen, superior colliculus, thalamic nucleus and cerebellum in symptomatic stages | Ooms et al., 2014 |
| HD97 inducible mouse | Basal ganglia | $^{3}$H-CP55,940 autoradiography<br>WIN55-mediated $^{35}$S-GTPγS binding | Decreased CB1 receptor mRNA levels in Caudate-Putamen.<br>Decreased CB1 receptor availability in Caudate-Putamen,Globus Pallidus, entopeduncular nucleus and substantia nigra pars reticulata<br>Decreased G-protein coupling in Globus Pallidus | Lastres-Becker et al., 2002 |
| Rat treated with 3-NP | Multiples brain regions | WIN55-mediated $^{35}$S-GTPγS binding<br>In situ hybridization | Reduction in CB1 receptor G-protein coupling before the Striatal degeneration.<br>Reduction in CB1 receptors mRNA levels and G-protein coupling after striatal degeneration | Lastres-Becker et al., 2004 |

several molecular targets (Britch et al., 2021). Nevertheless, the THC-related compound nabilone has been shown to promote a small improvement in motor symptoms of patients (Curtis et al., 2009). Despite the need of further studies to disentangle the potential role of THC and CBD in alleviating HD pathology, it could be suggested that Nabiximol effect on motor function can be explained by THC itself. Overall, the impact of exogenous cannabinoids on symptomatic HD is mild. This could be explained by the progressive loss of the CB1 receptors in HD and concomitant loss in the total signaling capacity, in other words, there are not enough CB1 receptors to trigger a neuroprotective role in later stages of HD symptomatology. Thus, it will be interesting to test the impact of CB1 receptor agonists in pre symptomatic HD and determine if this approach slows down HD progression.

Recently, it has been shown that astrocytes dysfunction in HD might be secondary to the neuronal impairment induced by mutant huntingtin in R6/2 mice (Gangwani et al., 2023), in other words, astrocytes are not the main root of HD neuropathology. Nevertheless, it has been shown that astrocytes do accumulate mutant huntingtin and participate in HD progression (Lee et al., 2022; Palpagama et al., 2019). Astrocyte $Ca^{2+}$ dynamics (i.e., calcium rises amplitude, area and frequency) are reduced in the R6/2 mice, impairing striatal tonic GABA release and promoting obsessive compulsive-like behaviors (Yu et al., 2018). In a following study, the same group showed that activation of $G_i$ signaling in astrocytes via a DREADD strategy, which result in astrocytes $Ca^{2+}$ elevations (Durkee et al., 2019), is able to correct the deficient $Ca^{2+}$ dynamics in R6/2 mice and improve their phenotype (Yu et al., 2020). In this context, CB1 receptors engagement increase both intracellular and mitochondrial $Ca^{2+}$ in astrocytes (Eraso-Pichot et al., 2023; Serrat et al., 2021), thus as CB1 receptors levels are reduced in HD, it is plausible that decreased astroglial CB1 receptors signaling in HD might participate in the altered $Ca^{2+}$ dynamics observed in the R2/6 HD mice (Yu et al., 2018, 2020).

Similar to AD, pre symptomatic brain glucose hypometabolism is a hallmark of HD (Antonini et al., 1996; Grafton et al., 1992; Kuwert et al., 1993), and also its cellular and molecular origin(s) are unknown. Interestingly, HD symptomatology can be alleviated by dietary anaplerotic therapy using triheptanoin (Adanyeguh et al., 2015). This triglyceride composed by three fatty acid of seven-carbon length is able to promote the replenishment of TCA intermediates, a key metabolic process that is carried out exclusively by astrocytes in the brain (Schousboe et al., 2019; Weber and Barros, 2015). Thus, it is plausible that triheptanoin is consumed specifically by astrocytes, which might cause a reduction in the amount of glucose consumed for replenishment of TCA intermediates. This might result in a glucose sparing phenomenon, in which the consumption of alternatives fuels by astrocytes might secure neurons glucose accessibility in the face of scarce brain glucose levels as observed in HD (Polyzos et al., 2019). Interestingly, this glucose sparing hypothesis have been also proposed for the beneficial effects of ketogenic diet on brain function (Valdebenito et al., 2016). The involvement of astrocytes in HD metabolic failure have been proposed to result from the reprogramming of astrocyte mitochondrial function toward lipid oxidation and concomitant increase in ROS production in the HdhQ (150/150) mouse model (Polyzos et al., 2019), which carries a longer CAG repetition of the exon 1 of human huntingtin when compared to other HD mouse models (Lin et al., 2001). Noteworthy, healthy astrocyte are able to metabolize lipids (Eraso-Pichot et al., 2018) and the loss of this capacity induce neuroinflammation and neurodegeneration (Mi et al., 2023). This contradictory data might be explained by the fatty acid accumulation and reduced availability of glucose in the striatum (Polyzos et al., 2019), which force astrocytes to rely heavily in lipid oxidation to sustain their own energy needs, at the expense of increasing ROS production. Alternatively, the ROS increase may not be due increased lipid oxidation but rather explained by impaired antioxidant capacity due a reduction in the ascorbic acid shuttle between astrocytes

and neurons in HD mouse models (Acuña et al., 2013; Boussicault et al., 2014; Lee et al., 2022). In this context, activation of CB1 receptors in astrocyte mitochondria reduce complex I activity and ROS production (Jimenez-Blasco et al., 2020), thus the effect of cannabinoids on HD symptomatology might potentially be related to the reduction of ROS production by astrocyte mitochondria. On this rationale, 3-NP neurotoxic effects result from inhibition of mitochondrial complex II and concomitant increase in ROS production (Túnez et al., 2010). Interestingly, administration of the synthetic cannabinoid WIN55,212–2 before 3-NP treatment protects rats from the deleterious effect of the neurotoxin (Maya-López et al., 2017). Consistent with this observation, deletion of CB1 receptors worsens the neurotoxic effect of 3-NP in mice (Mievis et al., 2011). In parallel to this putative reduction in ROS production induced by CB1 receptor activation, a reduction of astroglial glucose consumption induced by cannabinoids (Jimenez-Blasco et al., 2020), might spare enough glucose for neurons to increase their antioxidant capacity via pentose phosphate pathway (Bolaños and Almeida, 2010), thus potentially allowing neurons to better survive the oxidative stress that occurs during HD (Kumar and Ratan, 2016). Indeed, reducing the ROS levels caused by lipid oxidation using an electron scavenger, protect neurons from oxidative damage and improve motor symptoms in HD mice (Polyzos et al., 2019). Nevertheless, is important to note that the cannabinoid-mediated reduction of glucose metabolism reduces brain lactate availability and impact brain function (Jimenez-Blasco et al., 2020), thus the role of lactate in HD warrant a further description to understand if a reduction in lactate levels might be beneficial or noxious in the altered HD bioenergetics settings.

In summary, there is compelling evidence for reduced CB1 receptor signaling in HD. However, a better understanding of the cellular and molecular components involved of such deficit requires further attention. Noteworthy, deficits in CB1 receptor signaling in astrocytes might partially explain the beneficial effects of cannabinoids on HD.

## 5. Conclusion and future perspectives

The main brain ECS signaling hub, the CB1 receptors, are prominently expressed across the entire brain parenchyma and exert a powerful control of brain function and behavior. Thus, it is not surprising that this signaling system might be altered in pathological conditions. Indeed, several research lines on AD, PD and HD have found data consistent with aberrant ECS signaling in these neurodegenerative disorders. However, this knowledge had started to become narrow, as the field of brain ECS is evolving quickly, with new cellular and molecular substrates joining the complex array of intracellular and intercellular signaling triggered by CB1 receptors engagement. For instance, several studies were performed before the demonstration of functional expression of CB1 receptors in astrocytes and other glia cells. Moreover, the existence of mitochondrial associated CB1 receptors has radically changed the understanding about CB1 receptor signaling. In this rationale, the emerging concept of independent subcellular pools of CB1 receptor (Soria-Gomez et al., 2021) is an important aspect to be considered in future studies. Importantly, aging is considered the main risk factor for several neurodegenerative disorders (Hou et al., 2019), and surprisingly, we do not fully understand how the ECS evolve during aging. Indeed, just a handful of studies have looked into how aging shape the ECS signaling, but current data indicates that older people respond differently to exogenous cannabinoids (Bilkei-Gorzo et al., 2017; Mueller et al., 2021). Thus, it is recommended to apply with care the current knowledge about the ECS in young adulthood into the neurodegenerative disorders research, especially in AD and PD in which aging is a strong risk factor. In conclusion, the involvement of ECS and signaling warrant new interdisciplinary approaches to take into account the new discoveries about CB1 receptors expression in diverse brain cells and its direct control of mitochondrial function.

## Authors contribution

I·F-M., A.*E*-P. and G.M. contributed to the conceptualization and writing of the review. T.D.T and B.F.M. contributed by data curation and writing. All authors read and approved the manuscript version.

## Declaration of Competing Interest

The authors declare that there are no competing interests associated with the manuscript.

## Data availability

No data was used for the research described in the article.

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