Chapter 4

Cannabinoids and Motor Control of the Basal Ganglia: Therapeutic Potential in Movement Disorders

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Abstract

Cannabinoid receptors in the brain appear to be intimately involved in the motor control. Cannabinoid CB1 receptors are densely located in the basal ganglia (BG), a forebrain system that integrates cortical information to coordinate motor activity regulating signals. In fact, the administration of plant-derived, synthetic or endogenous cannabinoids produces several effects on motor function. These effects are paralleled to changes in the levels of different neurotransmitters in the BG, including GABA, dopamine and glutamate, all of which are important players in movement control.

Cannabinoid receptors also participate in the etiopathology of movement disorders such as Parkinson's disease (PD) or Huntington's disease (HD). In fact, both CB receptors and endocannabinoid levels are altered in the BG of patients with PD and HD and animal models of these diseases. The benefit of cannabinoids in PD or HD is not limited to the symptomatic amelioration, since several publications have revealed interesting neuroprotective and anti-inflammatory effects of these drugs. It has been suggested that cannabinoid modulation may constitute an important component in new therapeutic approaches to the treatment of motor disturbances.

Keywords: Basal Ganglia, endocannabinoids, Parkinson's disease, Huntington's disease, CB1 receptor, CB2 receptor, TRPV1

Abbreviation List

Δ^9-THC: Δ^9-Tetrahydrocannabinol

Δ^9-THCV: Δ^9-Tetrahydrocannabivarin

2-AG: 2-Arachidonoylglycerol

3-NP: 3-nitropropionic acid

6-OHDA: 6-hydroxidopamine

AEA: Anandamide

BDNF: Brain-derived neurotrophic factor

BG: Basal Ganglia

CAG: Cytosine-adenine-guanine

CBD: Cannabidiol

CNS: Central nervous system

ECS: Endocannabinoid system

FAAH: Fatty acid amide hydrolase

HD: Huntington's disease

HTT: huntingtin protein

Internal/external globus pallidus: GPi/GPe

LPS: Lipopolysaccharide

MAGL: Monoacylglycerol lipase

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

PD: Parkinson's disease

PEA: Palmitoylethanolamide

SNc: Substantia nigra pars compacta

SNr: Substantia nigra pars reticulata

SPN: Spiny projection neurons

STN: Subthalamic nucleus

TRPV1: Transient receptor potential vanilloid 1

VGLUT1: vesicular glutamate transporter 1

VGLUT2: vesicular glutamate transporter 2

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1. Introduction

The identification of more than 60 oxygen-containing aromatic hydrocarbon compounds, known as cannabinoids in the plant *Cannabis sativa*, led to the discovery of the endocannabinoid system (ECS) [1]. This system consists of two well-characterized seven transmembrane G-protein coupled receptors, CB1 [2] and CB2 [3], the transient receptor potential vanilloid 1 (TRPV1) channel, a number of endogenous ligands and associated enzymes for biosynthesis and degradation (for review see [4,5]). The endocannabinoids are lipids localized in the central nervous system (CNS) and peripheral tissue, being anandamide (AEA) and 2-arachidonoylglycerol (2-AG) the best characterized ones [4]. These endocannabinoids are synthesized, on demand, after neuronal depolarization, released into the extracellular space and after CB receptors activation they are uptaken by a specific transport protein located on both neurons and glial cells to be subsequently degraded by intracellular enzymes [6].

The CB1 receptor is one of the most abundant cannabinoid receptor in the neurons from the CNS whereas the CB2 receptor is more predominant in glial cells and peripheral tissues [7]. CB receptors are coupled to Gi/o proteins, negatively to adenylyl cyclase and positively to mitogen-activated protein kinase and ion channels. Thereby activation of these receptors exerts diverse responses as inhibition of neurotransmitter release including GABA, glutamate, noradrenalin and dopamine [6,8,9], gene transcription and cell proliferation, differentiation and survival [10]. Commonly, the ECS is described as a neuromodulatory system which interacts with other neurotransmitter systems and may be implicated in (patho)physiological functions among others, those related to motor activity, neuron proliferation and inflammatory process. Consequently the ECS appears as a promising target for drug development. *Cannabis sativa* derivatives have been used medically for thousands of years, however the psychoactive effects together with tolerance and its potential abuse have limited the clinical application. Nowadays numerous efforts are being made to develop non-psychotropic cannabinoids that could be used in several CNS disorders.

This review will focus on recent studies clarifying the role of the ECS as a target to develop new therapeutic tools to treat movement disorders.

2. Neuroanatomical distribution of the endocannabinoid system in the BG

The ECS is highly expressed in the Basal Ganglia (BG), which is a highly organized network of subcortical nuclei composed of the striatum (caudate and putamen), *subthalamic nucleus* (STN), internal and external *globus pallidus* (or entopeduncular nucleus in rodents, GPi/EP and GPe) and *substantia nigra* (*pars compacta*, SNc, and *pars reticulata*, SNr). The BG connects the cortex with the thalamus, creating the cortico–basal ganglia–thalamo–cortical loop, and plays a crucial role on controlling movement activity.

High levels of CB1 receptors are found in the striatum and motor cortex where they are mainly present in projecting terminals (reviewed in [11]). Thus, CB1 receptors have been observed in

glutamatergic corticostriatal afferences [12,13], striatal projections to the GPi/GPe and to the SNr [14,15] and also in subthalamonigral and subthalamopallidal terminals [15,16]. Moderate to dense CB2 immunoreactivity is also present in the cortex, striatum and SN [17] and is increased in several pathological conditions [18,19]. TRPV1 receptors have also been located in nigrostriatal terminals and on tyrosine hydroxylase-positive cells in the SNc [20,21].

The two most important endocannabinoid-synthesizing enzymes (N-acyl phosphatidylethanolamine phospholipase D and diacylglycerol lipase-alpha) as well as the endocannabinoid degradative enzymes (fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)) are found in the BG, particularly in the striatum [22–24]. Finally, both AEA and 2-AG are expressed within the BG and modulate the activity of the cortico–basal ganglia–thalamo–cortical loop leading to motor activity modulation (for review see [25]).

3. Motor effects of cannabinoids

Over the last three decades a wide range of experimental and clinical studies have demonstrated that the ECS plays a key role controlling motor function. Specifically, three lines of evidence support this idea. First, administration of plant-derived compounds, synthetic cannabinoids and endocannabinoids produces a variety of effects on motor activity in humans and laboratory animals. Second, endocannabinoids and their receptors are abundant in the BG and the cerebellum, two brain areas that exert direct control of motor function. Third, biochemical and functional alterations of the ECS have been related to the etiology of several movement disorders, since overactivity of the ECS signaling is associated with the progression of the nigral degeneration in patients with Parkinson's disease (PD) [26–28] and down-regulation of CB1 receptors has been reported in brain samples collected from patients with Huntington's disease (HD) [29–31].

Marijuana consumption affects psychomotor skills clearly reflected in poor performance of highly demanding tasks and potent impairment of motor coordination [32–34], interfering with driving skills and increasing the risk of injuries [35]. In experimental animal models, the motor effects of the endogenous ligand AEA are similar to those induced by the plant-derived cannabinoid agonist Δ^9-tetrahydrocannabinol (Δ^9-THC), but less pronounced and of shorter duration. The main motor outcomes of cannabinoid agonists are hypoactivity and catalepsy, however biphasic effects have been described depending on the drug and dose used. While relatively low doses of Δ^9-THC and AEA have been associated with a transient increase in motor activity, high doses produce motor inhibition and catalepsy [36–45]. Additionally, both drugs AEA and Δ^9-THC potentiate the catalepsy induced by a local administration of muscimol into the GP [46] and reduce stereotyped behaviors [40–42]. Δ^9-THC reduces the amphetamine-induced hyperlocomotion [47] and impairs fine motor control in rats [48].

Interestingly, cannabidiol (CBD), other plant-derived cannabinoid, has been proposed as a modulator of the effects induced by Δ^9-THC (reviewed in [49]). Several studies conclude that CBD attenuates some Δ^9-THC motor side effects such as catalepsy [50–52], while others show that high doses of CBD fail to prevent or exacerbate the pharmacological effects of Δ^9-THC,

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including hypoactivity [45,53]. Nevertheless, the influence of CBD on spontaneous locomotion seems to be limited [45,53–55] and it may be unrelated to the CB receptors interaction [49].

Preclinical studies using synthetic cannabinoid agents have highlighted the role of the ECS on the control of motor function. Thus, systemic administration of the agonists WIN 55,212-2, CP55,940 and HU210 usually causes inhibition of motor activity [45,56–61] and produces basal catalepsy [52,62–64]. Activation of CB1 receptors by the agonist CP55,940 enhances the catalepsy induced by dopaminergic antagonists [65] and genetic inactivation of either dopamine D2 receptors or adenosine A2A receptors reduces the motor depression produced by CP55,940 [63]. In fact, the inhibitory motor effects caused by an intrastriatal injection of the CB1 agonist WIN 55,212-2 are mediated by a functional interaction between the adenosine A2A and the CB1 receptors [66], which are present as heteromers in the rat corticostriatal terminals [67]. In line with this, the specific adenosine A2A receptor antagonist MSX-3 blocks the inhibitory effect of the CB1 receptor agonist CP 55,940 on the hyperactivity induced by the dopamine D2 receptor agonist quinpirole [58]. Although, a strong functional interaction between striatal A2A and CB1 receptors is accepted, the mechanisms of this interaction are still not clear since it has been proposed a stimulatory role as well as an inhibitory role of A2A receptors on CB1 receptor-dependent effects [68].

Pharmacological agents that indirectly elevate endocannabinoid levels by inhibiting either their uptake or the intracellular degradation have been proposed as promising therapeutic agents for the treatment of diverse diseases including movement disorders (for review see [69]). These pharmacological agents are also referred as indirect agonists and they also elicit some cannabimimetic motor effects, including hypoactivity. On one hand, the selective and potent inhibition of the endocannabinoids transport by the arachidonic acid derivative, UCM707 potentiates the hypokinetic effects caused by a non-efficacious dose of AEA [70]. Similarly, the selective blockade of the AEA transport by AM404 elevates circulating levels of the endocannabinoid and causes hypoactivity [71,72], likely by activating TRPV1 [73]. On the other hand, selective inhibition of the endocannabinoids metabolizing enzymes has brought interesting results suggesting the differential role of the endogenous agents, AEA and 2-AG, in the unwanted motor effects induced by cannabinoid compounds. Specifically, inhibition of MAGL, but not FAAH, causes CB1 receptor-mediated hypoactivity. However, neither FAAH nor MAGL produce cataleptic effects usually elicited by direct agonists [74,75]. Thus, the FAAH inhibitor URB597 does not significantly alter motor function at doses that induces analgesia [74] and a single or repeated administration of PF-04457845, a specific and irreversible FAAH inhibitor, is well tolerated in healthy humans [76]. Conversely, the MAGL inhibitor JZL184 reduces locomotor activity [77,78], and dual inhibitors JZL195 and AS-57 induce also catalepsy [75,79].

From a general point of view, the motor effects of direct and indirect agonists are usually mediated by stimulation of CB1 receptor since its pharmacological blockade prevents the above mentioned effects [64,72,75,80,81]. In addition, a high dose of the CB1 receptor antagonist SR141716A causes hyperlocomotion by itself [82,83] while a lower dose does not affect motor activity [84]. Also the CB1 receptor antagonist AM251 administrated alone fails to alter basal locomotion but diminishes the psychomotor effects induced by the co-administration of

amphetamine [85]. In agreement with these observations, mice lacking CB1 receptors exhibit several motor anomalies [86,87] and show less sensitivity to the psychomotor stimulants and sensitizing effects of the psychostimulants [88,89].

Although these findings provide evidence for the involvement of CB1 receptor-related mechanisms in motor control, other reports demonstrate that also the TRPV1 receptors can mediate effects of certain cannabinoids such as AEA [90]. The potential beneficial effects of cannabinoid agents in movement disorders are further reviewed here.

4. Alterations of the endocannabinoid system in movement disorders

4.1. Endocannabinoid system in Parkinson's disease

PD is the second most common neurodegenerative disorder, after Alzheimer's disease. It is a chronic and progressive neurodegenerative illness and its etiology is interpreted as a combination of genetic, environmental, and aging-related processes, although the exact cause of this degeneration is unknown. Clinical manifestation of the disease includes tremor at rest, worsening of voluntary movements, bradykinesia, muscle rigidity and postural instability [91,92]. All of these symptoms appear as a result of pathological processes, including neuroinflammation, mitochondrial dysfunction, oxidative stress, kinase pathways and calcium dysregulation, protein aggregation and prion-like processes, which result in a degeneration of dopamine neurons in the SNc and a subsequent dopaminergic depletion in the striatum, the main input nucleus of the BG neural circuit. [93].

Several components of the ECS are altered in movement disorders which have led to consider it as a possible target for developing new treatments for these disorders. The effects of cannabinoid compounds and their potential utility in PD has been tested, but inconsistent data have been produced, as there are many complex responses elicited by dopamine and its interaction with different cannabinoid mechanisms [94].

4.1.1. Endocannabinoid levels

The ECS in the BG becomes overactivated in PD. For instance, the cerebrospinal fluid of untreated patients with PD has at least two-fold higher levels of AEA, compared to controls, being this increase independent of either disease stage or progression [27]. Overall, results from preclinical studies support the clinical findings.

In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys, the levels of both AEA and 2-AG were determined throughout the BG after induction of parkinsonism and L-DOPA treatment. Both AEA and 2-AG levels were elevated in the striatum of untreated parkinsonian monkeys and returned to those found in the striatum of normal monkeys after treatment with L-DOPA [95]. These results are similar to those reported in rodent models of PD, where AEA levels were estimated to be higher in the BG output regions, as compared to the striatum or GPe, while 2-AG levels were similar throughout the BG regions analyzed [96]. Similarly, in a rat model of PD induced by unilateral nigral lesion with 6-hydroxidopamine

(6-OHDA), striatal levels of AEA, but not 2-AG levels, were increased. Moreover, decreased activity of the AEA membrane transporter and FAAH was observed, whereas the binding of AEA to CB receptors was unaffected [97]. In studies with reserpine-treated rats an increase of 2-AG levels in output BG regions, such as GP and SNr has been reported compared to other brain regions like the cortex, cerebellum, hippocampus, and striatum [98]. In mutant models of the disease, as the homozygous *Pink1* knockout mice, the levels of 2-AG and AEA were not altered in striatum, and no change was observed as for the activity of FAAH and MAGL, responsible for endocannabinoids hydrolysis. Although the levels of 2-AG remains unchanged in PD, this endocannabinoid has revealed its neuroprotective role in the MPTP mouse model [99] as well as palmitoylethanolamide (PEA) [100].

4.1.2. Cannabinoid receptors

CB1 availability is unevenly modified in patients with PD, which is decreased in the SN but relatively increased in nigrostriatal, mesolimbic, and mesocortical dopaminergic projection areas [101]. In *post-mortem* samples from patients with PD increased CB1 receptor binding in the caudate-putamen was found and a higher stimulation by CB1 receptor agonists of [35S]GTPγS binding was measured in the same brain areas [26]. Other studies performed in PD human brain have shown that the expression of CB1 receptor mRNA was decreased in the caudate nucleus, anterior dorsal putamen and GPe, but remained unchanged in the other brain areas examined [102]. When the relationship between CB1 receptors and dopamine D2/D3 receptor densities was analyzed by receptor autoradiography, unchanged CB1 receptor density in the putamen and caudate of patients with PD (treated with L-DOPA) was found together with a parallel decreased in the density levels of dopamine D2/D3 receptors in the same nuclei [103].

Studies in animal models also show disparity of results concerning CB1 receptors. In MPTP-lesioned marmosets, increase in CB1 receptor binding was also confirmed in the caudate-putamen [26]. In contrast, in the reserpine-treated rat model of PD a topographically organized reduction in CB1 receptor mRNA expression in the striatum was found [98]. However, in other studies with 6-OHDA-lesioned rats, no significant change in CB1 receptor expression or binding was detected, although an increase in CB1 receptor mRNA levels in the striatum was found [104,105]. In *Pink1* knockout mice, however, a significant reduction of binding ability of CB1 receptor agonists was found [106].

Regarding CB2 receptors, in neurotoxin rat models of PD, when 6-OHDA or lipopolysaccharide (LPS) is injected into the striatum, increased expression of the CB2 receptor and proportionally increased microglial activation was found [107]. Other CB receptors may have a role in PD treatment, thus the pharmacological blockade of TRPV1 receptors, which have been implicated in the modulation of dopamine transmission in the BG, attenuates the 6-OHDA induced hypokinesia [108]. TRPV1 receptors, where AEA binds, may play opposite roles to CB1 receptors in order to treat L-DOPA-induced dyskinesia [94,109]. Although it seem that the ECS suffers dramatic modifications in PD, so far clinical and preclinical studies show no conclusive results.

4.2. Endocannabinoid system in Huntington's disease

HD is a rare autosomal-dominant progressive neurodegenerative disease that affects 4–10 per 100,000 people in Western countries [110]. It is caused by the mutation in the IT15 gene (*HTT)* that encodes the huntingtin protein(HTT) and consists in an expanded cytosine-adenine-guanine (CAG) repeat that yields an abnormally long polyglutamine sequence in HTT [111]. Healthy subjects have less than 35 CAG repeats, while genes with more than 39–40 CAG repeats (or more) encode pathogenic HTT. Although physiological HTT is widely found in the brain, the mutation leads to the expression of the aberrant protein harmful only to specific neuron populations. Indeed, the prominent degeneration of GABAergic spiny projecting neurons (SPN) in the striatum [112] and to a lesser extent, of glutamatergic cortical pyramidal neurons [113,114] are the hallmarks of the disease. In late stages of the disease other brain areas and neurons may also be affected, producing a complex disease. The clinical manifestation can appear early, at the ages of 30–50 years, and progressively worsen over the following years. On the course of the disease, the patient can suffer from movement disorders, cognitive disability and psychiatric symptoms such as personality changes, depression or memory loss, among others [115]. The early stages of the disease are characterized by choreic involuntary movements and cognitive impairment, which are related to mutant HTT aggregation and aberrant neurotransmission in the striatopallidal SPN and corticostriatal neurons, respectively (reviewed in [116]). In more advanced phases of the disease, when the direct pathway in the BG is also affected, the patients display parkinsonian-like symptoms, as bradykinesia and rigidity [117].

4.2.1. Endocannabinoid levels

As mentioned for PD, in HD The ECS also suffers notorious modifications on the course of the disease in the BG [30,31,118]. In *post-mortem* tissue, higher expression of FAAH was observed in the caudate-putamen from HD brains [119] while the opposite effect was found in the cortex [120].

The activity of the ECS has also been investigated in animal models of HD without consistent results, probably due to the different models and ages selected for the studies. In the R6/1 transgenic model of HD, significant decrease in AEA levels were detected in the hippocampus in contrast to increased 2-AG concentrations only found in the cortex at 12 weeks of age, prior to the motor disturbances [121]. Another study in R6/2 transgenic mice, which differ in CAG repeats number from R6/1 mice and show severe motor and cognitive defects at earlier ages, also reported decreased in cortical 2-AG during motor presymptomatic stages [122]. In symptomatic R6/2 mice, AEA, 2-AG and PEA were markedly decreased in the striatum and in a lesser extent in the hippocampus or cortex [122]. Other study performed also in R6/2 mice found increased 2-AG but unchanged AEA levels in the striatum [123]. As for the enzymes' activity, Bari et al. found increased FAAH and decreased MAGL activity in the cortex together with reduced activity of AEA and 2-AG metabolic-enzymes at different ages in the striatum, which disagrees with the higher expression of FAAH reported by others [119]. The use of other animal models, such us the 3-nitropropionic acid (3-NP)-lesion rat, showed decreased AEA and 2-AG in the striatum but suggested increased AEA levels in the SN [124].

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So far studies regarding enzyme activity and endocannabinoid levels in HD are limited and offer inconsistent results although overall endocannabinoid levels seem to be reduced in different brain areas. More homogeneous preclinical studies together with clinical investigations will be needed for clarifying these founds.

4.2.2. Cannabinoid receptors

Autoradiographical and immunohistochemical studies in human *post-mortem* tissue demonstrated that early stages of the disease are characterized by a loss of CB1, dopamine D2 and adenosine A2A receptors in the caudate nucleus, putamen and GPe, which corresponds to the deterioration of striatopallidal SPNs [30,118,125]. Later in the disease, when the striatonigral pathway also degenerates, even greater down-regulation of striatal and nigral CB1 receptors is observed [30]. *In vivo* imaging of CB1 in patients confirmed the down-expression of these receptors in cortical and subcortical structures, starting early in the development of the disease [126]. Despite the variety of animal models available for studying the disease, most preclinical studies back up the observations from human tissue. In transgenic mice, such as the HD94 or R6/2 transgenic models, loss of mRNA levels, binding, receptor expression and activation of GTP-binding proteins for cannabinoid CB1 receptors have been reported primarily in SPNs belonging to the indirect pathway in the early phases of the disease accompanied or not by cortical and hippocampal alterations [121,123,125,127–129]. In models induced by the administration of 3-NP, where striatal neuronal loss is produced, additional loss of CB1 receptors is also observed [124,130,131]. Small animal PET studies performed in transgenic HD rat and mouse models, have also confirmed reduced CB1 receptor binding in the striatum and GPe in all stages, as well as alterations in the cortex, hippocampus, thalamic nuclei or cerebellum in more advanced phases of the disease [132,133]. Results from human brain and most animal models coincide in reporting down-regulation of striatal CB1 receptors in HD, which has been proposed to be induced by mutant HTT that controls gene promoter activity via repressor element 1 silencing transcription factor [119]. In this respect, genetic CB1 receptor deletion has been proven to worsen motor symptomatology and to exacerbate striatal degeneration by increasing excitotoxic damage and decreasing brain-derived neurotrophic factors [119,134,135]. Although rescuing CB1 receptors prevents the striatal morphological modifications observed in mice models of HD, it failed to improve motor deterioration [136].

Regarding CB2 receptors in the HD brain, studies performed in *post-mortem* human tissue suggest up-regulation of CB2 receptors on CD68-positive microglial cells [137] or slight increase on brain blood vessels [138] but not on astrocytic cells. These results agree in part with preclinical studies where up-regulation of CB2 receptors has been observed in the striatal microglial of R6/2 mice and striatal microglia and astrocytes in a rat model of HD induced by intrastriatal injection of malonate (mitochondrial complex II inhibitor) [137,139]. This compensatory increase of CB2 receptors may have a neuroprotective effect on the disease [137]. In this line, CB2 agonists have been proposed to decrease striatal neurodegeneration in malonate-lesioned rats [139]. In addition, CB2 depletion has been documented to accelerate the onset of the disease and aggravate the motor disabilities in a mouse model of HD [137,140].

Less attention has been paid to the TRPV1 channels, which also play an important role in the ECS. So far, only one publication has studied these receptors reporting no modification in TRPV1 binding in R6/2 mice at any age [123].

In general, preclinical and clinical studies have well characterized a down-regulation of CB1 receptors at different stages of HD, which may cause a role in the progression of the disease. Less is known about CB2 or TRPV1 receptors and further investigations are required to clarify their role in the neuropathology of the disease.

5. Potential therapeutic role of cannabinoids in movement disorders

5.1. Parkinson's disease

Currently, pharmacological treatment for PD is focused on dopaminergic replacement, which controls the symptoms in both early and advanced stages [141]. However, its chronic use is limited due to the development of severe and disabling side effects, such as motor fluctuations or L-DOPA-induced dyskinesia. Besides, none of the available treatments are capable of slowing or stopping the disease progression. Cannabinoid-based therapies have been proposed as a promising approach for PD treatment, not only for their antiparkinsonian properties, but also for the neuroprotective and anti-inflammatory effects of these compounds.

5.1.1. Cannabinoids for the treatment of motor symptoms

Studies in animal models and patients with PD have indicated that both CB1 agonists and antagonists used alone or as coadjuvants, could be useful to treat different symptoms of this movement disorder. Thus, CB1 agonists have been shown to improve motor impairment in animal models of PD [142–145] and to reduce tremor associated with the hyperactivity of the STN [145,146]. However, because of the hypokinetic profile of the cannabinoid agonists, it is unlikely that these drugs would be useful for alleviating bradykinesia in PD patients. In fact, the administration of agonists to humans or MTPT-lesioned primates enhanced motor disability (for review [34]).

On the other hand, behavioral changes in parkinsonian rodents also improved with the administration of CB1 antagonists [147–149]. It has been suggested that blocking CB1 receptors could be useful in particular conditions, as when the patients do not respond to dopaminergic therapy or in advanced phases of the disease [147,148,150]. It is also important to consider the therapeutic benefits of TRPV1 receptor antagonists, given their role in regulating dopamine release from nigral neurons [151].

Cannabinoids also may be beneficial in treating L-DOPA-induced dyskinesia. Indeed, administration of CB1 agonists to parkinsonian rats chronically treated with L-DOPA reduced the occurrence of dyskinesia [109,152,153] without reducing the efficacy of L-DOPA to improve motor performance. In MPTP-lesioned monkeys and patients with PD the results are mixed. Indeed, both CB1 agonist and antagonists showed antidyskinetic effect [95,154–157] while plant-derived cannabinoids failed to improve motor disability [158,159].

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5.1.2. Cannabinoids as neuroprotective agents

In vivo as well as *in vitro* preclinical studies in animal models of PD have revealed that cannabinoid receptor modulation can be potentially useful for protecting dopaminergic neurons from progressive neurodegeneration. Although CB1 receptor-mediated effects cannot be excluded, some authors argue that CB1 receptors may have a minimal implication in neuroprotection [10,160–162]. It seems plausible that neuroprotection is principally mediated by the antioxidant properties of the cannabinoids [160,163,164], given that oxidative stress is a major hallmark in the pathogenesis of PD. The effect of numerous phytocannabinoids, as Δ^9-THC, CBD and Δ^9-Tetrahydrocannabivarin (Δ^9-THCV), has been investigated in experimental models of PD (6-OHDA-lesioned rodents, MPTP or LPS-lesioned mice) [160,163,165]. These studies have showed that cannabinoids could be useful for developing novel neuroprotective therapies in PD due to their CB receptors-independent antioxidant actions. Double-blind trial carried out in patients with PD tried to evaluate the neuroprotective effect of CBD administration but definitive conclusions were not established [166].

Neuroprotection has also been provided by synthetic cannabinoids such as the endocannabinoid transporter inhibitor/vanilloid agonist AM404, or the CB1/CB2 receptors agonist CP55,940, which also produce antioxidant effects via cannabinoid receptor-independent mechanisms [163,167]. By contrast, selective CB1 or CB2 agonists failed to protect these neurons [163].

5.1.3. Cannabinoids as anti-inflammatory agents

Substantial evidence supports that inflammation plays a pivotal role in the death of neurons in the BG in PD. Activated microglia has been found in *post-mortem* brains from patients with PD [168] and elevated levels of inflammatory cytokines have been measured in the cerebrospinal fluid of patients [169–171]. Cannabinoid compounds have demonstrated anti-inflammatory properties. Concretely, CB2 receptor agonists are the most promising cannabinoids to treat the inflammatory processes related to neurodegenerative disorders, although other cannabinoid agonists have also showed anti-inflammatory activity [172]. In fact, the selective CB1 receptor agonist arachidonoyl-2-chloroethylamide and other non-selective cannabinoid agonists have revealed strong anti-inflammatory properties [173].

CB2 receptor is expressed on microglia and it is strongly up-regulated when these cells are activated [174]. *In vitro* activation of microglial CB2 receptors leads to suppression of the release of pro-inflammatory cytokines reducing neurotoxicity [175]. The beneficial effect of CB2 receptor stimulation has also been proved in animal models of PD [161,165]. Moreover, an increase of sensitivity to the neurotoxin LPS in CB2 receptor knockout mice has been described [165] and the overexpression of this receptor subtype reduced the recruitment of glial cells to the lesion and decreased the level of various oxidative parameters [176].

Apart from the CB2 receptor, several studies have corroborated the anti-inflammatory potential of targeting CB1 receptor in PD. WIN 55,212-2 or HU 210 administration decreases the number of activated microglia and reduces the mRNA levels of the proinflammatory cytokine IL-6 in MPTP mice and LPS-treated rats [162,177,178]. In another study, 2 week pre-

treatment with Δ^9-THC and CBD, followed by 6-OHDA injection, decreased the loss of dopaminergic neurons in hemiparkinsonian rats [160].

All these studies suggest that the CB1 and CB2 receptors could be potential targets for anti-inflammatory intervention in PD.

5.2. Huntington's disease

To date, the treatment of HD is merely symptomatic and focuses on the restoration of the neurotransmitter imbalance that occurs in the disease. For this reason, GABA agonists, dopamine depleting agents, neuroleptics, anti-glutamatergic agents, antidepressants or acetylcholinesterase inhibitors are often used for ameliorating the symptoms (for review see [179]), despite not being able to cure or stop the progression of the disease. In this situation cannabinoid compounds may play a promising therapeutic role as it has been proven in other neurodegenerative diseases [180,181]. Indeed, activation of cannabinoid receptors facilitates the activation of intracellular mechanisms related to cell homeostasis, repair and survival. Moreover, several pre-clinical and clinical studies have showed that cannabinoids can be useful in HD. The effects of cannabinoid compounds on HD can be divided in three different actions: improvement of motor symptoms, neuroprotection and anti-inflammatory activity.

5.2.1. Cannabinoids for the treatment of motor symptoms

As mentioned above, the most characteristic feature of HD is the motor impairment which varies along the progression of the disease. In this context, cannabinoid compounds have been tested for treating these motor symptoms in animal models of HD, some of them showing anti-hyperkinetic activity. The administration of the endocannabinoid re-uptake inhibitor, AM404, reduced hyperkinetic movements and restored the neurochemical alterations (dopamine and GABA reduction) in the HD rat model with bilateral striatal injection of 3-NP [130]. However, the anti-hyperkinetic effect showed by AM404 seems to be mainly consequence of TRPV1 receptor activation, and not CB1-dependent [130]. In the same rat model of HD, the administration of UCM707, another endocannabinoid uptake inhibitor, also showed anti-hyperkinetic activity that may be due to the recovery of GABAergic and glutamatergic function in the GP and SN, respectively [182]. In addition, Arvanil, a hybrid endocannabinoid and vanilloid compound, has also demonstrated anti-hyperkinetic activity, although it could not restore the neurochemical alterations in the 3-NP rat model of HD [183]. Similarly, the CB1 receptor agonist CP55,940 has showed anti-hyperkinetic activity, without changing dopamine and GABA levels [184]. Other compounds, VDM11 (endocannabinoid re-uptake inhibitor) and AM374 (endocannabinoid hydrolysis inhibitor), have not demonstrated any significant effect on hyperkinetic movements in the same HD model [184]. The chronic, but not the acute administration of the CB1 receptor agonist WIN 55,212-2 prevented the appearance of motor impairment in the R6/1 transgenic mice model of HD, without improving the social and cognitive deficits [185]. So far, the clinical use of plant-derived cannabinoids and synthetic analogues has shown disappointing results in the treatment of the motor symptoms. A case report and a pilot study of nabilone in patients with HD showed that the effect of this drug on

HD motor symptoms is limited [186,187]. Other studies have demonstrated that the administration of nabilone or CBD did not improve the hyperkinetic alterations associated with HD [188,189]. The lack of therapeutic efficacy may lie on the mechanism of action of the cannabinoid agonists used. These cannabinoid drugs were unable to activate TRPV1 receptors, which have been proven to mediate anti-hyperkinetic in 3-NP-lesioned rats. Thus, the most appropriate compounds for future clinical trials, at least in the early stages of the disease, may be those able to activate both CB1 and TRPV1 receptors [190].

5.2.2. Cannabinoids as neuroprotective agents

The neuroprotective properties of the cannabinoids make them very interesting tools to stop the progression of HD. In fact, cannabinoid compounds may reduce cytotoxic processes that occur in neurons and glial cells in neurodegenerative diseases [181]. The protective effects are consequence of the intracellular signaling pathways activated by cannabinoid compounds [116], and are mediated by the activation of CB1, CB2 or TRPV1 receptors, but also due to CB receptor independent processes [172].

Cannabinoid CB1 receptors are located in neuronal glutamatergic terminals at presynaptic and postsynaptic levels. The activation of these receptors by cannabinoid agonists decreases glutamate release and limits the glutamatergic excitotoxicity in neurodegenerative processes [172]. Furthermore, CB1 receptor stimulation activates the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin complex 1 pathway, protecting cells from excitotoxic damage, and facilitating brain-derived neurotrophic factor (BDNF) release [191]. The activation of CB1 receptors also diminishes the activity of voltage-sensitive calcium channels [192], reducing calcium dependent damaging pathways. Moreover, cannabinoid compounds activating CB1 receptors are also involved in some other mechanisms related to cell protection and survival, such as GABAergic signaling [193,194] or blood supply to lesioned brain areas [195]. On the other hand, CB2 receptors are mainly located in glial cells and their activation also supports cannabinoids-mediated neuroprotection. In fact, CB2 receptor activation reduces cytotoxic factors release and generation of reactive oxygen and nitric oxide-derived substances [10]. However, cannabinoids also induce CB receptor independent neuroprotective mechanisms. Some cannabinoid compounds can act on NMDA glutamatergic receptors, reducing high glutamate levels at postsynaptic levels and excitotoxicity. Moreover, cannabinoids restore the balance between oxidative and antioxidant mechanisms, mainly, by blocking reactive oxygen substances [196] but also facilitating endogenous antioxidant activity [163,197].

Several pre-clinical studies have been performed to clarify the role of cannabinoids in CB1 receptors mediated neuroprotection in HD. In PC12 cells expressing HTT, CB1 receptor stimulation showed different effects. Activation of CB1 receptors, coupled to Gi/o, induced cell protection by inhibiting cAMP and ERK phosphorylation. However, CB1 receptors could also couple to Gs, which stimulated cAMP and favored cell death in this HD model [198]. Similar results were also obtained in the *in vitro* model of striatal SPNs expressing wild-type ($STHdh^{Q7/Q7}$) or mutant HTT ($STHdh^{Q111/Q111}$) [199]. Studies in rodent models of HD have showed that cannabinoid compounds acting on CB1 receptors can reduce or delay the neurodegeneration associated with this disease [116]. The striatal injection of quinolinic acid

in rats increases the glutamatergic transmission, and therefore, the excitotoxicity, mimicking some of the characteristic features of HD [200]. In this rat model of HD, the administration of the CB1 receptor agonist WIN 55,212-2 diminished the increment of glutamate levels induced by the quinolinic acid. In addition, WIN 55,212-2 also reduced the effect of quinolinic acid on corticostriatal local field potential recordings *in vitro*. The effects of WIN 55,212-2 were blocked by the CB1 receptor antagonist AM 251, demonstrating that the effects observed were CB1-dependent [200]. Thus, WIN 55,212-2 protected the striatum from the damage induced by quinolinic acid, although, this CB1 receptor agonist could not modify the motor abnormalities induced by quinolinic acid [200]. In R6/2 mice, the administration of the Δ^9-THC improved the symptoms, the neuropathology and the molecular pathology related to this HD model, and induced BDNF expression in the striatum [119]. Moreover, the depletion of CB1 receptors in these transgenic mice impaired all the pathological features expressed by this HD model, and reduced BDNF expression [119]. Additionally, in R6/2 mice, the striatal injection of a recombinant adeno-associated viral vector encoding CB1 receptor induced the expression of CB1 receptors and BDNF and normalized the molecular pathological signs observed in this well established transgenic mice model of HD [191]. Interestingly, genetic rescue of CB1 receptors in the SPNs prevented the loss of vesicular glutamate transporter 1 and 2 (VGLUT1 and VGLUT2) and synaptophysin in the striatum, although it did not improve the motor phenotype expressed by R6/2 mice [136]. Moreover, enriched environment delayed the onset of motor alterations and the loss of CB1 receptors in R6/1 mice, slowing the progression of the disease [201,202]. All these studies support the role of CB1 receptors and CB1 agonists as useful therapeutic tools to reduce or delay the progression of HD. However, not all the studies have showed that CB1 receptor agonists induce protective effects. Indeed, chronic administration of HU210, Δ^9-THC or URB597 did not modify the progressive impairment of motor activity in the transgenic R6/1 mice model of HD [203]. Additionally, in the malonate-lesioned rat model of HD, the administration of UCM707 did not delay the degeneration observed in this model [182]. Thus, further studies are needed to investigate and clarify the implication of CB1 receptors in HD and the potential therapeutic effects of CB1 receptor agonists.

Cannabinoid compounds that activate CB2 receptors have showed neuroprotective effects in HD [139]. The administration of the CB2 receptor agonist HU-308 in the quinolinic acid-lesioned mice attenuated glial activation and reduced the neuronal damage in the striatum [137]. Likewise, in the malonate-lesioned rat model of HD, the administration of the selective CB2 receptor agonist HU-308 protected striatal neurons from the apoptotic mechanisms activated by malonate [139]. This neuroprotection was blocked by the administration of the selective CB2 receptor antagonist SR144528, ratifying that the effect observed was CB2-dependent [139]. The neuroprotective effects of CB2 receptor agonists are associated with the reduction of the toxicity caused by reactive microglial cells [116,137]. The activation of CB2 receptors can also induce the expression of pro-survival substances [10,204]. In contrast, CB2 receptor-deficient R6/2 mice showed accelerated progression of the HD phenotype expressed by this model [137]. In fact, the ablation of CB2 receptors in these mice increased the glial activation and the sensitivity to striatal neurodegeneration induced by excitotoxic processes [137]. Thus, both in genetic and in toxin-lesioned rodent models of HD cannabinoids displayed CB2 receptor mediated protective effects [137,139].

Finally, cannabinoid compounds may also exert neuroprotective effects independent of CB1 or CB2 receptor activation in animal models of HD. This CB receptor independent protection displayed by some cannabinoids (i.e. Δ^9-THC or CBC) is related to the blockage of reactive oxygen molecules [172]. The capacity to block reactive oxygen molecules may be due to the phenolic structures of these cannabinoid compounds. Indeed, in 3-NP-lesioned rat model of HD, the administration of CBC reduced the striatal atrophy produced by this toxin [197]. Thus, cannabinoid compounds may be useful to protect cells from the cytotoxicity associated with oxidative processes.

As mentioned above, clinical studies have been developed to examine the effect of cannabinoids on HD. However, most of these studies were designed to analyze the effect of specific cannabinoid compounds on specific symptoms, and not to study the neuroprotective effect of cannabinoids [116]. Moreover, results obtained from animal models of HD have showed that combination of cannabinoids can be more useful to protect neurons than single cannabinoids [116]. In fact, Sativex®, a combination of Δ^9-THC and CBC, has showed protective effect on striatal neurons in some rodent models of HD [205,206]. A clinical trial in patients with HD concluded that Sativex® was safe and well tolerated, but it was not able to stop or slow the progression of the neurodegeneration (see https://clinicaltrials.gov/ct2/show/NCT01502046).

5.2.3. Cannabinoids as anti-inflammatory agents

As mentioned before, CB2 receptors are mainly located in glial cells, and are poorly expressed in the striatum in healthy condition. However, the striatal expression of these receptors is increased in patients with and animal models of HD. In HD, the reactive microglia may release inflammatory cytokines, reactive oxygen substances or nitric oxide [10,207,208]. Cannabinoid compounds activating CB2 receptors in glial cells can reduce the release of these factors, and promote the release of some anti-inflammatory cytokines (i.e. IL-10, IL-1ra) [209,210]. Moreover, it has been demonstrated that CB2 receptor agonists improve striatal inflammation in different rodent models of HD [137,139]. Interestingly, CB2 receptors are not involved in the psychotrophic effects induced by cannabinoid compounds. This property makes CB2 receptor agonists valuable compounds for future therapeutic approaches in HD.

6. Concluding remarks

To date, vast number of preclinical evidence have demonstrated that the ECS controls the motor activity in both physiological and pathological states. Cannabinoid compounds have been proven to ameliorate motor symptoms and drug-induced side effects. In addition, the anti-inflammatory and neuroprotective properties of these agents make them promising drugs to delay the progression of neurodegenerative diseases. For these reasons, further basic and clinical cannabis-based research could bring a new light into the treatment of movement disorders, such as PD and HD.

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