Chapter 14
Cannabinoids and Levodopa-Induced Dyskinesia

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Abstract The endocannabinoid system modulates the release of excitatory and inhibitory neurotransmitters in several brain areas implicated in motor control. Cannabinoid and dopamine receptors are highly abundant and often co-expressed in the basal ganglia circuitry, and the cross talk between these two systems regulates short- and long-term synaptic plasticity in the striatum. Dysregulation of the endocannabinoid system has been reported in animal models of Parkinson's disease and parkinsonian patients and is exacerbated in dyskinetic states, following chronic levodopa administration.

This chapter reviews recent investigations on the relationships between endocannabinoids and other neurotransmitter/neuromodulator systems in the basal ganglia, with the intent to underline their relevance for the pathophysiology of levodopa-induced dyskinesia and discuss new pharmacological approaches for their treatment.

Keywords Endocannabinoid • Anandamide • CB1 • Dopamine • Parkinson's disease • Levodopa • Striatum

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Introduction

Although levodopa remains the gold standard for the treatment of motor symptoms in Parkinson's disease (PD), its long-term use leads to the development of abnormal involuntary movement, collectively termed dyskinesia, in as many as 90–95 % of PD patients receiving treatment [1–3].

The molecular mechanisms associated with LID development are not fully understood, but several factors, including neurotransmitter abnormalities, pulsatile stimulation of dopamine receptors, and maladaptive plasticity within the striatum, are known to play a role [4].

To date, the only FDA-approved drug for the treatment of dyskinesia is the NMDA antagonist amantadine [5, 6]. This drug, however, has a short therapeutic time window, is poorly tolerated, and can worsen dyskinesia upon discontinuation or induce psychiatric complications [5, 7]. Thus, there is an urgent need to develop alternative antidyskinetic therapies targeting non-dopaminergic systems to avoid possible interferences with the antiparkinsonian effects of L-DOPA.

In the last decade, several studies have pointed to the endocannabinoid system as an important modulator of synaptic transmission and plasticity in the basal ganglia circuitry. As this system regulates dopamine-induced motor activation and is required for the coordination and fine-tuning of movement [8, 9], it represents a potential pharmacological target for the treatment of motor disorders. Indeed, both exogenous and endogenous cannabinoids show antiparkinsonian and antidyskinetic activity in animal models of PD and patients.

In this chapter, we will review the most relevant studies on the role played by the endocannabinoid system in LID, discuss the complex interactions between endocannabinoids and several neurotransmitters regulating basal ganglia function [10, 11], and provide a conceptual frame to address some conflicting findings reported in the literature.

The Endocannabinoid System

The endocannabinoid system consists of a family of lipid signaling molecules (endocannabinoids) released on demand from membrane lipid precursors, the enzymes responsible for their synthesis and degradation and distinct metabotropic (cannabinoid), ionotropic, and nuclear receptors activated by these ligands [12, 13].

Among the multiple endocannabinoids identified so far [14], arachidonoyl ethanolamine (anandamide) [15, 16] and 2-arachidonoyl glycerol (2-AG) [17] represent the two most studied examples.

Anandamide is synthesized in a Ca^{++}-dependent manner from N-arachidonoyl phosphatidylethanolamine by phospholipase D (PLD) [18, 19] or via alternative pathways, such as those initiated by alpha-beta-hydrolase 4 [20]. 2-AG is produced by diacylglycerol lipases (DAGLα and β) acting on membrane acyl arachidonoyl

glycerols [21, 22]. As in the case of anandamide, multiple biosynthetic pathways have been reported for 2-AG, which can also derive from the hydrolysis of phosphatidic acid or lysophospholipids [23, 24].

The biological actions of anandamide are terminated by facilitated diffusion into cells via a carrier-mediated transport [25], followed by enzymatic hydrolysis via a fatty acid amide hydrolase (FAAH) [26–28]. To date, there is no consensus on the existence of an endocannabinoid transporter [29], and its molecular identity has not been yet identified. Anandamide can be also metabolized by lipoxygenases [30] and cyclooxygenases (such as COX-2) [31–33]. In particular, the COX-2 metabolic pathway may become physiologically relevant under conditions promoting endocannabinoid or COX-2 upregulation, as in the course of neurodegenerative processes [34].

Concerning 2-AG, although this lipid can be metabolized by FAAH and cyclooxygenases [35, 36], in the brain it is mainly hydrolyzed by a monoacylglycerolipase (MAGL), which is localized in presynaptic elements [37]. Interestingly, pharmacological blockade of FAAH by URB597 may decrease brain 2-AG in vitro via a mechanism involving TRPV1 activation and DAGL inhibition [38, 39]. This decrease, however, has not been confirmed in vivo by other groups [40–43], suggesting that it might be limited to specific brain areas.

The endocannabinoids can activate $G_{i/o}$ protein-coupled cannabinoid receptors (CB1 and CB2), some members of the transient receptor potential (TRP) family, as well as nuclear peroxisome proliferator-activated receptors (PPAR) [44]. Endocannabinoids can also serve as allosteric modulators or bind to other metabotropic receptors, including GPR55 [45–47] – a cloned orphan receptor activated by the CB1 antagonists rimonabant and AM251 [48] – and GPR18 [49]. However, the physiological roles of these receptors remain unknown, and neither anandamide nor 2-AG has shown consistent pharmacological effects following GPR55 stimulation [50].

In rodents and humans, CB1 receptors are highly expressed in the peripheral and central nervous system (CNS) [51, 52], whereas CB2 receptors are mainly restricted to immunocompetent cells, lymphoid organs, and microglia [44, 53, 54]. The "segregation" of CB2 to the immune system has been challenged by recent studies showing their presence in neurons and glial cells throughout the brain, including the substantia nigra pars reticulata (SNpr) and the striatum [55–58]. Also, CB2 receptors are upregulated in activated microglia and astrocytes in response to neurotoxic insults and neuroinflammatory events [59–62].

Within the basal ganglia, CB1 receptors are generally expressed on presynaptic elements, including GABAergic striatofugal neurons [63, 64], striatal parvalbumin-positive interneurons [65, 66], glutamatergic terminals from the cortex [67] and the subthalamic nucleus [68], and serotonergic afferents [69, 70] (see Fig. 14.1). It is now well established that activation of presynaptic CB1 receptors by retrogradely mobilized endocannabinoids inhibits the release of several neurotransmitters involved in basal ganglia function [71, 72].

Endocannabinoids and CB1 receptors have been implicated in three main forms of plasticity at striatal synapses: (1) short-term depolarization-induced suppression

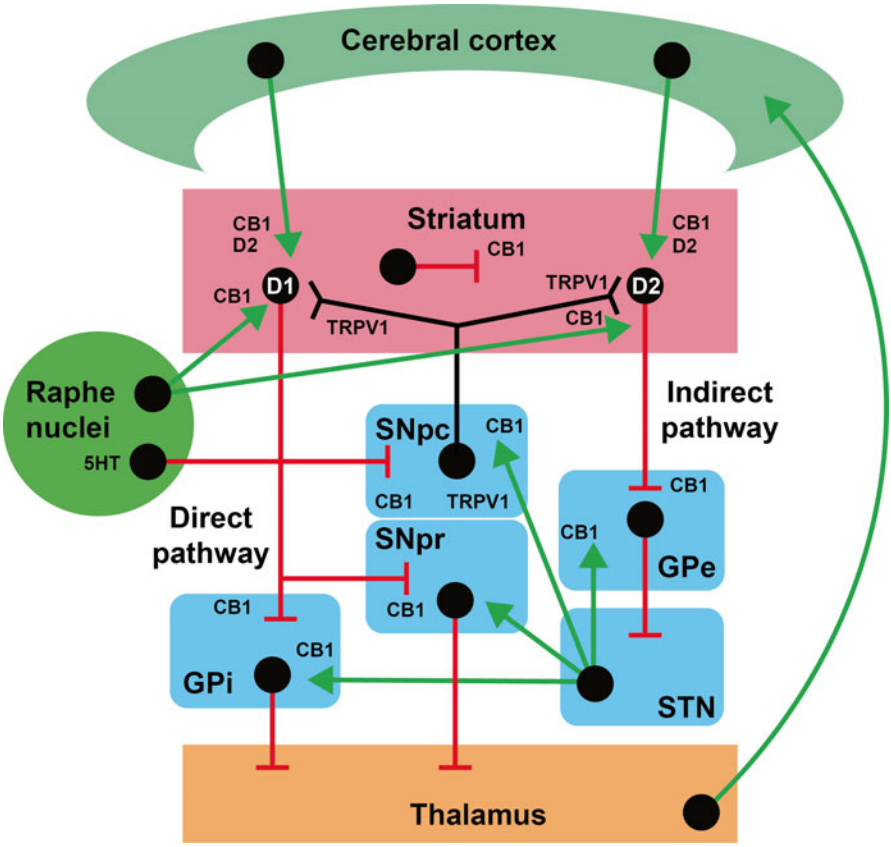

Fig. 14.1 Schematic illustration of the basal ganglia motor circuit showing striatofugal "direct" and "indirect" projections to the output nuclei and afferent projections from the cortex and raphe nuclei to the striatum. *GPi* globus pallidus pars interna, *GPe* globus pallidus pars externa, *SNpc* substantia nigra pars compacta, *SNpr* substantia nigra pars reticulata, *STN* subthalamic nucleus. Glutamatergic (*green*), GABAergic (*red*), and serotonergic projections and expression of different receptor subtypes are also indicated

of excitation (DSE) or inhibition (DSI), (2) short-term depression dependent by activation of postsynaptic Gq-coupled receptors, and (3) long-term depression (LTD) (for review, see [73]). Also, concomitant activation of CB1 and other metabotropic receptors can promote the coupling of CB1 to G isoforms other than $G_{i/o}$ [74, 75] or the formation of heterodimers with D2 and mu-opioid receptors [76, 77], leading to different downstream signaling pathways than those traditionally activated by cannabinoids.

Studies on cannabinoid agonists administered to CB1 knockout mice support the existence of non-CB1/CB2 receptors regulating synaptic transmission throughout the body (for review, see [52]).

As previously mentioned, some exogenous and endogenous cannabinoids can target at least five distinct TRP channels [78]. In particular, anandamide can bind to TRPV1 receptors [79], which are expressed in the striatum, globus pallidus, and the substantia nigra pars compacta (SNpc) [80–82]. As anandamide affinity for TRPV1 is quite low, it is not clear whether this lipid might serve as an endovanilloid ligand under physiological conditions [83, 84]. Nevertheless, blockade of FAAH activity has been shown to enhance anandamide potency at TRPV1 receptors in vitro [85]. In addition, there is evidence for a cross talk between CB1 and TRPV1 receptors, as CB1 stimulation can alter the phosphorylation state of TRPV1 and consequently its function [86].

Some cannabinoid compounds, including anandamide, noladin ether, virodhamine, and WIN55,212-2, can also bind different subtypes of PPAR receptors and enhance the expression of their target genes [87]. In particular, anandamide has been shown to activate □□□□ PPARα [88] and PPARγ □□□□□ [89]. These receptors, which are known to increase insulin sensitivity and modulate glucose and lipid metabolism, are also expressed in neuronal and glial cells of the basal ganglia [90, 91]. Although their role in the CNS is still largely unexplored, recent studies indicate that PPARα □□□□ and □□□□□ PPARγ agonists have antioxidant and neuroprotective activity in animal models of PD [92–95], Alzheimer's disease [96, 97], cerebral ischemia [98], and traumatic brain injury [99, 100], and they can reverse haloperidol-induced oral dyskinesia in rats [101].

Pharmacological Effects

Effects on PD Motor Symptoms

In general, systemic administration of exogenous cannabinoids, or enhancement of endocannabinoid tone via pharmacological blockade of their catabolic enzymes or reuptake, decreases locomotor activity in a CB1-dependent manner [28, 102–104]. In line with these observations, CB1 knockout mice exhibit motor abnormalities [105, 106] and suppression of cocaine-induced hyperlocomotion [107]. However, some of the cannabinoid-induced motor effects are not elicited via activation of CB1 receptors. For instance, anandamide produces catalepsy in both CB1 knockout mice and wild-type controls [108], and elevation of endocannabinoid tone in these animals produces hypokinesia via a TRPV1-mediated mechanism [109]. Also, pharmacological blockade of TRPV1 receptors in 6-OHDA rats has been shown to unmask the antidyskinetic effects of the FAAH inhibitor URB597 [103] (see below). These observations suggest that, under conditions in which anandamide reaches supraphysiological concentrations and consequently activates TRPV1, these channels can influence motor behaviors presumably by affecting the firing rate of nigrostriatal neurons and dopamine transmission [110].

In the context of PD, several research groups have found increased CB1 mRNA and receptor binding in the striatum of animal models [111, 112] and PD patients [113]. Numerous studies have also shown abnormal endocannabinoid levels, although there is no consensus on the direction of endocannabinoid fluctuations. While some reports indicate an increase of endocannabinoid levels in the basal ganglia of dopamine-depleted rodents [114–116], other studies showed decreased or unaltered endocannabinoid tone [103, 117, 118]. These discrepancies may be attributable to species-specific differences among PD models or to the physiological state of the animals at the time of the experiments, which is known to affect endocannabinoid release. Interestingly, the administration of levodopa to 6-OHDA rats failed to elevate anandamide levels [103, 117] and further increased CB1 expression in the striatum [119], suggesting that levodopa is not able to correct the endocannabinoid dysfunction associated with dopamine denervation. This dysfunction likely causes the disruption of the plasticity observed at corticostriatal synapses in PD models [118–121]. In this regard, elevation of endocannabinoid tone has been shown to rescue striatal LTD and to alleviate motor deficits associated with the nigrostriatal lesion [118]. Although these data point to a deficit (rather than an enhancement) of endocannabinoid mobilization in PD, improvement of motor symptoms has been achieved not only with administration of cannabinoid agonists but also with CB1 receptor antagonists in either rodents [122–124] or nonhuman primates [125] (Table 14.1). Explaining these paradoxical findings is challenging, although the answer may lie in the multiple site of actions engaged by cannabinoid drugs when administered systemically. Indeed, while increased endocannabinoid transmission may alleviate PD symptoms by reducing striatal glutamate release [71, 115], on the other hand, activation of CB1 on striatofugal terminals of the "indirect" pathway may lead to increased GABAergic drive to the external globus pallidus (GPe), which may amplify the inhibitory output of the basal ganglia and consequently contribute to PD symptoms. Therefore, in this case, CB1 antagonism may produce antiparkinsonian effects by limiting GABA release from striatopallidal projections. Finally, other studies have hypothesized that CB1 antagonists elicit antiparkinsonian effects only in animals with severe nigrostriatal lesions [123, 126], which may differentially affect endocannabinoid production and CB1 expression in the striatum and GPe of these animals versus those with less severe lesions.

Effects on LID

As endocannabinoids counteract dopamine-mediated hyperactivity [103, 136, 137] and given the fact that increased corticostriatal glutamate transmission contributes to dyskinesias [138, 139], stimulation of CB1 receptors should alleviate dyskinetic symptoms by (1) reducing levodopa-induced sensitization of dopamine receptors, (2) normalizing aberrant glutamate release, and (3) rebalancing maladaptive plasticity in

Table 14.1 Pharmacological effects of cannabinoid agents on PD motor symptoms and dyskinesia

Cannabinoid agent	Pharmacology	PD motor symptoms	Dyskinesia
THC (Cannabis)	CB1/CB2 agonist	Alleviate motor deficits in PD models [126] or no effect [122, 127]	No effect in PD patients [127]
Nabilone	CB1/CB2 agonist	Improve levodopa antiparkinsonian action [128]	Antidyskinetic in PD models [128]. Can reduce dyskinesia in PD patients [129]
URB597	FAAH inhibitor	Alleviate motor deficits in PD models [118]	Antidyskinetic in PD models in the presence of a TRPV1 blocker [103]
WIN55,212-2	CB1/CB2 agonist	Induce hypokinesia in rodents [103, 130]	Antidyskinetic in PD models [103, 117, 131]
HU-210	CB1/CB2 agonist	Impair motor function [132]	Alleviate some AIM subtypes [132]
SR141716A (rimonabant)	CB1 antagonist	Alleviate motor deficits in PD models [123–125] or no effect [122, 133]	Antidyskinetic in PD models [125] or no effect [117]. Can precipitate AIMs in non-dyskinetic animals [132]
AM251	CB1 antagonist	Alleviate motor deficits in PD models [123]	No effect [103, 132]
CE	CB1 antagonist	Enhance antiparkinsonian action of levodopa [134]	No effect [134]
Oleylethanolamide (OEA)	TRPV1 antagonist	No effect [135]	Antidyskinetic in PD models [135]

the denervated striatum. In support of this hypothesis, several groups have shown cannabinoid-mediated improvement of levodopa-induced abnormal involuntary movements (AIMs) in rodent models and nonhuman primates [103, 118, 128, 131, 132] and PD patients [129] (Table 14.1).

The antidyskinetic effects of cannabinoid agonists do not seem to result from a generalized motor suppression, as they were obtained using doses that did not produce hypomotility or catalepsy [103, 126]. Nevertheless, as in the case of PD motor deficits, significant antidyskinetic effects [125, 130], or no effects [134], were also observed with CB1 antagonists (Table 14.1). The rationale for blocking CB1 receptors as a pharmacological approach to treat dyskinesia is based on the observations that endocannabinoid transmission is elevated in dyskinetic animals [140] and PD patients [113] and that genetic deletion of CB1 receptors prevents the development of severe abnormal movements in mice [140]. However, neither striatal endocannabinoid levels nor CB1 upregulation has been correlated to LID expression or severity [125, 141].

Overall, these discrepancies reveal some limitations in generalizing cannabinoid effects across different animal models and may be ascribed to the multiple sites of

action of cannabinoid agents (see above), which complicate the translation of these findings into new pharmacotherapies.

So far, studies carried out in PD patients have been inconclusive. While a randomized, double-blind, placebo-controlled pilot study by Sieradzan et al. [129] has shown an antidyskinetic action of the cannabinoid agonist nabilone in PD patients [129], other reports have not confirmed any beneficial effects of either cannabinoid agonists [127] or antagonists [133] on LID. However, the study of Carroll et al. [127] evaluated the effects of oral cannabis, which has a highly variable pharmacokinetics and a more complex pharmacological profile than synthetic cannabinoid agonists. In addition, the assessment of dyskinesia was based on patient self-reported questionnaires, which are often inaccurate in identifying symptoms [142]. On the other hand, the dose of the CB1 antagonist rimonabant used in the study of Mesnage et al. [133] was significantly lower than that used by van der Stelt and coworkers [125]. Thus, new and larger-scale clinical studies are necessary to confirm the antidyskinetic properties of cannabinoid agents in humans.

Pharmacological blockade of FAAH, which elevates anandamide and other acylethanolamides in those brain areas where they are actively synthesized, did not reduce levodopa-induced AIMs in 6-OHDA rats [103]. These findings suggest that increasing anandamide tone is not sufficient to alleviate dyskinesia, possibly because of the concomitant stimulation of CB1 and TRPV1 receptors, which exert opposite effects within the basal ganglia circuitry. In support of this hypothesis, coadministration of the FAAH inhibitor URB597 and the TRPV1 antagonist capsazepine produced a significant antidyskinetic effect in 6-OHDA rats [103, 131]. In addition, a recent study by Gonzalez-Aparicio [143] has shown that oleylethanolamide (OEA), a structural analog of anandamide that does not bind to CB1 but has antagonistic activity at TRPV1 receptors, can reduce levodopa-induced AIM via a TRPV1-mediated mechanism [135]. These observations differ from those reported by Lee et al. [143], showing that the administration of either URB597 or the TRPV1 agonist capsaicin alone reduced levodopa-induced hyperactivity in reserpine-treated rats [143]. However, it is important to note that hyperactivity in reserpine-treated rodents has not been validated as an appropriate measure of dyskinesia [144].

Although TRPV1 blockade seems necessary to unmask the antidyskinetic effect of URB597, the beneficial action of this drug is only partially mediated by CB1 receptors, since pretreatment with the CB1 antagonist AM251 did not fully reverse the combined effect of URB597 and capsazepine (CPZ) [103]. Interestingly, administration of the nonselective PPAR antagonist BADGE completely blocked the URB597+CPZ antidyskinetic effect (unpublished observations), suggesting a PPAR-dependent mechanism. Whether the involvement of PPAR in this response reflects a direct action of anandamide, or of other lipid signaling molecules elevated by FAAH blockade, on these nuclear receptors is still unclear. Nevertheless, a recent study has shown that PPARα □□□□□ and □□□□□ PPARγ agonists administered individually or in combination with antipsychotics can alleviate haloperidol-induced oral dyskinesias [101].

Endocannabinoid Modulation of Basal Ganglia Circuitry: Pathophysiology and Implications for LID

According to the classical model of basal ganglia organization (see Fig. 14.1), striatal MSN receive excitatory glutamatergic projections from the cerebral cortex. MSN are in turn modulated by nigrostriatal dopaminergic afferents that exert excitatory or inhibitory effects on "direct" and "indirect" striatofugal pathways via dopamine D1 and D2 receptors, respectively.

Although CB1 are not present on dopaminergic neurons [145], they co-localize with D1/D2-like receptors in the dorsal striatum and indirectly affect dopamine output by modulating neurotransmitter release from projecting inhibitory and excitatory terminals via stimulation of CB1 receptors [64, 67, 68, 72, 146, 147]. The overall effect of cannabinoids on dopamine release in the caudate-putamen remains controversial, as some studies have shown a decrease [72], an increase [148], or no effect at all [149, 150]. Anandamide- and endocannabinoid-enhancing drugs, such as FAAH inhibitors, can also modulate nigrostriatal dopamine transmission by acting at TRPV1 [109, 110, 151, 152] or PPAR receptors [153].

Stimulation of dopamine D1- and D2-like receptors has been shown to affect striatal endocannabinoids in opposite ways: for example, while D1 agonists tend to decrease anandamide [154], D2-like agonists increase it [103, 117, 136, 155]. These effects may depend on the ability of D1 and D2 agonists to enhance or diminish excitatory postsynaptic currents in striatal MSN, respectively, and suggest a dopamine-mediated control of endocannabinoid mobilization [156]. Indeed, studies have shown that LTD at corticostriatal synapses is regulated by D2 receptors [118, 157]. Although the precise site of this modulation is still the subject of debate, it appears to be restricted to glutamatergic projections onto MSN of the indirect pathway [118, 158] and to be mediated by anandamide or 2-AG, depending on the frequency of stimulation applied to the glutamatergic afferents [159–161].

Endocannabinoids, in particular anandamide, also mediate synaptic depression at GABAergic afferents onto striatal MSN [155, 162–164] to produce disinhibition of MSN activation.

Interestingly, endocannabinoid-mediated LTD at corticostriatal synapses is profoundly compromised after striatal dopamine denervation [118] or blockade of D2 receptors [157, 165, 166] and completely lost in dyskinetic – but not in non-dyskinetic – parkinsonian rats treated with levodopa [167].

In line with these observations, behavioral studies indicate that the anandamide elevation observed after administration of dopaminergic agonists may serve as an inhibitory feedback signal to offset dopamine-induced hyperactivity [136, 137, 168]. Thus, abnormalities in dopamine and endocannabinoid-mediated plasticity may disrupt this feedback mechanism and lead to motor disturbances, particularly upon long-term activation of dopamine receptors.

Recent studies have added a further level of complexity, showing a competitive interaction between dopamine D2 and adenosine A_{2A} receptors in the induction of endocannabinoid-mediated plasticity, such that D2 receptor activation promotes

LTD, whereas A_{2A} activation promotes LTP [158, 169]. Also, coadministration of A_{2A} and CB1 agonists has been shown to partially inhibit the CB1-dependent decrease of glutamate transmission [170]. The presence of A2A receptors on glutamatergic terminals projecting onto MNS spines [171] suggests that these might be the anatomical substrate for these complex interactions.

CB1 receptors are also expressed on serotonergic raphe-striatal fibers [69] (Fig. 14.1), which are able to (1) convert levodopa into dopamine and release it as a "false neurotransmitter," thus contributing to LID development [172]; (2) influence nigrostriatal dopamine release [173]; and consequently (3) affect the dopamine-mediated and CB1-dependent control of glutamate release [174]. Therefore, we could speculate that cannabinoid agents may exert their antidyskinetic effects by dampening the ectopic dopamine release from serotonergic terminals and/or by controlling dopamine transmission indirectly via inhibition of 5-HT release [175, 176].

Molecular Mechanisms

Overactivity of D1-positive striatofugal neurons of the direct pathway has been long known to be involved in LID [177–179]. Dopamine denervation leads to a high-affinity D1 receptor state in 6-OHDA rats [180, 181], and D1 agonist-induced GTPγS binding has been correlated with LID severity in MPTP-treated primates [182]. D1 overactivity is also accompanied by dysregulation of the cAMP/protein kinase A (PKA) signaling cascade and increased signaling of the dopamine- and cAMP-regulated phosphoprotein-32 kDa (DARPP-32), a key integrator of dopaminergic and glutamatergic inputs in the striatum [131, 183, 184].

Administration of the cannabinoid agonist WIN55,212-2 has been shown to alleviate levodopa-induced AIM in 6-OHDA rats and to reverse the concomitant overactivity of striatal PKA [131]. In keeping with these observations, blockade of PKA signaling has been proven as an effective strategy to reduce AIM expression [185, 186], possibly by preventing PKA-mediated cytoskeleton modifications, which may contribute to the long-term aberrant plasticity underlying striatal dysfunction in dyskinesia [185, 187]. The reduction of PKA activity elicited by cannabinoids may result from the direct activation of CB1 receptors, which are negatively linked to adenylyl cyclase and co-localized on D1-positive striatal neurons [69].

PKA-induced phosphorylation at the threonine (Thr)-34 site converts DARPP-32 into an inhibitor of protein phosphatase-1 (PP1) [188]. Although DARPP-32 phosphorylation appears to be required for the expression of CB1-mediated motor effects, such as catalepsy [189], WIN55,212-2 administration to dyskinetic rats produced a dephosphorylation of DARPP-32 at Thr-34 that was only partially reversed by the CB1 antagonist AM251 even at doses that fully blocked WIN55,212-2 antidyskinetic effect [131]. This discrepancy may depend on different biochemical or functional aspects underlying the behaviors measured in these studies (catalepsy versus AIM) and/or, as previously mentioned, on species-specific

differences among animal models. Interestingly, Polissidis et al. [190] have shown that WIN55,212-2 can produce opposite effects on striatal Thr-34 phosphorylation across different rat strains [190].

Concluding Remarks

Experimental evidence indicates that systemic administration of cannabinoids reverses the aberrant levodopa-induced overactivity of downstream signaling that may lead to long-term maladaptive changes in striatal plasticity. However, both direct (or indirect) cannabinoid agonists and antagonists have shown antidyskinetic actions in preclinical models, and experimental evidence for their efficacy in clinical settings is still limited. Given the modulatory action played by the endocannabinoid system in the basal ganglia, understanding its dysfunction in PD and reconciling conflicting data may have important implications for the pathophysiology and treatment of levodopa-associated motor complications.

In addition, the therapeutic potentials of modulating endocannabinoid levels or targeting non-CB receptors activated by endocannabinoids, such as TRP channels and PPAR receptors, have not been fully explored. These approaches may offer more effective and specific pharmacological actions than those observed with traditional cannabinoid agents. Furthermore, as some of these drugs have shown anti-inflammatory and neuroprotective properties in the CNS [191], their application in PD therapy appears particularly appealing, as they may delay/halt the progressive neurodegenerative process occurring in this pathology.

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