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Endocannabinoid modulation of dopaminergic motor circuits

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There is substantial evidence supporting a role for the endocannabinoid system as a modulator of the dopaminergic activity in the basal ganglia, 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 mediated primarily through the CB_1 receptors that are densely located in the dopamine-enriched basal ganglia networks, suggesting that the motor effects of endocannabinoids are due, at least in part, to modulation of dopaminergic transmission. On the other hand, there are profound changes in CB_1 receptor cannabinoid signaling in the basal ganglia circuits after dopamine depletion (as happens in Parkinson's disease) and following l-DOPA replacement therapy. Therefore, it has been suggested that endocannabinoid system modulation may constitute an important component in new therapeutic approaches to the treatment of motor disturbances. In this article we will review studies supporting the endocannabinoid modulation of dopaminergic motor circuits.

Keywords: endocannabinoids, dopamine, basal ganglia, motor circuits, electrophysiology

The discovery and the following investigation of the endocannabinoid system have demonstrated its implication in a large variety of functions such as regulation of appetite and energy metabolism, pain and inflammation, neuroprotection, and motor control. The endocannabinoid system is also a modulator of the basal ganglia circuitry functionality (Benarroch, 2007; Fernandez-Ruiz, 2009) and therefore, it may be considered as a potential pharmacological target for the treatment of movement disorders. This review is focused on the endocannabinoid modulation of dopaminergic motor circuits.

NEUROANATOMICAL EVIDENCES SUPPORTING DOPAMINERGIC-ENDOCANNABINOID INTERACTION

The cannabinoid receptors, endocannabinoids and the proteins for their biosynthesis and degradation constitute the key components of the endocannabinoid system (Di Marzo et al., 1998). CB_1 receptors and endocannabinoids are highly expressed in the basal ganglia and have close connections with the dopaminergic system, being involved in the central regulation of motor functions.

To date, two cannabinoid receptor subtypes have been identified by molecular cloning, cannabinoid receptor type 1 (CB1) (Matsuda et al., 1990) and cannabinoid receptor type 2 (CB2) (Munro et al., 1993). The vast majority of CB_1 receptors are located in the central nervous system while CB_2 receptors are expressed primarily in cells of the immune system (Munro et al., 1993), microglia, blood vessels and some neurons (Van Sickle et al., 2005; Gong et al., 2006). Both CB_1 and CB_2 are seven transmembrane $G_{i/o}$-coupled receptors that activate similar intracellular signaling pathways (Mackie, 2008). The discovery of the cannabinoid receptors led to the identification of the so-called natural ligands of the cannabinoid receptors, anandamide (Devane et al., 1992) and 2-arachidonoylglycerol (2-AG) (Devane et al., 1992; Mechoulam et al., 1995) which are synthesized "on demand" in response to elevations of intracellular calcium (Di Marzo et al., 1994).

Although the expression of CB_2 receptors has remained controversial (Atwood and Mackie, 2010), mRNA for this receptor has been found in neurons and glial cells from the *substantia nigra pars reticulata* (SNpr) and the striatum (Gong et al., 2006). As for CB_1 receptor, high levels are expressed within the basal ganglia (Herkenham et al., 1990; Mailleux and Vanderhaeghen, 1992; Tsou et al., 1998; Mackie, 2005; Martin et al., 2008). While mRNA for this receptor is found in striatal GABAergic medium spiny neurons (Mailleux and Vanderhaeghen, 1992) and in the *subthalamic nucleus* (STN), the expression of the receptor protein is mainly located at the terminal level. Thus, CB_1 receptors have been observed in subthalamonigral and subthalamopallidal terminals (Mailleux and Vanderhaeghen, 1992; Tsou et al., 1998), glutamatergic corticostriatal afferences (Gerdeman and Lovinger, 2001; Kofalvi et al., 2005), and striatal projections to the *globus pallidus* (GPi and GPe) and to the SNpr (Herkenham et al., 1991; Tsou et al., 1998; **Figure 1**).

Neurons expressing D_1 receptors form the direct pathway, which projects to the GPi and the SNpr, while neurons expressing D_2 receptors constitute the indirect pathway, projecting to the GPe (**Figure 1**) (Paul et al., 1992; O'Connor, 1998; Nicola et al., 2000; Onn et al., 2000; Svenningsson et al., 2000). A potential interaction between the D_1/D_2 and CB_1 receptors at the level on the G-protein/adenylyl cyclase signal transduction mechanism has been suggested (Giuffrida et al., 1999; Meschler and Howlett, 2001). Combined activation of CB_1 and D_1 receptors results in a net decrease in adenylyl cyclase, a subsequent decrease in the inhibitory activity of direct striatal projection neurons and finally

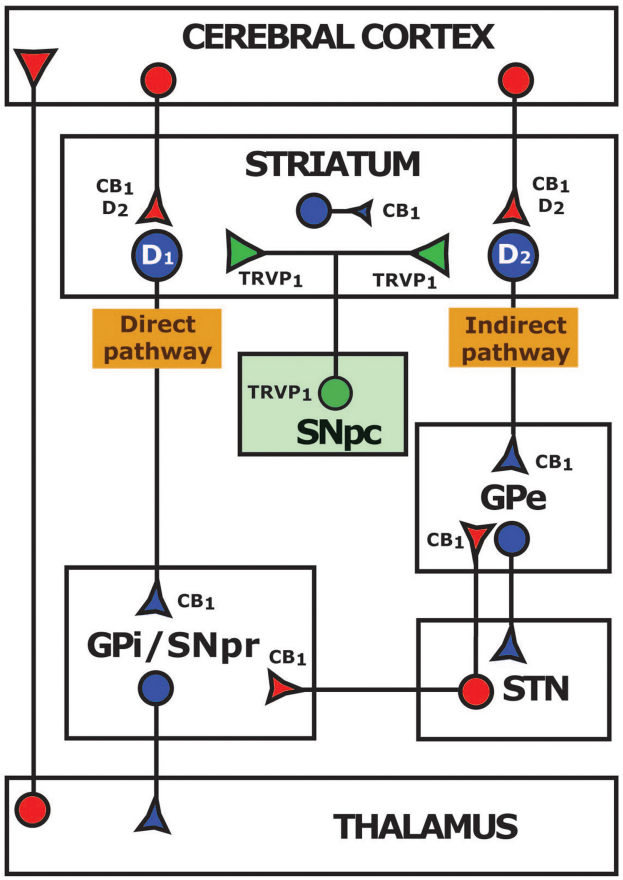

FIGURE 1 | Distribution of CB_1 and $TRPV_1$ receptors and their coexpression with dopaminergic D_1 and D_2 receptors in a simplified diagram of the basal ganglia circuits. GABAergic inhibitory pathways are represented in blue and glutamatergic excitatory pathways in red. Modulatory dopaminergic connections are indicated in green. CB_1, cannabinoid receptor type 1; $TRPV_1$, transient receptor potential vanilloid type 1; D_1, dopaminergic receptor type 1; D_2, dopaminergic receptor type 2; GPe, *external globus pallidus*; GPi, *internal globus pallidus*; STN, *subthalamic nucleus*; SNpc, *substantia nigra pars compacta*; SNpr, *substantia nigra pars reticulata*.

a decreased motor response due to enhanced activation of SNpr neurons. Conversely, activation of CB_1 and D_2 receptors together stimulates adenylyl cyclase (Glass and Felder, 1997), potentiating the indirect striatal pathway neurons that in turn activate neurons of the STN, also resulting in motor inhibition (Brotchie, 2003; van der Stelt and Di Marzo, 2003). These data indicate that endocannabinoid system acting on striatal CB_1 receptors play a significant role in the regulation of basal ganglia motor circuits. Although CB_1/D_2 receptor heterodimerization has been demonstrated in transfected cells by co-immunoprecipitation and Forster Resonance Energy Transfer (FRET) techniques (Kearn et al., 2005; Marcellino et al., 2008), functionality of those heteromers in striatal glutamatergic terminals is not supported by recent studies (Kreitzer and Malenka, 2007).

In the last years, the transient receptor potential vanilloid type 1 ($TRPV_1$) has gained attention for its ability to bind cannabinoids. Although neuronal expression and functionality of $TRPV_1$ channels are controversial (Mezey et al., 2000; Cristino et al., 2006; Cavanaugh et al., 2011), this receptor is present in the basal ganglia. Indeed, $TRPV_1$ is located on nigrostriatal terminals and on tyrosine hydroxylase positive cells in the *substantia nigra pars compacta* (SNpc) (Mezey et al., 2000; Micale et al., 2009) which makes it a good candidate for directly modulating dopaminergic neurotransmission (**Figure 1**). On the other hand, the orphan G-protein-coupled receptor 55 (GPR55) has been identified as another possible cannabinoid receptor (Ryberg et al., 2007) that, in contrast to classical CB_1 and CB_2, is coupled to G_q, $G_{\alpha 12}$ and $G_{\alpha 13}$ proteins (Sharir and Abood, 2010). Despite its high expression in the striatum (Sawzdargo et al., 1999), conflicting pharmacological findings make difficult to consider the GPR55 as a novel cannabinoid receptor (Oka et al., 2007; Lauckner et al., 2008; Sharir and Abood, 2010). Future investigations will clarify the role of $TRPV_1$ and GPR55 in modulating basal ganglia circuits.

FUNCTIONAL INTERACTIONS BETWEEN ENDOCANNABINOID AND DOPAMINERGIC SYSTEMS IN THE BASAL GANGLIA

In accordance with its neuroanatomical distribution, functional and behavioral studies have suggested that the endocannabinoid system can act as an indirect modulator of dopaminergic neurotransmission in the basal ganglia.

BEHAVIORAL STUDIES

Several influences of cannabinoids on motor activity depend on the cannabinoids influence on the dopaminergic system. Systemic administration of synthetic and endogenous cannabinoids (Δ^9-THC, WIN 55,212-2, CP 55,940, or anandamide) characteristically induces inhibition of motor behavior and catalepsy in rodents (Prescott et al., 1992; Crawley et al., 1993; Navarro et al., 1993; Anderson et al., 1995; Romero et al., 1995; de Lago et al., 2004). Moreover, the anandamide transport inhibitor, AM404, or inhibitors of anandamide hydrolysis produce hypokinesia in rats (Compton and Martin, 1997; Gonzalez et al., 1999). These hypokinetic effects can be reversed by the selective CB_1 receptor antagonist, rimonabant, which in itself causes hyperlocomotion in healthy controls (Compton et al., 1996). In agreement with these observations, mice lacking CB_1 receptors exhibit several motor anomalies (Ledent et al., 1999; Zimmer et al., 1999). Although these findings provide evidence for the involvement of CB_1-related mechanisms in motor control, other reports demonstrate that also the $TRPV_1$ receptors can mediate effects of certain cannabinoids such as anandamide (de Lago et al., 2004).

It has been hypothesized that the inhibition of motor behavior mediated by cannabinoids could be related to a reduction in dopaminergic circuitry activity. Rotational studies in rats receiving local injections of cannabinoid compounds into the basal ganglia suggest that dopamine-cannabinoid interaction is not a direct mechanism. For instance, cannabinoids increase or decrease motor behavior when locally administered into the direct (Sanudo-Pena et al., 1996, 1998) or indirect pathway, respectively (Sanudo-Pena and Walker, 1997; Miller et al., 1998). Neuroanatomical studies showing that CB_1 receptors are not present on dopaminergic neurons or terminals (Julian et al., 2003; Matyas et al., 2006) suggest that CB_1-mediated modifications of nigrostriatal dopaminergic

circuits are exerted indirectly by modulation of inhibitory or excitatory inputs to the midbrain dopamine neurons. Indeed, cannabinoids are known to dampen both glutamate and GABA transmission in the basal ganglia (Szabo et al., 2000; Gerdeman and Lovinger, 2001; Wallmichrath and Szabo, 2002).

ELECTROPHYSIOLOGICAL AND NEUROCHEMICAL STUDIES

In vivo electrophysiological studies have shown that cannabinoid agonists increase the action potential firing rate of SNpc neurons (French et al., 1997; Melis et al., 2000; Morera-Herreras et al., 2008). Since CB_1 receptors are poorly expressed in SNpc neurons (Julian et al., 2003; Matyas et al., 2006), or even absent, the action of cannabinoids is indirectly exerted on dopaminergic neurons through other nuclei. In line with this, in the SNpr the CB_1 receptors are located on subthalamonigral terminals and their activation inhibits glutamate release (Szabo et al., 2000) resulting in a reduction of GABAergic transmission and, consequently, in an increased activity of SNpc cells (Morera-Herreras et al., 2008).

The increased activity of SNpc neurons observed after CB_1 receptor activation is in agreement with *in vivo* microdialysis experiments showing enhanced dopamine release in the striatum after exogenous or endogenous cannabinoid agonists administration (Tanda et al., 1997; Solinas et al., 2006). However, this effect is not mediated locally at the terminal level, but rather involves changes in the firing activity of SNpc neurons, since *in vitro* studies in striatal slices have shown that CB_1 activation has no effect on dopamine release (Kofalvi et al., 2005). Contrary to CB_1-mediated mechanisms, the effects of endocannabinoids on dopamine transmission may be mediated by direct mechanisms. Indeed, the endocannabinoid anandamide and some analogs (but not classic cannabinoid as Δ^9-THC), acting via postsynaptic $TRPV_1$ receptors, may reduce nigrostriatal dopaminergic cell activity (de Lago et al., 2004). However, other authors have reported an increase of dopamine release after activation of $TRPV_1$ receptors in the SNpc (Marinelli et al., 2003, 2007), although this enhancement may be mediated by $TRPV_1$ receptors located in glutamatergic terminals in the SNpc rather than by receptors located in dopaminergic terminals.

PATHOLOGICAL IMPLICATIONS OF THE INTERACTION BETWEEN DOPAMINE AND THE ENDOCANNABINOID SYSTEM

As described above, neuroanatomical studies have located cannabinoid receptors in the basal ganglia, and it is widely accepted that the endocannabinoid system influence physiological motor function. These facts predict that pharmacological modulation of the endocannabinoid system may also be beneficial under pathological conditions pertaining to decreased dopamine signaling or the chronic treatment with L-DOPA.

ROLE OF THE CANNABINOID SYSTEM IN PARKINSON'S DISEASE

In Parkinson's disease (PD), the progression of the neurodegenerative pathology and the appearance of major motor symptoms are related to increased endocannabinoid levels (Pisani et al., 2005, 2010). Several studies have also found increased CB_1 receptor levels in the striatum of parkinsonian monkeys and human patients (Lastres-Becker et al., 2001; Van Laere et al., 2012). In rat models of PD, publications supporting increased (Gubellini et al., 2002; Maccarrone et al., 2003; Gonzalez et al., 2005), decreased (Silverdale et al., 2001; Ferrer et al., 2003; Walsh et al., 2010b), or no modification (Romero et al., 2000; Kreitzer and Malenka, 2007) of endocannabinoid tone have been reported. The heterogeneous results obtained in animal models may depend on methodological differences such as the way of inducing parkinsonism or more importantly on the period of recovery after the lesion before performing experiments (Romero et al., 2000).

Studies in animal models and patients of PD have indicated that dopaminergic neuronal degeneration produces an imbalance between the direct and the indirect basal ganglia pathways. This imbalance is manifested as reduced activity of striatal GABAergic neurons in the direct pathway and hyperactivity in the indirect pathway striatal neurons. Moreover, glutamatergic input from the cortex to the striatum is augmented after dopaminergic denervation (Tang et al., 2001; Tseng et al., 2001; Gubellini et al., 2002; Mallet et al., 2006). Within the basal ganglia, CB_1 receptors are principally expressed on presynaptic cortical glutamatergic terminals and presynaptic striatal GABAergic terminals (Benarroch, 2007). The activation of CB_1 receptors reduces the glutamate release from the cortex to the striatum (Gerdeman and Lovinger, 2001; Gubellini et al., 2002; Brown et al., 2003) and GABA release to the SNpr (Wallmichrath and Szabo, 2002). In addition, endocannabinoids and CB_1 receptors play an important physiological role in the long- and short-term regulation of the synaptic transmission in the basal ganglia shaping the striatal output and therefore modulating motor activities. The two classic forms of long-term synaptic plasticity, long-term potentiation and long-term depression (LTD) are expressed at corticostriatal synapses and abolished in animal models of PD (Centonze et al., 1999; Picconi et al., 2005; Calabresi et al., 2007; Kreitzer and Malenka, 2007). Using different LTD induction paradigms it has been described that this form of plasticity is mostly controlled by endocannabinoids (Shen et al., 2008; Lovinger, 2010). Although probably other mechanisms are also involved in the dopaminergic control of striatal plasticity, pharmacological manipulation of the endocannabinoid system under parkinsonian conditions has been proved not only to rescue LTD in striatum but also to improve the motor deficits evident after dopaminergic denervation (Kreitzer and Malenka, 2007).

In line with this, behavioral studies have shown that modulation of the endocannabinoid system can have a therapeutic impact in animal models of PD. Behavioral changes caused by the induction of parkinsonism in rats have been improved by the administration of CB_1 receptor antagonists both in unilateral and bilateral PD models in rodents (Fernandez-Espejo et al., 2005; Gonzalez et al., 2006; Kelsey et al., 2009). In MPTP-lesioned marmosets, CB_1 antagonist administration increased locomotor activity but failed to improve bradykinesia or posture (van der Stelt et al., 2005). On the other hand, co-administration of L-DOPA with CB_1 antagonists added a positive improvement of the motor symptoms assigned to the antiparkinsonian drug in parkinsonian animals (Kelsey et al., 2009). The latter data suggest that combined therapy with antiparkinsonian drugs and cannabinoid antagonists may permit a reduction of L-DOPA dose and therefore, delay

the emergence of the motor side effects induced by the chronic treatment with L-DOPA.

The benefit of cannabinoids in PD is not limited to the symptomatic amelioration. Lately, several reports have revealed interesting neuroprotective and anti-inflammatory effects of these drugs in cell cultures and animal models of PD (Lastres-Becker et al., 2005; Garcia-Arencibia et al., 2007; Fernandez-Ruiz et al., 2011; Jeon et al., 2011; Carroll et al., 2012). Although CB_1 receptor-mediated effects cannot be excluded, some authors argue that CB_1 receptors may have a minimal implication in neuroprotection (Lastres-Becker et al., 2005; Fernandez-Ruiz et al., 2007; Price et al., 2009; Chung et al., 2011). It seems plausible that neuroprotection is principally mediated by the antioxidant effect of cannabinoids and CB_1 receptor-independent properties (Lastres-Becker et al., 2005; Garcia-Arencibia et al., 2007; Carroll et al., 2012), while in parallel, activation of CB_2 receptors in astrocytes and microglial cells is responsible for the observed anti-inflammatory effect. Although the exact mechanisms should be further investigated, cannabinoid receptor modulation can be potentially useful for protecting dopaminergic neurons from progressive neurodegeneration in PD.

IMPLICATION OF THE CANNABINOID SYSTEM IN L-DOPA INDUCED DYSKINESIA

The emerging role of the endocannabinoid system as modulator of neurotransmission in the basal ganglia identifies it as a potential pharmacological target for treating motor complications derived from the chronic treatment with L-DOPA. L-DOPA induced dyskinesia (LID) constitute one of the most disabling complications derived from the long-term therapy with L-DOPA affecting up to 40% of PD patients after 5 years of treatment (Ahlskog and Muenter, 2001). Cannabinoid agonists could exert antidyskinetic effect by regulating glutamatergic release in the striatum and/or by re-establishing endocannabinoid-mediated synaptic plasticity affected by dopaminergic denervation. In this sense, pharmacological agents with antidyskinetic properties such as serotonergic $5\text{-}HT_{1B}$ agonists are able to ameliorate the motor complications by depressing the glutamatergic corticostriatal transmission (Mathur et al., 2011).

Cannabinoid agents have been proposed as promising tools for treating LID, however, different studies in animal models and patients show certain discrepancies. Administration of cannabinoid agonists to parkinsonian rats receiving chronic L-DOPA treatment attenuated LID via CB_1-related mechanisms (Ferrer et al., 2003; Morgese et al., 2007; Martinez et al., 2012) and genetic deletion of CB_1 receptors prevented the development of severe dyskinetic movements in mice (Perez-Rial et al., 2011). Although the cited studies do not report any reduction of the efficacy of L-DOPA to improve the motor performance, a recent publication suggests that the antidyskinetic effect of cannabinoid agonists seem to be based on their general motor suppressant (Walsh et al., 2010a). In MPTP-lesioned monkeys and PD patients contradictory results have been found since CB_1 receptor activation (Silverdale et al., 2001; Fox et al., 2002) or blockage (van der Stelt et al., 2005) ameliorated LID. Other studies in patients have failed to find any correlation between CB_1 receptor expression and severity of dyskinesia (van der Stelt et al., 2005) or attribute any positive effect of cannabinoid agent administration in LID (Carroll et al., 2004; Mesnage et al., 2004).

Taken together, changes in the cannabinoid system are observed after dopaminergic denervation and manipulation of this system has proved to have beneficial effects on parkinsonian symptoms in animal models and PD patients. However, the putative role of cannabinoids in LID is still a matter of controversy. The complex localization of the cannabinoid receptors at different sites in the basal ganglia circuits may contribute to the paradoxical observed effects. Further investigations are needed to clarify the role of the cannabinoid system in LID.

In conclusion, the endocannabinoid system modulates nigrostriatal dopamine transmission both via direct and indirect mechanisms. This system has an important role in dopamine-related movement disorders, as PD, and represents a framework for novel therapeutic approaches in the future.

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