Endocannabinoid modulation of dopaminergic motor circuits

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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). CB1 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 CB1 receptors are located in the central nervous system while CB2 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 CB1 and CB2 are seven transmembrane G-protein-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 CB2 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 CB1 receptor, high levels are expressed within the basal ganglia (Herkenham et al., 1991; Malleux 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 (Malleux and Vanderhaeghen, 1992) and in the subthalamic nucleus (STN), the expression of the receptor protein is mainly located at the terminal level. Thus, CB1 receptors have been observed in subthalamonigral and subthalamopallidal terminals (Malleux and Vanderhaeghen, 1992; Tsou et al., 1998), glutamatergic corticostriatal afferences (Gerarden and Lovinger, 2001; Kobalvi 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 D1 receptors form the direct pathway, which projects to the GPi and the SNpr, while neurons expressing D2 receptors constitute the indirect pathway, projecting to the GPe (Figure 1) (Paul et al., 1992; O’Connor, 1998; Nicola et al., 2000; Oon et al., 2000; Svenningsson et al., 2000). A potential interaction between the D1/D2 and CB1 receptors at the level on the G-protein/adenyl cyclase signal transduction mechanism has been suggested (Giufrida et al., 1999; Meschler and Howlett, 2001). Combined activation of CB1 and D1 receptors results in a net decrease in adenyl cyclase, a subsequent decrease in the inhibitory activity of direct striatal projection neurons and finally...
Although neuronal expression and functionality of TRPV1 channels are controversial (Morera-Herreras et al., 2010), this receptor is present in the basal ganglia. Indeed, TRPV1 is located on nigrostriatal terminals and on tyrosine hydroxylase positive cells in the substantia nigra pars compacta (SNpc) (Morera-Herreras et al., 2000; Miclea 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 CB1 and CB2, is coupled to Gq, Go12 and Go13 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 TRPV1 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 (Δ9-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; González et al., 1999). These hypokinetic effects can be reversed by the selective CB1 receptor antagonist, rimonabant, which in itself causes hyperlocomotion in healthy controls (Compton et al., 1996). In agreement with these observations, mice lacking CB1 receptors exhibit several motor anomalies (Ledent et al., 1999; Zimmer et al., 1999). Although these findings provide evidence for the involvement of CB1-related mechanisms in motor control, other reports demonstrate that also the TRPV1 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 CB1 receptors are not present on dopaminergic neurons or terminals (Julian et al., 2003; Matyas et al., 2006) suggest that CB1-mediated modifications of nigrostriatal dopaminergic
circuit dynamics 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; Gerdean 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 CB1 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 CB1 receptors are located on subthalamonicglial 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 CB1 receptor activation is in agreement with in vitro 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 CB1 activation has no effect on dopamine release (Kofalvi et al., 2005). Contrary to CB1-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 cannabinoids as Δ9-THC), acting via postsynaptic TRPV1 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 TRPV1 receptors in the SNpc (Marinelli et al., 2003, 2007), although this enhancement may be mediated by TRPV1 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 CB1 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, CB1 receptors are principally expressed on presynaptic cortical glutamatergic terminals and presynaptic striatal GABAergic terminals (Benarroch, 2007). The activation of CB1 receptors reduces the glutamate release from the cortex to the striatum (Gerdean 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 CB1 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 CB1 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, CB1 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 CB1 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; Leon et al., 2011; Carroll et al., 2012). Although CB1 receptor-mediated effects cannot be excluded, some authors argue that CB1 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 CB1 receptor-independent properties (Lastres-Becker et al., 2005; Garcia-Arencibia et al., 2007; Carroll et al., 2012), while in parallel, activation of CB2 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 Mueenter, 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 antidysonptic properties such as serotonergic 5-HT1B 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 CB1-related mechanisms (Ferrer et al., 2003; Morgese et al., 2007; Martinez et al., 2012) and genetic deletion of CB1 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 CB1 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 CB1 receptor expression and severity of dyskinesia (van der Stelt et al., 2005) or attribute any positive effect of cannabinoid 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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