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REVIEW ARTICLE

Cannabinoid–dopamine interactions in the physiology and physiopathology of the basal ganglia

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Endocannabinoids and their receptors play a modulatory role in the control of dopamine transmission in the basal ganglia. However, this influence is generally indirect and exerted through the modulation of GABA and glutamate inputs received by nigrostriatal dopaminergic neurons, which lack cannabinoid CB_1 receptors although they may produce endocannabinoids. Additional evidence suggests that CB_2 receptors may be located in nigrostriatal dopaminergic neurons, and that certain eicosanoid-related cannabinoids may directly activate $TRPV_1$ receptors, which have been found in nigrostriatal dopaminergic neurons, thus allowing in both cases a direct regulation of dopamine transmission by specific cannabinoids. In addition, CB_1 receptors form heteromers with dopaminergic receptors which provide another pathway to direct interactions between both systems, in this case at the postsynaptic level. Through these direct mechanisms or through indirect mechanisms involving GABA or glutamate neurons, cannabinoids may interact with dopaminergic transmission in the basal ganglia and this is likely to have important effects on dopamine-related functions in these structures (i.e. control of movement) and, particularly, on different pathologies affecting these processes, in particular, Parkinson's disease, but also dyskinesia, dystonia and other pathological conditions. The present review will address the current literature supporting these cannabinoid–dopamine interactions at the basal ganglia, with emphasis on aspects dealing with the physiopathological consequences of these interactions.

LINKED ARTICLES

This article is part of a themed section on Updating Neuropathology and Neuropharmacology of Monoaminergic Systems. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v173.13/issuetoc

Abbreviations

Δ^9-THC, Δ^9-tetrahydrocannabinol; FAAH, fatty acid amide hydrolase

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Table of Links

TARGETS
GPCRs[a]
Adenosine A_{2A} receptors
Cannabinoid CB_1 receptors
Cannabinoid CB_2 receptors
Dopamine D_1 receptors
Dopamine D_2 receptors
Enzymes[b]
FAAH, fatty acid amide hydrolase
Monoacylglycerol lipase
Ion Channels[c]
TRPV1 channels
Transporters[d]
Dopamine transporter, DAT
Nuclear hormone receptors[e]
PPAR-α
PPAR-γ

LIGANDS
2-arachidonoyl glycerol
AM251
Anandamide
Dopamine
Levodopa
Methanandamide
NADA, N-arachidonoyl-dopamine
Oleoyl ethanolamide
Rimonabant
Δ^9-tetrahydrocannabivarin
Δ^9-THC, Δ^9-tetrahydrocannabinol
WIN55,212-2

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c,d,e]Alexander *et al.*, 2013a,b,c,d,e).

Overview of the endocannabinoid signalling system and its interaction with neurotransmitter systems

It is well established that the endocannabinoid system, formed by different signalling lipids, the enzymes involved in their synthesis and degradation, and their target receptors, plays a modulatory function in important processes of the CNS. This includes the control of movement (see Fernández-Ruiz, 2009), learning and memory (see Zanettini *et al.*, 2011), emotional behaviour (see McLaughlin and Gobbi, 2012), nociception (see Guindon and Hohmann, 2009), brain reward (see Solinas *et al.*, 2008), feeding behaviour (see Kirkham, 2009) and emesis (see Parker *et al.*, 2011), among others. This modulatory function is exerted through the ability of endocannabinoids and their receptors to participate in the retrograde signalling in different synapses located in those brain structures that regulate these processes (Castillo *et al.*, 2012). This is facilitated by the presynaptic location of cannabinoid CB_1 receptors, the key neuronal cannabinoid receptor type, that allow endocannabinoids to directly modulate the function of most of neurotransmitters including glutamate, GABA, opioid peptides, acetylcholine and 5-HT (see Heifets and Castillo, 2009; Kano *et al.*, 2009). This function is particularly important in the case of glutamatergic and GABAergic synapses, in which, through well-defined processes of short- and long-lasting synaptic depression, it prevents an excess of excitation or inhibition, respectively, (Lovinger, 2008) that may lead to pathological conditions if prolonged and/or enhanced.

Dopamine has been also linked to the action of cannabinoids (see Fernández-Ruiz *et al.*, 2010; El Khoury *et al.*, 2012). However, the different subpopulations of dopaminergic neurons within the CNS and, in particular, those neurons whose cell bodies are located in the substantia nigra and that project to the caudate-putamen, the so-called nigrostriatal dopaminergic neurons, do not appear to contain cannabinoid CB_1 receptors (see Fernández-Ruiz, 2009; Fernández-Ruiz *et al.*, 2010), the cannabinoid receptor type mostly involved in the control of synaptic activity. CB_1 receptors are also absent from other dopaminergic neuronal subpopulations (e.g. mesocorticolimbic neurons), although this does not exclude possible interactions between cannabinoids and dopamine in the control of those behaviours (e.g. brain reward, motivation, emotion) regulated by these neurons in physiological and physiopathological conditions (e.g. addiction). However, this has been the subject of a recent review (Fernández-Ruiz *et al.*, 2010) and will not be addressed in the present one, which will concentrate exclusively in these interactions at the level of the basal ganglia.

Nigrostriatal dopaminergic neurons exert a regulatory action on different effector neurons within the basal ganglia thus influencing the control of movement. Although these neurons do not contain CB_1 receptors, they are significantly affected by either the activation or the blockade of the endocannabinoid system, leading to important changes in the motor activity (Fernández-Ruiz, 2009; Fernández-Ruiz *et al.*,

2010). It is generally accepted that these effects are exerted through CB_1 receptors located in other neuronal subpopulations (i.e. GABAergic, glutamatergic and opioidergic neurons). These neurons are located in the close vicinity of, and connected with, dopaminergic neurons (see van der Stelt and Di Marzo, 2003). It is also important to note that these midbrain dopaminergic neurons, although lacking CB_1 receptors, may produce and release endocannabinoid ligands from their somas and dendrites (as shown for the midbrain dopaminergic neurons located in the ventral-tegmental area; Melis *et al.*, 2004; Riegel and Lupica, 2004), thus facilitating the retrograde signalling function of these transmitters and CB_1 receptors in excitatory and inhibitory synapses (reviewed in Seutin, 2005). Lastly, even though most of the cannabinoid effects on dopaminergic transmission are indirect and exerted through GABA- and/or glutamate-containing neurons, there are some recent studies that propose additional or alternative mechanisms that involve a closer relationship between the endocannabinoid and the dopaminergic systems (see below).

Cannabinoid–dopamine interactions at the basal ganglia

As mentioned above, there is solid anatomical, biochemical, physiological and pharmacological evidence that supports the idea that dopamine is the key regulatory transmitter in the control of movement exerted at the basal ganglia level (see Smith and Villalba, 2008). The activation of dopaminergic transmission in this circuitry produces hyperkinesia, whereas its inhibition results in a reduction of movement. By contrast, activation of the endocannabinoid system has been associated with motor inhibition and even catalepsy (see Fernández-Ruiz, 2009), so that it has been widely speculated that the hypokinetic effect of cannabinoid agonists might be produced through a reduction in dopaminergic activity, given their ability to modify the action of several substances acting on the dopamine system. For example, cannabinoid agonists potentiated reserpine-induced hypokinesia (Moss *et al.*, 1981) and dopamine receptor antagonist-induced catalepsy (Anderson *et al.*, 1996), whereas they reduced quinpirole-induced hyperlocomotion (Marcellino *et al.*, 2008) and amphetamine-induced hyperactivity (Gorriti *et al.*, 1999) in laboratory rodents (for a complete summary of the behavioural data associated with the activation of CB_1 receptor-mediated signals within the basal ganglia, see Fernández-Ruiz and Gonzáles, 2005; Fernández-Ruiz, 2009). Based on these data, several authors have proposed the idea of an inverse correlation between the two transmitter systems, with a reduced endocannabinoid tone accompanied by increased dopaminergic activity occurring in hyperkinetic conditions, and the opposite associated with a reduction in movement (see Fernández-Ruiz, 2009). However, there are recent reports of a long-lasting activation of striatal dopaminergic function, reflected in an enhanced tyrosine hydroxylase expression, by CB_1 receptor agonists (Bosier *et al.*, 2012). The inverse correlation between both systems has been proposed for physiological conditions and also for pathological events, for example, Parkinson's disease, the most prevalent disorder affecting the basal ganglia (Obeso *et al.*, 2008). The endocannabinoid system becomes hyperactivated in Parkinson's disease in parallel to the dopamine deficiency produced by the progressive degeneration of nigrostriatal dopaminergic neurons, resulting in the occurrence of motor symptoms such as bradykinesia, rigidity and tremor (see Fernández-Ruiz, 2009). As will be discussed in the last section, this inverse correlation may serve for the development of cannabinoid-based therapies for this disease.

As mentioned above, the most intriguing aspect of this pharmacological interaction between both systems is that it occurs in the absence of CB_1 receptors on the dopaminergic neurons (Herkenham *et al.*, 1991a), which would imply that the mechanism enabling this interaction would be largely, if not exclusively, indirect and based on the necessary mediation of GABA- and/or glutamate-containing neurons that do contain these receptors (see Fernández-Ruiz, 2009; Fernández-Ruiz *et al.*, 2010). However, three recent experimental observations have challenged this classic idea. First, certain eicosanoid-derived cannabinoids, including anandamide, *N*-arachidonoyl-dopamine (NADA) and AM404, have been found to bind and activate TRPV1 receptors (see Starowicz *et al.*, 2007). Also, these receptors have been located in dopaminergic neurons within the basal ganglia (Mezey *et al.*, 2000), allowing a direct action of these endocannabinoid/endovanilloid compounds on dopaminergic transmission. Second, there is also recent evidence that indicates that CB_1 receptors are able to form heteromers with other metabotropic receptors, including the dopamine D_1 and D_2 receptor types located, among others, in striatal projection neurons, enabling both systems to directly interact at postsynaptic level (see Ferré *et al.*, 2009). These studies have provided interesting novel insights in terms of the function and therapeutic potential of the endocannabinoid signalling in the basal ganglia, as well as its interaction with dopaminergic transmission, from both basic and clinical perspectives. Lastly, CB_2 receptors have recently been identified in nigrostriatal dopaminergic neurons in the human brain (García *et al.*, 2015), enabling endocannabinoids to act through the other major cannabinoid receptor type to directly modulate dopaminergic transmission, although the distribution of this receptor type in the brain is much more restricted than that of the CB_1 receptor and is frequently associated with pathological conditions (Fernández-Ruiz *et al.*, 2007). These mechanisms will be addressed in more detail below, after examining the classical indirect mechanism first proposed to explain the endocannabinoid–dopamine interactions (see Figure 1 for a representative diagram of these interactions).

Effects of cannabinoids on dopaminergic transmission exerted through CB_1 receptors located in GABAergic and glutamatergic neurons

As mentioned above, the abundant presence of endocannabinoid elements, that is, CB_1 receptors and their endogenous ligands, in the basal ganglia (Herkenham *et al.*, 1991b; Mailleux and Vanderhaeghen, 1992; Tsou *et al.*, 1998; Bisogno *et al.*, 1999; Breivogel and Sim-Selley, 2009), supports the idea that the endocannabinoid system plays an important modulatory role in the function of these brain structures (see Fernández-Ruiz, 2009). It is generally accepted that those

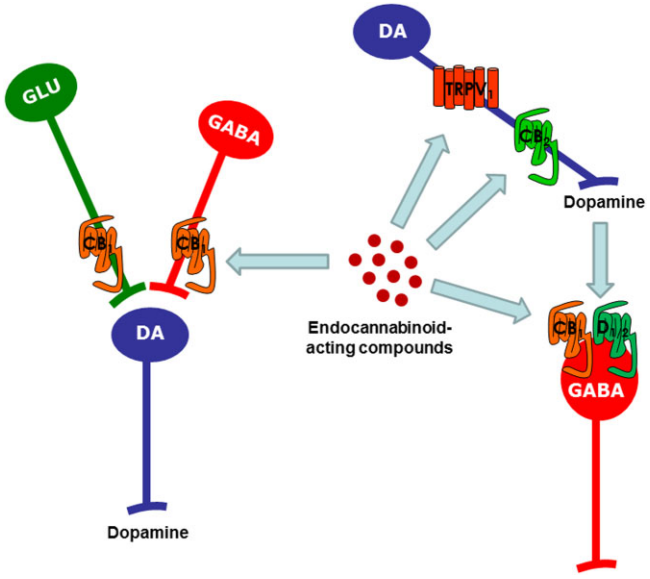

Figure 1
Summary of the different neuronal mechanisms proposed to explain the interactions between the endocannabinoid signalling system and dopaminergic transmission at the level of the basal ganglia.

substances that enhance the endocannabinoid activity, preferentially the direct agonists of the CB_1 receptor, generate a dose-dependent motor inhibition in laboratory animals that may even produce catalepsia with the highest doses (see Fernández-Ruiz, 2009). This has been also observed in human smokers of cannabis and is associated with a detrimental effect on striatal dopaminergic functioning (Kowal *et al.*, 2011). Similar results were obtained by administering the so-called indirect cannabinoid agonists that are inhibitors of the endocannabinoid inactivation processes, for example, the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase and the endocannabinoid transporter (Fernández-Ruiz, 2009). These hypokinetic effects were generally reversed by the administration of rimonabant or other CB_1 receptor antagonists, supporting the idea that this receptor type is the key cannabinoid receptor involved in motor effects of cannabinoid compounds. In addition, rimonabant and other antagonists of CB_1 receptors produce by themselves a certain degree of hyperlocomotion, because many of them are inverse agonists (see Fernández-Ruiz, 2009), whereas mice lacking CB_1 receptors exhibited several motor anomalies (see Valverde *et al.*, 2005), supporting the key role played by these receptors (for a complete summary of the behavioural data associated with the activation/inhibition of CB_1 receptor-mediated signals within the basal ganglia, see Fernández-Ruiz and Gonzáles, 2005; Fernández-Ruiz, 2009).

A priori, the motor effects of cannabinoid agonists were explained as the normal consequence of their activity on those neuronal subpopulations that contain CB_1 receptors within the basal ganglia circuitry. Striatal projection GABAergic neurons and subthalamonigral glutamatergic neurons were the first CB_1 receptor-containing neurons identified in relation with the motor effects of cannabinoids (Herkenham *et al.*, 1991a; Mailleux and Vanderhaeghen, 1992; Tsou *et al.*, 1998; Fusco *et al.*, 2004). Further studies, conducted mostly with immunohistochemical procedures, demonstrated that CB_1 receptors were also located in corticostriatal glutamatergic afferences (Köfalvi *et al.*, 2005; Uchigashima *et al.*, 2007) and in some subpopulations of striatal GABA interneurons (Fusco *et al.*, 2004; Uchigashima *et al.*, 2007). In all cases, the neurons containing CB_1 receptors are GABAergic or glutamatergic neurons, thus supporting the idea that the first event associated with the activation of these receptors is an alteration in the activity of GABA and glutamate synapses but not the dopaminergic synapses. The changes in this neurotransmitter would occur secondarily to a primary effect on GABA or glutamate transmission, and they would be due to the connection of dopaminergic transmission with these neurons. However, as mentioned above, it is also possible that dopaminergic neurons located in the substantia nigra may be responsible for producing endocannabinoids for the activation of CB_1 receptors located in GABAergic or glutamatergic neurons, as found for dopaminergic neurons located in the ventral tegmental area (Melis *et al.*, 2004; Riegel and Lupica, 2004). In addition, endocannabinoids may be also produced by striatal-projecting neurons in order to target CB_1 receptors located in corticostriatal glutamatergic neurons and inhibit glutamate release, a response that appears to be regulated by the interaction of D_2 and adenosine A_{2A} receptors located in striatal cholinergic interneurons (Tozzi *et al.*, 2011). All these findings are supported by the different anatomical studies mentioned above, but also by numerous pharmacological, electrophysiological and neurochemical studies that addressed the interaction of cannabinoid agonists with substances acting on the dopamine system, in relation to the motor effects in laboratory animals, studies that have been mentioned in the above section.

Effects of eicosanoid-related cannabinoids exerted through TRPV1 receptors located in dopaminergic neurons

As mentioned above, further investigations have, however, provided new elements to re-evaluate the idea that the effects of endocannabinoids on dopaminergic transmission in the basal ganglia are necessarily indirect and mediated by CB_1 receptors located in GABA- or glutamate-containing neurons. For example, it is now well known that anandamide and some of its analogues, for example, AM404, but not classic cannabinoids such as. Δ^9-tetrahydrocannabinol (Δ^9-THC), may behave as full agonists for the TRPV1 receptors (see Starowicz *et al.*, 2007). These receptors have been identified in the basal ganglia located, among other markers, in nigrostriatal dopaminergic neurons (Mezey *et al.*, 2000). The activation of these receptors with capsaicin or with other potential vanilloid ligands produced hypokinesia in rats (Di Marzo *et al.*, 2001). Anandamide produced the same behavioural effect accompanied by a reduction in the activity of dopaminergic terminals in the striatum (de Lago *et al.*, 2004), and this effect was reversed by capsazapine, thus supporting that it is exerted by the activation of TRPV1 receptors (de Lago *et al.*, 2004). Further *in vitro* studies using perfused striatal fragments confirmed the activity of anandamide and the lack of effect of classic cannabinoids, such as Δ^9-THC, that do not bind to vanilloid-like receptors, indicating that the TRPV1, rather than the CB_1 receptor, is the key target

involved in these effects (de Lago *et al*., 2004). Other authors reported that the activation of TRPV1 receptors in the substantia nigra *pars compacta*, rather than producing an inhibition, stimulated dopamine release, although these effects seem to be mediated by TRPV1 receptors located in glutamatergic neurons, rather than by those located in dopaminergic terminals (Marinelli *et al*., 2003; 2007).

Another interesting compound active at the TRPV1 receptor is NADA, an arachidonic acid derivative with properties of endocannabinoid and endovanilloid ligands (Starowicz *et al*., 2007). NADA seems to be synthesized through the conjugation of an arachidonic acid molecule directly with dopamine (Hu *et al*., 2009), excluding earlier suggestions that it would be synthesized through the hydroxylation of *N*-arachidonoyl-tyrosine followed by decarboxylation, by the same enzymes as those involved in dopamine synthesis. Its physiological significance is yet poorly understood, but some evidence suggests that it can serve as an antioxidant and neuroprotective compound (Bobrov *et al*., 2008). In addition, making the issue even more complex, a further study by Ferreira *et al*. (2009) revealed that *N*-acyldopamines, such as NADA, were able to control the activity of dopaminergic terminals in the striatum via ion channels other than TRPV1 receptors, an effect that was not observed with anandamide or capsaicin. Importantly, NADA was likely to be synthesized in the substantia nigra in conditions of hyperactivity (Marinelli *et al*., 2007).

Another recent observation that makes the issue even more complex suggests that anandamide may inhibit the dopamine transporter function by a receptor-independent mechanism, an effect found in heterologous cells and synaptosomal preparations and mimicked by the anandamide analogue methanandamide, not by arachidonic acid (Oz *et al*., 2010). In addition, inhibition of FAAH or COX-2 failed to alter the effect of anandamide, thus indicating that this effect is not related to the metabolism of this endocannabinoid (Oz *et al*., 2010). Authors also found that the effect was not attenuated by *Pertussis* toxin, excluding the involvement of CB_1, CB_2 or GPR55 receptors, but not excluding that of TRPV1 receptors. Other authors also reported an inhibition of the dopamine transporter by different cannabinoid ligands in the rodent striatum (Price *et al*., 2007; Pandolfo *et al*., 2011). The inhibition was seen with the non-selective cannabinoid agonists WIN55,212-2 and O-2545, and also with cannabidiol and NADA, but not with anandamide and 2-arachidonoyl glycerol (Pandolfo *et al*., 2011). The effect was also seen with various CB_1 receptor antagonists/inverse agonists such as AM251 (Pandolfo *et al*., 2011). As expected, authors concluded that these effects were likely to be CB_1 receptor-independent (Pandolfo *et al*., 2011).

Interaction of CB_1 and dopamine receptors at the postsynaptic level

As mentioned above, CB_1 receptors do not appear to be located in dopaminergic neurons, with the only exception of a study that described direct interactions of the CB_1 receptor with the D_2 presynaptic receptor, which would be only possible if both receptors are located in the same neurons (O'Neill *et al*., 2009). However, most of the authors believe that CB_1 receptors are not located on dopaminergic neurons, but in striatal GABAergic projection neurons (striatonigral and striatopallidal pathways, respectively), in which they co-localize with D_1 or D_2 receptors (Hermann *et al*., 2002; Martín *et al*., 2008). This may facilitate postsynaptic interactions between endocannabinoids and dopamine at the level of G-protein/adenylyl cyclase signal transduction (Giuffrida *et al*., 1999; Meschler and Howlett, 2001; Nguyen *et al*., 2012). In addition, there is strong evidence supporting the formation of heteromers between CB_1 and D_2 receptors, and also adenosine A_{2A} receptors (see Ferré *et al*., 2009; Brugarolas *et al*., 2014). These CB_1, D_2 and A_{2A} receptor heteromers were found in the dendritic spines of GABAergic neurons projecting to the globus pallidus, but their functional properties and their role in striatal function still need further investigation (see Ferré *et al*., 2009). This type of postsynaptic mechanism facilitates the direct interaction between cannabinoids and dopamine allowing, in this case, a bidirectional regulation, endocannabinoids to dopamine and *vice versa*. Thus, on one side, the motor effects of CB_1 receptor agonists have been associated with an activation of signalling via the neuronal phosphoprotein DARPP-32, which has been linked to intracellular responses elicited by D_1 and D_2 receptors in the striatal projection neurons, whereas the genetic inactivation of DARPP-32 resulted in an attenuation in the motor effects of cannabinoids (Andersson *et al*., 2005). On the other side, D_2 receptors controlled anandamide production in the striatum. This may serve as an inhibitory feedback mechanism counteracting dopamine-induced facilitation of psychomotor activity (Giuffrida *et al*., 1999), as well as controlling $G_{i/o}$ protein availability for CB_1 receptors (González *et al*., 2009) and facilitating endocannabinoid-mediated long-term synaptic depression of GABAergic neurons (Kreitzer and Malenka, 2007), an effect also seen in the ventral tegmental area (Pan *et al*., 2008). A similar interaction of endocannabinoids with D_1 receptors has been recently proposed (Martín *et al*., 2008) and this proposal has been extended to glutamatergic synapses in which dopamine and its receptors also promote endocannabinoid-mediated synaptic depression (see Lovinger and Mathur, 2012). In fact, the changes in corticostriatal glutamatergic synapses derived from the deficiency in dopamine occurring in Parkinson's disease have been proposed as a key factor in the pathogenesis of this disease (Lovinger and Mathur, 2012). Similarly, the formation of receptor heteromers (e.g. CB_1, D_1/D_2, A_{2A}) in striatal neurons may be of interest from a pharmacological point of view for the treatment of Parkinson's disease symptoms, in particular, levodopa-induced dyskinesias. However, a recent study has demonstrated that levodopa disrupts the crosstalk between A_{2A}-CB_1-D_2 receptors in experimental models of Parkinson's disease in rodents (Pinna *et al*., 2014) and primates (Bonaventura *et al*., 2014).

Location of CB_2 receptors in nigrostriatal dopaminergic neurons

Recent evidence indicates that the TRPV1 receptor is not the only neuronal receptor other than the CB_1 receptor that may be involved in the action of cannabinoids in the basal ganglia. Some recent studies showed that CB_2 receptors, a receptor type preferentially associated with glial elements within the CNS, particularly when these become overactive in conditions of brain damage (see Fernández-Ruiz *et al*., 2007), may be also present in neurons of the basal ganglia in

primates, in particular, in the pallidothalamic-projecting neurons (Lanciego *et al.*, 2011). In addition, we have just found, using *post mortem* human tissues, that CB_2 receptors were also located in nigrostriatal dopaminergic neurons (García *et al.*, 2015), which supports the idea that those cannabinoids that target the CB_2 receptor may influence the activity of these dopaminergic neurons through effects on their neuronal firing and/or the control of synaptic activity. Although this has not been investigated yet in dopaminergic neurons located in the substantia nigra, such effects have been recently described for dopaminergic neurons located in the neighbouring ventral tegmental area (Zhang *et al.*, 2014). These authors identified CB_2 receptors in these dopaminergic neurons in mice and demonstrated that their activation functionally modulated dopaminergic neuronal excitability and related behavioural consequences, for example, drug self-administration (Zhang *et al.*, 2014), so it is probable that this also occurs with the CB_2 receptors located in nigral neurons. At present, the most important observation related to the presence of CB_2 receptors in nigrostriatal dopaminergic neurons is their marked reduction in the substantia nigra of Parkinson's disease patients (García *et al.*, 2015), which supports the possibility that this receptor may be used as a biomarker of nigral degeneration in this disease.

Relevance of cannabinoid–dopamine interactions in the basal ganglia in pathological conditions

The ability of the endocannabinoid signalling system to modulate dopaminergic transmission at the basal ganglia, by acting indirectly at CB_1 receptors located in neurons for other neurotransmitters, or directly at TRPV1 or CB_2 receptors located in dopaminergic neurons or through postsynaptic interactions between CB_1 and D_1/D_2 receptors, enables this system to be pharmacologically manipulated in order to normalize dopaminergic transmission and, subsequently, to alleviate dopamine-related motor symptoms, in conditions of dopamine deficiency, overactivity or dysregulation as those that occur in various basal ganglia disorders (see van der Stelt and Di Marzo, 2003; Fernández-Ruiz, 2009; García-Arencibia *et al.*, 2009; Pisani *et al.*, 2011). To date, most studies have concentrated on Parkinson's disease, the major basal ganglia disorder characterized by the progressive death of nigral dopaminergic neurons and dopaminergic denervation of the striatum, and have addressed the issue mainly at the preclinical level, using different models of experimental Parkinsonism (see Fernández-Ruiz, 2009; García-Arencibia *et al.*, 2009; Pisani *et al.*, 2011). The issue has been also studied at the clinical level in patients affected by Parkinson's disease or by other pathological conditions related to the basal ganglia function, such as Gilles de la Tourette's syndrome, dystonia and dyskinesia. However, the few clinical trials conducted so far have not revealed many positive results (Frankel *et al.*, 1990; Sieradzan *et al.*, 2001; Fox *et al.*, 2002; Müller-Vahl *et al.*, 2002; 2003; Jabusch *et al.*, 2004; Mesnage *et al.*, 2004; Fabbrini *et al.*, 2007).

The preclinical studies using models of experimental Parkinsonism have investigated both agonists and antagonists for the CB_1 receptor, used alone or as coadjuvants, and have concentrated first in the alleviation of specific motor symptoms (see Brotchie, 2003; Fernández-Ruiz, 2009; García-Arencibia *et al.*, 2009; Pisani *et al.*, 2011). There is also evidence that cannabinoids may serve to delay and arrest the progression of this disease (see Brotchie, 2003; Fernández-Ruiz, 2009; García-Arencibia *et al.*, 2009; Pisani *et al.*, 2011), although this potential will not be addressed here.

As regards the Parkinsonian symptoms that may be potentially alleviated by manipulating the endocannabinoid system, one relevant example is the tremor that is associated with the frequent overactivity of the subthalamic nucleus occurring in Parkinson's disease. CB_1 receptor agonists have been investigated for the reduction of tremor, with positive results in experimental Parkinsonism (Sañudo-Peña *et al.*, 1999), providing a neurobiological support for the anecdotal data (e.g. surveys) that indicated that Parkinsonian patients who self-medicated with cannabis obtained benefits in the reduction of tremor (see Venderová *et al.*, 2004). However, the few clinical studies conducted to validate the potential of CB_1 receptor agonists against tremor in patients did not confirm these positive effects (Frankel *et al.*, 1990).

Another Parkinsonian symptom investigated in relation to the activity of the CB_1 receptor is bradykinesia. Blockade of CB_1 receptors with rimonabant or with other antagonists reduced akinesia and motor inhibition in experimental models of Parkinson's disease (Fernández-Espejo *et al.*, 2005; González *et al.*, 2006; Kelsey *et al.*, 2009; García *et al.*, 2011), although a few studies showed conflicting results (Di Marzo *et al.*, 2000; Meschler *et al.*, 2001). However, again the only clinical trial conducted with CB_1 receptor antagonists in Parkinsonian patients did not confirm the positive effects found in experimental models, although the study was conducted with a group of patients who were all good responders to levodopa (Mesnage *et al.*, 2004). It is possible that the blockade of CB_1 receptors would be more effective in patients who are weak responders to levodopa or in disease states in which the classic dopaminergic therapy does not work. If this possibility were to be confirmed, it would represent an important advance in the development of novel antiParkinsonian agents. This can be concluded from the preclinical studies that demonstrated that rimonabant was more effective when used at low doses (González *et al.*, 2006; Kelsey *et al.*, 2009) and in very advanced phases of the disease characterized by extreme nigral damage (Fernández-Espejo *et al.*, 2005), conditions that were not completely reproduced in the clinical trial. In addition, these studies also demonstrated that the positive effects of rimonabant (González *et al.*, 2006), as well as of other antagonists such as Δ^9-tetrahydrocannabivarin (García *et al.*, 2011), were independent of dopaminergic transmission and related to an enhancement of glutamatergic transmission at the striatal level (García-Arencibia *et al.*, 2008; García *et al.*, 2011). It is important to note that the usefulness of CB_1 receptor antagonists in this disease agrees with the pharmacological strategy derived from the results of several studies demonstrating up-regulation of CB_1 receptors and other elements of this signalling system in Parkinson's disease (Mailleux and Vanderhaeghen, 1993; Di Marzo *et al.*, 2000; Lastres-Becker *et al.*, 2001; Gubellini *et al.*, 2002). As mentioned above, there is an imbalance between dopamine,

which goes down, and endocannabinoids, which go up, in the basal ganglia once nigral damage is already evident, which supports the potential of CB_1 receptor antagonists in this disease. This type of response has been observed in rats treated acutely with reserpine (Di Marzo *et al.*, 2000) or chronically with dopaminergic antagonists (Mailleux and Vanderhaeghen, 1993), or after the damage of nigrostriatal neurons with 6-hydroxydopamine (Mailleux and Vanderhaeghen, 1993; Gubellini *et al.*, 2002) or MPTP (Lastres-Becker *et al.*, 2001) in different laboratory animals. It was also found in patients (Lastres-Becker *et al.*, 2001; Pisani *et al.*, 2005). In support of this concept of imbalance, classic dopaminergic replacement therapy with levodopa reversed this endocannabinoid overactivity (Lastres-Becker *et al.*, 2001; Maccarrone *et al.*, 2003). By contrast, Kreitzer and Malenka (2007) demonstrated that endocannabinoid retrograde signalling was absent in the indirect pathway in experimental Parkinsonism, and they found benefits for Parkinsonian motor deficits in these experimental models with a combination of D_2 agonists and inhibitors of endocannabinoid degradation which elevated the endocannabinoid tone. This emphasizes the complexity of the basal ganglia circuitry, due to the multiplicity of neuronal sites for the generation of endocannabinoids and CB_1 receptor-mediated signals.

The occurrence of dyskinesia associated with prolonged therapy of dopaminergic replacement with levodopa represents the major complicating factor in the treatment of patients affected by Parkinson's disease (Fabbrini *et al.*, 2007; Iravani and Jenner, 2011). Numerous studies conducted in the last 15 years have demonstrated that it can be pharmacologically reduced with certain cannabinoid compounds, although this finding is controversial, because of the opposing effects exerted by the different targets activated by the active cannabinoids. For example, CB_1 receptor agonists have shown antidyskinetic effects (Ferrer *et al.*, 2003; Martinez *et al.*, 2012) and a normalization of the signalling mechanisms (e.g. cAMP/PKA activation) involved in the dyskinetic anomalies (Martinez *et al.*, 2012). However, the clinical validation of this potential of CB_1 receptor agonists has produced controversial results (Sieradzan *et al.*, 2001; Carroll *et al.*, 2004). This controversy has been also found in the preclinical studies, for example, the benefits of the activation of CB_1 receptors against levodopa-induced dyskinesia were not found with the so-called indirect cannabinoid agonists, e.g. FAAH inhibitors, presumably because they are also able to activate TRPV1 receptors in addition to CB_1 receptors (Morgese *et al.*, 2007). In fact, only when combined with a TRPV1 receptor antagonist, were FAAH inhibitors able to show antidyskinetic properties, thus indicating that CB_1 and TRPV1 receptors work in opposite directions to control levodopa-induced dyskinesia (Morgese *et al.*, 2007). On the other hand, another conflicting result derived from studies showing that CB_1 receptor antagonists also reduced and/or delayed levodopa-induced dyskinesia (see Fabbrini *et al.*, 2007). Their administration in combination with levodopa produces some interesting synergies in relation with motor symptoms but also with disease progression (Gutiérrez-Valdez *et al.*, 2013). Again, this indicates the complexity of the neuronal circuitry in which both CB_1 agonists and antagonists may provide the same type of therapeutic benefit, a fact presumably related to the presence of these receptors in both excitatory and inhibitory synapses within the basal ganglia circuitry. Lastly, a recent study added more complexity by suggesting that certain cannabinoids (e.g. anandamide) may reduce levodopa-induced dyskinesias by activating PPAR-γ (Martinez *et al.*, 2015). Beneficial effects were also reported in relation with oleoyl-ethanolamide, an endocannabinoid-related lipid, which is an endogenous ligand for PPAR-α receptor, but authors attributed its antidyskinetic effects to the blockade of TRPV1 receptors rather than the activation of PPAR-α receptors (González-Aparicio and Moratalla, 2014).

Lastly, it is also important to consider the therapeutic benefits that the antagonists of $TRPV_1$ receptors can offer for the treatment of motor defects in Parkinson's disease, given their well-demonstrated role in regulating dopamine release from nigral neurons (de Lago *et al.*, 2004). For example, they are necessary for unmasking the anti-dyskinetic effects of FAAH inhibitors or other cannabinoid agonists able to directly or indirectly activate TRPV1 receptors (Morgese *et al.*, 2007). However, given that they are located in the neuronal subpopulation that degenerates in this disease (Carroll *et al.*, 2004), it is necessary to assume that this target would experience a loss of efficacy in parallel to the progression of the disease, a highly relevant consideration in a disorder whose first motor symptoms appear when an important loss of dopaminergic neurons has already occurred.

Concluding remarks

In this article, we have reviewed the established findings and the recent advances in cannabinoid–dopamine interactions paying emphasis in a process in which dopamine has been proposed as a key regulatory neurotransmitter, the function of the basal ganglia and the control of movement. We have explored the mechanisms underlying these interactions, which demonstrate how compounds active at the endocannabinoid system can interfere with this process. In most of the cases, we have concluded that dopaminergic neurons do not contain CB_1 receptors but that these receptors are located on neurons present in regions innervated by dopaminergic neurons, which allows relevant bidirectional interactions. However, we have also presented evidence indicating that endocannabinoid–dopamine interactions are not exerted exclusively by indirect pathways, and that additional direct mechanisms may also facilitate these interactions, for example, through TRPV1 and CB_2 receptors located in dopaminergic neurons as well as through postsynaptic interactions of CB_1 receptors with D_1/D_2 receptors. Lastly, we have reviewed those diseases characterized by either deficiency or dysregulation of dopaminergic transmission, such as Parkinson's disease, and in which cannabinoids might be of therapeutic potential possibly through actions that facilitate, among others, a normalization of dopaminergic transmission.

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Conflict of interest

The authors declare that they have no conflict of interest in relation to this review article.

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