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Cannabinoid Control of Motor Function at the Basal Ganglia

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Abstract Classic and novel data strengthen the idea of a prominent role for the endocannabinoid signaling system in the control of movement. This finding is supported by three-fold evidence: (1) the abundance of the cannabinoid CB_1 receptor subtype, but also of CB_2 and vanilloid VR1 receptors, as well as of endocannabinoids in the basal ganglia and the cerebellum, the areas that control movement; (2) the demonstration of a powerful action, mostly of an inhibitory nature, of plant-derived, synthetic, and endogenous cannabinoids on motor activity, exerted by modulating the activity of various classic neurotransmitters; and (3) the occurrence of marked changes in endocannabinoid transmission in the basal ganglia of humans affected by several motor disorders, an event corroborated in animal

models of these neurological diseases. This three-fold evidence has provided support to the idea that cannabinoid-based compounds, which act at key steps of the endocannabinoid transmission [receptors, transporter, fatty acid amide hydrolase (FAAH)], might be of interest because of their potential ability to alleviate motor symptoms and/or provide neuroprotection in a variety of neurological pathologies directly affecting basal ganglia structures, such as Parkinson's disease and Huntington's chorea, or indirectly, such as multiple sclerosis and Alzheimer's disease. The present chapter will review the knowledge on this issue, trying to establish future lines for research into the therapeutic potential of the endocannabinoid system in motor disorders.

Keywords Cannabinoids · Cannabinoid receptors · Movement · Basal ganglia · Motor disorders

1 Function of the Endocannabinoid Signaling System in Motor Regions

The finding that the endocannabinoid system might be involved in the regulation of motor behavior is based on three series of different but complementary studies. A first group of studies, mainly dealing with pharmacological aspects, addressed the motor effects of plant-derived, synthetic, and endogenous cannabinoids in humans and laboratory animals (for reviews see Consroe 1998; Romero et al. 2002). In general, these studies demonstrated that cannabinoid agonists have powerful actions, mostly inhibitory effects, on motor activity (Crawley et al. 1993; Fride and Mechoulam 1993; Wickens and Pertwee 1993; Smith et al. 1994; Romero et al. 1995a and 1995b; for reviews see Sañudo-Peña et al. 1999; Romero et al. 2002). These studies also demonstrated that there exist differences in magnitude and duration for motor effects of the different cannabinoids, but these are mostly attributable to their differences in receptor affinity, potency, and/or metabolic stability. These motor effects are likely the consequence of the capability of cannabinoids to interact with specific neurotransmitters in the basal ganglia structures (for reviews see Sañudo-Peña et al. 1999; Romero et al. 2002; Fernández-Ruiz et al. 2002).

A second set of studies addressed the location and quantification of diverse elements of the endocannabinoid system in motor regions. They demonstrated that endocannabinoids and their receptors, in comparison with other brain structures, are abundant in the basal ganglia and also in the cerebellum, two brain structures directly involved in the control of movement (Herkenham et al. 1991a,b; Mailleux and Vanderhaeghen 1992a; Tsou et al. 1998a,b; Bisogno et al. 1999). Finally, in a third group of studies, possibly the most recent ones, the objective was to examine whether CB_1 receptors or other key proteins of the endocannabinoid system are altered in the basal ganglia of humans affected by several neurological diseases directly or indirectly related to motor function (Glass et al. 1993, 2000; Richfield and Herkenham 1994; Lastres-Becker et al. 2001a; for reviews see Consroe 1998; Fernández-Ruiz et al. 2002). These observations have been corroborated in different animal models of these motor disorders (Zeng et al. 1999; Romero et al.

2000; Page et al. 2000; Lastres-Becker et al. 2001a, 2002a,b). The present chapter will consider all of this previous pharmacological, biochemical, anatomical, and pathological evidence, and also the extent to which existing data support the hypothesis that modulators of the endocannabinoid system have therapeutic potential for the treatment of motor disorders.

1.1 Motor Effects of Cannabinoid-Based Compounds

Among a variety of effects, the consumption of cannabis by humans affects psychomotor activity, reflected by a global impairment of performance (especially in complex and demanding tasks) and resulting in an increased motor activity followed by inertia and incoordination, ataxia, tremulousness, and weakness (for reviews see Dewey 1986; Consroe 1998). Similar results were obtained in experiments with laboratory animals where the administration of plant-derived, synthetic, or endogenous cannabinoids, in particular (–)-Δ^9-tetrahydrocannabinol (Δ^9-THC), the prototypical tricyclic cannabinoid derived from *Cannabis sativa*, produced dose-dependent impairments in a variety of motor tests (open-field, ring test, actimeter, rotarod), thus stressing the relevance of endocannabinoid transmission in the control of motor function by the basal ganglia (for reviews see Di Marzo et al. 1998; Sañudo-Peña et al. 1999; Romero et al. 2002; Fernández-Ruiz et al. 2002).

1.1.1 Effects of Plant-Derived, Synthetic, or Endogenous Cannabinoid Agonists

Among the most notable effects, the administration of Δ^9-THC produced a reduction of spontaneous activity and induction of catalepsy in mice (Pertwee et al. 1988), whereas in rats it reduced ambulation, and spontaneous or induced stereotypic behaviors (Navarro et al. 1993; Romero et al. 1995a), increased inactivity (Rodríguez de Fonseca et al. 1994; Romero et al. 1995a), potentiated reserpine-induced hypokinesia (Moss et al. 1981) while reducing amphetamine-induced hyperlocomotion (Gorriti et al. 1999), increased circling behavior (Jarbe et al. 1998), and disrupted fine motor control (McLaughlin et al. 2000). Many other effects have been also documented (see Table 1 for a summary). Other plant-derived cannabinoids also produced motor inhibition (Hiltunen et al. 1988), although their effects were weak compared with those caused by Δ^9-THC in concordance with their lower affinity for the cannabinoid CB_1 receptor. By contrast, synthetic cannabinoids produced powerful inhibitory effects in a variety of motor tests and animal models (for reviews, see Consroe 1998; Sañudo-Peña et al. 1999; Romero et al. 2002; Table 1 for a summary).

The inhibitory effects reported for plant-derived or synthetic cannabinoids were, in general, mimicked by endocannabinoids, mainly anandamide (see Table 1 for a summary). Thus, Fride and Mechoulam (1993) reported a decrease in rearing behavior and immobility in mice, results that were reproduced by Crawley et al. (1993) and Smith et al. (1994). In addition, Wickens and Pertwee (1993) found that

Table 1. Motor effects of cannabinoid-related compounds in laboratory animals

Compound(s)		Motor effects
Plant-derived cannabinoids	Δ^9-THC	Reduction of spontaneous and stereotypic activity in rats (Navarro et al. 1993; Romero et al. 1995a,b; Jarbe et al. 1998)
		Reduction of spontaneous motor activity and induction of catalepsy (basal and muscimol-induced) in mice (Pertwee et al. 1988; Wickens and Pertwee 1993)
		Increase in reserpine-induced hypokinesia in rats (Moss et al. 1981)
		Increase in inactivity in rats (Rodríguez de Fonseca et al. 1994; Romero et al. 1995a,b: Jarbe et al. 1998)
		Reduction of amphetamine-induced hyperlocomotion in rats (Gorriti et al. 1999)
		Disruption of fine motor control in rats (McLaughlin et al. 2000)
		Increase in motor activity at low doses (Sañudo-Peña et al. 2000)
	CBD and CBN	Motor inhibition, but of lesser magnitude than Δ^9-THC (Hiltunen et al. 1988)
Synthetic cannabinoids	CP 55,940, HU210, WIN 55,212-2	Powerful effects causing motor inhibition in rats (reviewed by Romero et al. 2002)
		Turning behavior at low doses in mice (Souilhac et al. 1995)
Endocannabinoids	Anandamide	Immobility and decreased rearing behavior in rodents (Fride and Mechoulam 1993; Crawley et al. 1993; Smith et al. 1994)
		Reduction of ambulation and stereotypy, and increase of inactivity in rats (as with Δ^9-THC, but its effects were of shorter duration) (Romero et al. 1995a and 1995b)
		Potentiation of muscimol-induced catalepsy (Wickens and Pertwee 1993)
		Turning behavior at low doses in mice (Souilhac et al. 1995)
Endocannabinoid analogs	*R*-methanandamide (AM356)	Decreased ambulation and stereotypy and increased inactivity in rats (effects of longer duration than anandamide, similar to Δ^9-THC) (Romero et al. 1996; Jarbe et al. 1998)
Transporter inhibitors	AM404, VDM11, OMDM2, UCM707	Decreased ambulation and increased inactivity in rats (González et al. 1999; Beltramo et al. 2000)
		Potentiated anandamide-induced motor inhibition (de Lago et al. 2002 and 2004a)
Receptor antagonists	SR141716A (CB_1)	Antagonized motor effects of cannabinoid agonists (Souilhac et al. 1995; Di Marzo et al. 2001)
		Induction of stereotypies and hyperlocomotion (Compton et al. 1996)
	Capsazepine (VR1)	Antagonized motor effects of anandamide (de Lago et al. 2004b)

muscimol-induced catalepsy in rats was potentiated by anandamide and by Δ^9-THC. In our laboratory, we found that anandamide inhibited motor and stereotypic behaviors in a dose-related manner as did Δ^9-THC (Romero et al. 1995a), but, unlike the time-course for the response exhibited by this plant-derived cannabinoid, the time-course of the response to anandamide showed a biphasic pattern that probably reflected its conversion to active metabolite(s) (Romero et al. 1995b). *R*-(+)-methanandamide, a more stable analog of anandamide, produced a dose-dependent motor inhibition in the open-field test with almost the same potency as Δ^9-THC and with a duration of action longer than that of anandamide and almost comparable to that of Δ^9-THC (Romero et al. 1996a; Jarbe et al. 1998). In contrast with the above studies that used a range of doses producing exclusively hypokinetic effects, there are also a few studies showing that lower doses of anandamide, Δ^9-THC, or other cannabinoids increase motor behavior in mice (Souilhac et al. 1995) or rats (Sañudo-Peña et al. 2000).

1.1.2
Effects of Inhibitors of Endocannabinoid Inactivation

The above evidence was obtained with compounds that act directly at the CB_1 receptor, the cannabinoid receptor subtype involved in the psychoactive effects of cannabis derivatives. Similar results were observed with inhibitors of endocannabinoid inactivation, so-called indirect agonists, which act by prolonging the action of endocannabinoids at their receptors. These reuptake inhibitors were AM404 (González et al. 1999; Beltramo et al. 2000), VDM11 (de Lago et al. 2004a), UCM707 (de Lago et al. 2002), and OMDM2 (de Lago et al. 2004a) (see Table 1 for details). The most interesting aspect of the motor effects of these compounds was their ability to potentiate the hypokinetic effects of subeffective doses of anandamide, an effect that was particularly notable in experiments with UCM707 (de Lago et al. 2002). The use of these compounds in the clinic might represent an interesting option for those diseases, such as Huntington's disease (HD) or other hyperkinetic disorders, where a hypofunction of endocannabinoid transmission has been documented (see Fernández-Ruiz et al. 2002 for a review).

1.1.3
Effects of Cannabinoid Receptor Antagonists

The motor effects of cannabinoid agonists are usually prevented by SR141716, a selective CB_1 receptor antagonist (Souilhac et al. 1995; Di Marzo et al. 2001; for a review see Consroe 1998), thus suggesting that they are CB_1 receptor-mediated (see Table 1). However, the administration of SR141716 by itself can cause hyperlocomotion (Compton et al. 1996). All these data are compatible with the idea that the pharmacological blockade of CB_1 receptors might be of value for the treatment of hypokinetic signs of the sort that occur in Parkinson's disease (PD) and related disorders (see Fernández-Ruiz et al. 2002 for a review), an issue that will be discussed in detail below.

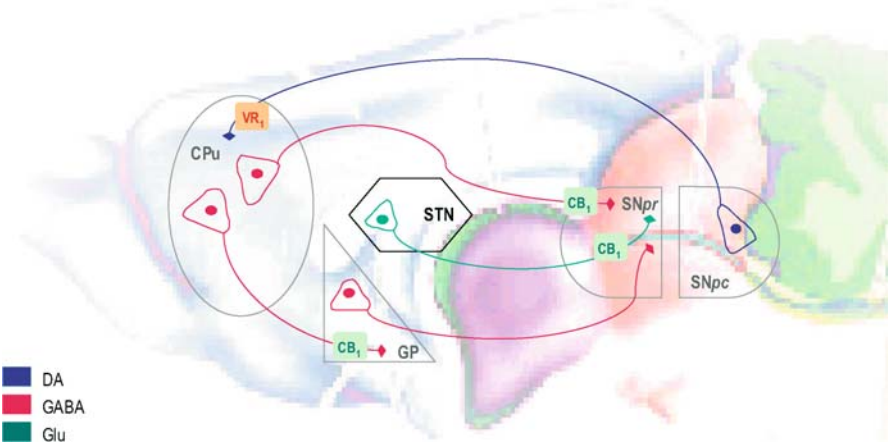

Fig. 1. Distribution of CB_1 and VR1 receptors in the basal ganglia circuitry in rats. *CPU*, caudate-putamen; *GP*, globus pallidus; *STN*, subthalamic nucleus; *SNpr*, substantia nigra pars reticulata; *SNpc*, substantia nigra pars compacta

In addition, recent evidence has demonstrated that vanilloid VR1 receptors might also be involved in the motor effects of certain cannabinoids that include those with an eicosanoid structure but exclude classical cannabinoids (de Lago et al. 2004b). Thus, motor inhibition produced by anandamide has been found to be reversed by capsazepine but not by SR141716 (de Lago et al. 2004b; see Table 1), which agrees with previous observations that: (1) the activation of VR1 receptors with their classic agonist, capsaicin, also produced hypokinesia (Di Marzo et al. 2001), and (2) the antihyperkinetic activity of AM404 in rat models of HD depends on its ability to directly activate VR1 receptors rather than to block the endocannabinoid transporter (Lastres-Becker et al. 2002a, 2003a). These pharmacological data suggest that the VR1 receptor may be another target through which anandamide and its analogs are able to affect motor function and provide therapeutic benefits in motor disorders. The recent detection of VR1 receptors in the basal ganglia (Mezey et al. 2000) supports this hypothesis.

1.2 Control of Different Neurotransmitters by Cannabinoids in Motor Regions

As indicated above, the administration of different cannabinoids impairs movement in rodents and humans. It is expected that this effect depends on the direct or indirect action of cannabinoids on the levels of several neurotransmitters that have been classically involved in the control of basal ganglia function. Three neurotransmitters seem to be influenced by cannabinoids in this circuitry, dopamine, γ-aminobutyric acid (GABA), and glutamate. In the case of the last two neurotransmitters, a direct action is possible since GABAergic and glutamatergic neurons in the basal ganglia contain CB_1 receptors located presynaptically (see Fig. 1). This

enables endocannabinoids to directly influence presynaptic events, such as synthesis, release, or reuptake (see Fernández-Ruiz et al. 2002 for a review). In contrast, dopaminergic neurons do not contain CB_1 receptors (Herkenham et al. 1991b). However, these receptors are abundantly expressed in the caudate-putamen, which is innervated by dopamine-releasing neurons (Herkenham et al. 1991a; Mailleux and Vanderhaeghen 1992a; Tsou et al. 1998a), thus allowing an indirect interaction. In addition, recent data showing that VR1 receptors present in the basal ganglia are likely located in nigrostriatal dopaminergic neurons (Mezey et al. 2000) open up the possibility that some cannabinoids may have a direct effect on dopaminergic transmission (de Lago et al. 2004b).

1.2.1 γ-Aminobutyric Acid

The involvement of GABAergic transmission in motor effects of cannabinoids has been documented in several studies (for a review see Fernández-Ruiz et al. 2002). We reported that the blockade of $GABA_B$, but not $GABA_A$, receptors attenuated most of the signs of motor inhibition caused by the administration of cannabinoid agonists in rats (Romero et al. 1996b). This is consistent with results obtained by Miller and Walker (1995, 1996) in a series of electrophysiological studies. These indicated that cannabinoids can modulate GABA release in vivo in the globus pallidus and substantia nigra. However, the effects were very modest. More recently, neurochemical studies demonstrated that the administration of cannabinoids did not affect GABA synthesis or release in the basal ganglia of naïve animals (Maneuf et al. 1996; Romero et al. 1998a; Lastres-Becker et al. 2002a), although cannabinoids were effective in increasing both processes in animals with lesions of striatal GABAergic neurons of the sort that occur in HD (Lastres-Becker et al. 2002a). In addition, the stimulation of CB_1 receptors located on axonal terminals of striatal GABAergic neurons resulted in an inhibition of GABA reuptake in globus pallidus slices (Maneuf et al. 1996) or substantia nigra synaptosomes (Romero et al. 1998a), and hence in the potentiation of GABAergic transmission. These observations are concordant with the finding by Gueudet et al. (1995) that the blockade of CB_1 receptors in striatal projection neurons with SR141716 reduced inhibitory GABAergic tone, thereby allowing the firing of nigrostriatal dopaminergic neurons. The authors concluded that endocannabinoid transmission might increase the action of striatal GABAergic neurons in the substantia nigra, producing a decrease of the stimulation of nigral dopaminergic neurons (Gueudet et al. 1995). However, other studies have reported opposite effects. Thus, Tersigni and Rosenberg (1996) reported an increase by cannabinoids in the activity of nigral neurons without any alteration of GABAergic activity. Other authors have observed inhibition rather than stimulation of GABAergic neurons by cannabinoid agonists via a presynaptic action in the substantia nigra (Chan et al. 1998) or the striatum (Szabo et al. 1998). Therefore, further studies will be required to elucidate the complex interaction of cannabinoids with GABAergic transmission in the basal ganglia.

1.2.2 Glutamate

Cannabinoids may also exert a direct action on glutamate-releasing neurons in the basal ganglia due to the location of CB_1 receptors in subthalamonigral glutamatergic neurons (Mailleux and Vanderhaeghen 1992a; see Fig. 1). This has been demonstrated in a series of electrophysiological studies showing a modification by cannabinoid agonists of the activity of pallidal and nigral neurons, which was exerted by inhibiting glutamate release from subthalamonigral terminals (Sañudo-Peña and Walker 1997; Szabo et al. 2000). The involvement of CB_1 receptors in these effects seems very likely, since they were reversed by SR141716 (Sañudo-Peña et al. 1999; Szabo et al. 2000). In behavioral studies, reductions in motor activity have been observed that probably resulted from a glutamate-lowering effect of cannabinoids (Miller et al. 1998). In addition, a recent electrophysiological study by Gerdeman and Lovinger (2001) demonstrated that cannabinoids were also able to inhibit glutamate release from afferent terminals in the striatum, this effect being also blocked by SR141716. This points to the possibility that CB_1 receptors are also located in cortical afferents projecting to the caudate-putamen which are glutamatergic. In contrast, Herkenham et al. (1991b) found that excitotoxic lesions of the striatum led to an almost complete disappearance of CB_1 receptors. Therefore, it remains to be demonstrated whether the inhibitory effect of cannabinoids on striatal glutamate release is caused by the activation of CB_1 receptors located presynaptically on afferent terminals in the striatum, or whether it is an indirect effect mediated by CB_1 receptors that are located elsewhere.

1.2.3 Dopamine

Dopamine transmission is also affected by cannabinoids in the basal ganglia circuitry, as revealed by the findings that cannabinoids potentiated reserpine-induced hypokinesia (Moss et al. 1981), while reducing amphetamine-induced hyperactivity (Gorriti et al. 1999). Despite the lack of selectivity of reserpine and amphetamine, it appears likely that both acted in the basal ganglia circuitry to modulate dopaminergic transmission. There is also evidence from several neurochemical studies that cannabinoids reduce the activity of nigrostriatal dopaminergic neurons (Romero et al. 1995a,b; Cadogan et al. 1997; see Romero et al. 2002; van der Stelt and Di Marzo 2003 for recent reviews), an effect that is consistent with the ability of cannabinoid receptor agonists to produce hypokinesia. However, in other studies cannabinoids have been found to increase rather than decrease dopaminergic transmission (Sakurai-Yamashita et al. 1989; see also Romero et al. 2002; van der Stelt and Di Marzo 2003 for recent reviews).

We have reported that anandamide and AM404 reduced the activity of tyrosine hydroxylase in the caudate-putamen and the substantia nigra (Romero et al. 1995a,b; González et al. 1999). However, these effects were small and transient possibly because CB_1 receptors are not located on nigrostriatal dopaminergic neurons

(Herkenham et al. 1991b). In concordance with this idea, cannabinoid agonists and antagonists failed to inhibit electrically evoked dopamine release in the striatum (Szabo et al. 1999), although the matter has still to be clarified, since other studies have shown opposite effects of cannabinoids on striatal dopamine release in vitro (increases rather than decreases) (see van der Stelt and Di Marzo 2003 for details). The absence of CB_1 receptors from nigrostriatal dopaminergic neurons would support the hypothesis that the changes in the activity of these neurons produced by classical cannabinoids in vivo were caused indirectly through an effect on GABAergic transmission (Maneuf et al. 1996; Romero et al. 1998a). However, two additional mechanisms are also possible. First, CB_1 receptors might interact with D_1 or D_2 dopaminergic receptors at the level of G protein/adenylyl cyclase signal transduction mechanisms (Giuffrida et al. 1999; Meschler and Howlett 2001), since they colocalize in striatal projection neurons (Herkenham et al. 1991b). Second, certain cannabinoid agonists, such as anandamide and some analogs, but not classical cannabinoids, would be able to directly influence dopaminergic transmission through the activation of vanilloid VR1 receptors, which have been detected in nigrostriatal dopaminergic neurons (Mezey et al. 2000; see Fig. 1). In support of this, we have recently reported that the hypokinetic action and the dopamine-lowering effect of anandamide were both reversed by capsazepine, an antagonist of VR1 receptors, and, more importantly, we have found a direct effect of anandamide on dopamine release in vitro, an effect that was also reversed by capsazepine (de Lago et al. 2004b). Classical cannabinoids, such as Δ^9-THC, that do not bind to vanilloid-like receptors were not able to produce this effect (de Lago et al. 2004b). This is in concordance with the observation that anandamide reduced dopamine release from striatal slices (Cadogan et al. 1997), although these authors also found a dopamine-lowering effect after application of the classical cannabinoid CP 55,940 (Cadogan et al. 1997).

1.3 Presence of Elements of the Endocannabinoid System in Motor Regions

Several studies have addressed the identification and quantification of diverse elements of the endocannabinoid signaling system in the basal ganglia, as a way to establish the importance of the role played by this system in the control of motor function (for a review see Romero et al. 2002). Most of the studies focused on cannabinoid receptors, mainly the CB_1 subtype and more recently the functionally related receptor subtype, VR1, but some studies have dealt with other key proteins of the endocannabinoid system (for review see Romero et al. 2002).

1.3.1 Cannabinoid and Vanilloid Receptors

Autoradiographic studies have demonstrated conclusively that the basal ganglia are among the brain structures containing the highest levels of both binding sites

and mRNA expression for the CB_1 receptor (for a review see Romero et al. 2002). In particular, the three nuclei that receive striatal efferent outputs (globus pallidus, entopeduncular nucleus, and substantia nigra pars reticulata), contain high levels of cannabinoid receptor binding sites (Herkenham et al. 1991a), whereas CB_1 receptor-mRNA transcripts are present in the caudate-putamen, which lacks striatal outflow nuclei (Mailleux and Vanderhaeghen 1992a). This observation is compatible with the idea that CB_1 receptors are presynaptically located in striatal projection neurons (see Fig. 1), a notion that has been supported by a series of anatomical studies in which specific neuronal subpopulations in the basal ganglia were lesioned (Herkenham et al. 1991b), and, more recently, by analysis of the cellular distribution of this receptor subtype in the basal ganglia using immunohistochemical techniques (Tsou et al. 1998a). CB_1 receptors are located in both striatonigral (the so-called "direct" striatal efferent pathway) and striatopallidal (the so-called "indirect" striatal efferent pathway) projection neurons, which use GABA as a neurotransmitter. In both pathways, CB_1 receptors are co-expressed with other markers, such as glutamic acid decarboxylase, prodynorphin, substance P, or proenkephalin, as well as D_1 or D_2 dopaminergic receptors (Hohmann and Herkenham 2000). In contrast, intrinsic striatal neurons, that contain somatostatin or acetylcholine, do not contain CB_1 receptors (Hohmann and Herkenham 2000). Another subpopulation of CB_1 receptors in the basal ganglia is located on subthalamopallidal and/or subthalamonigral glutamatergic terminals (see Fig. 1), as revealed by the presence of measurable levels of mRNA for this receptor in the subthalamic nucleus, together with the absence of detectable levels of cannabinoid receptor binding in that structure (Mailleux and Vanderhaeghen 1992a). Finally, CB_1 receptors are also located in GABAergic and glutamatergic neurons in the cerebellum, another brain structure involved in motor function (Herkenham et al. 1991a). These neurons are most likely associated with the effects of cannabinoids on posture and balance (Consroe 1998), although the neurochemical basis for these effects has been poorly explored (see Iversen 2003 for review).

These anatomical data reinforce the notion that CB_1 receptors play an important role in the mediation of motor effects of cannabinoid agonists, an idea that is supported by results obtained when studying motor function in mice deficient in CB_1 receptor gene expression (Ledent et al. 1999; Zimmer et al. 1999). These knockout mice exhibited significant motor disturbances, although the two models developed so far have yielded conflicting results, since a trend to hyperlocomotion was observed in one of these two models (Ledent et al. 1999) and hypoactivity was evident in the other (Zimmer et al. 1999).

CB_2 receptors are not present in motor regions in basal conditions, except in the cerebellum where Nuñez et al. (2004) recently demonstrated immunoreactivity for this receptor subtype in perivascular microglial cells of healthy human brains, but not in rat brain. This is concordant with previous data published by Skaper et al. (1996) working with mouse cerebellar cultures, and suggests that this receptor subtype might play a role in various cerebellar processes in normal conditions, although it most likely takes on a more important role when a neurodegenerative event takes place. Thus, recent studies have demonstrated that CB_2 receptors are significantly induced in different brain structures, including the basal ganglia, in

response to different types of insults, including injury or inflammation (Benito et al. 2003; Aroyo et al. 2005). In these conditions, they are possibly located in glial cells (activated astrocytes, reactive microglia) rather than in neurons, playing a role in events related to the protective and/or cytotoxic influences that the different glial cells exert on neuronal survival (see Chen and Swanson 2003 for a review).

Finally, we must also mention the importance of the recent report of vanilloid VR1 receptors in the basal ganglia (Mezey et al. 2000). These receptors are molecular integrators of nociceptive stimuli, abundant on sensory neurons, but they have also been located in the basal ganglia circuitry colocalized with tyrosine hydroxylase, which means that they are located in nigrostriatal dopaminergic neurons (Mezey et al. 2000; see Fig. 1). As mentioned above, recent pharmacological and neurochemical studies have established the involvement of these receptors in the control of motor function (Di Marzo et al. 2001) and in the production of motor effects by certain cannabinoid receptor agonists (de Lago et al. 2004b).

1.3.2
Endocannabinoid Ligands

Endogenous cannabinoid receptor ligands, anandamide and 2-arachidonoylglycerol, are also present in the basal ganglia (Bisogno et al. 1999; Di Marzo et al. 2000a) in concentrations that are in general higher than those measured in the whole brain.

Two key regions involved in the control of movement, the globus pallidus and the substantia nigra, contain not only the highest densities of CB_1 receptors in the brain (Herkenham et al. 1991a) but also the highest levels of endocannabinoids, particularly of anandamide (Di Marzo et al. 2000a). The phenotype of the nerve cells that produce endocannabinoids in the basal ganglia is presently unknown, although the precursor of anandamide, *N*-arachidonoylphosphatidylethanolamine, has been found in the basal ganglia (Di Marzo et al. 2000b), which supports the existence of in situ synthesis for this endocannabinoid. The synthesis of anandamide seems sensitive to dopamine. Thus, Giuffrida et al. (1999) reported that, in the striatum, it is regulated by dopaminergic D_2 receptors, which was interpreted by these authors as an indication that the endocannabinoid system serves as an inhibitory feedback mechanism that counteracts dopamine-induced facilitation of psychomotor activity (Giuffrida et al. 1999).

1.3.3
Endocannabinoid Inactivation

Despite the fact that the endocannabinoid transporter has not yet been isolated or cloned, a situation that has led to some controversy about its existence (Glaser et al. 2003), there are several anandamide analogs that behave in vitro as endocannabinoid transport inhibitors (Giuffrida et al. 2001) and that, in vivo, produce significant effects on motor function (for review see Fernández-Ruiz et al. 2002).

These include compounds such as AM404 (González et al. 1999; Beltramo et al. 2000), VDM11 (de Lago et al. 2004a), and UCM707 (de Lago et al. 2002). Based on this pharmacological evidence, it is to be expected that the transporter for endocannabinoids is abundantly concentrated in the basal ganglia and other motor regions.

Fatty acid amide hydrolase (FAAH), the enzyme involved in the degradation of anandamide, is also present in high levels in all regions of the basal ganglia, in particular in the globus pallidus and the substantia nigra (Desarnaud et al. 1995; Tsou et al. 1998b). As to monoacylglycerol-lipase, the enzyme involved in the degradation of the other important endocannabinoid, 2-arachidonoylglycerol, this has also been detected in the basal ganglia and, to a greater extent, in the cerebellum (see Dinh et al. 2002 for a review). However, these enzymes accept as substrates various *N*-acylethanolamines or mono-acylglycerols, respectively, and so lack the specificity that would allow them to be used as selective markers of endocannabinoid transmission.

2
Potential Therapeutic Applications of Cannabinoids in Motor Disorders

From what has been stated above, it can be hypothesized that compounds affecting endocannabinoid transmission might be useful for reducing motor deterioration in both hyper- and hypokinetic disorders (for reviews see Consroe 1998; Müller-Vahl et al. 1999c; Fernández-Ruiz et al. 2002). To date, much research has been directed at the search for compounds able to alleviate motor symptoms in these disorders (see Fernández-Ruiz et al. 2002; van der Stelt and Di Marzo 2003), but evidence has also been obtained that cannabinoid-related compounds might be neuroprotectant substances (Grundy 2002; Romero et al. 2002). In this chapter, we review the evidence supporting the first of these potential clinical applications, because the potential of cannabinoids to influence cell viability is addressed in another chapter of this book (see contribution by Guzmán).

2.1
General Aspects

Senescence is a physiological process, characterized, in part, by a slow but progressive impairment of motor function, but with no evident signs of a disease state (Schut 1998). This correlates with a decrease in the activity of most of the neurotransmitters acting in the basal ganglia, particularly dopamine and GABA (for a review see Francis et al. 1993). Endocannabinoid transmission is also influenced by normal senescence, since the population of CB_1 receptors was reduced in the basal ganglia of aged rats with no signs of neurological disease (Mailleux and Vanderhaeghen 1992b; Romero et al. 1998b). However, the changes observed in CB_1 receptors in the postmortem basal ganglia of humans affected by several neurodegenerative motor diseases, as well as in animal models of these disorders, are much more dramatic (for reviews see Fernández-Ruiz et al. 2002; Lastres-

Becker et al. 2003b). Among these disorders, PD and HD are the two diseases directly related to the control of movement that have attracted most interest in terms of a potential application of cannabinoids for both alleviation of symptoms and delay/arrest of neurodegeneration (for a review see Fernández-Ruiz et al. 2002). Another interesting motor disorder in which cannabinoids might be effective is Gilles de la Tourette's syndrome (Müller-Vahl 2003 for a review). Finally, together with these classic motor disorders, other diseases not directly related to the control of movement in origin but exhibiting strong motor symptoms, such as Alzheimer's disease (Pazos et al. 2004 for a review) or multiple sclerosis (Baker and Pryce 2003 for a review), have also been examined as potential therapeutic targets for cannabinoid-based compounds.

2.2 Huntington's Disease

HD is an inherited neurodegenerative disorder caused by an unstable expansion of a CAG repeat in exon 1 of the human huntingtin gene. Translation through the CAG span results in a polyglutamine tract near the N-terminus of this protein, which leads to toxicity predominantly of striatal projection neurons (for a recent review see Cattaneo et al. 2001). The symptoms of this disease are primarily characterized by motor disturbances, such as chorea and dystonia, a consequence of the progressive degeneration of the striatum due to the selective death of striatal projection neurons (Berardelli et al. 1999). Secondarily, patients are also affected by cognitive decline (Reddy et al. 1999).

2.2.1 Changes in Endocannabinoid Transmission

Studies in postmortem human tissue have clearly demonstrated that, in HD, there is an almost complete disappearance of CB_1 receptors in the substantia nigra, in the lateral part of the globus pallidus and, to a lesser extent, in the putamen (Glass et al. 1993, 2000; Richfield and Herkenham 1994). This loss of CB_1 receptors is concordant with the characteristic neuronal loss observed in HD that predominantly affects medium-spiny GABAergic neurons, which contain the major population of CB_1 receptors present in basal ganglia structures (Herkenham et al. 1991b; Hohmann and Herkenham 2000). It is also consistent with the finding that other phenotypic markers for these neurons, such as substance P, enkephalin, calcineurin, calbindin, and receptors for neurotransmitters, such as adenosine or dopamine, are also depleted in HD (Hersch and Ferrante 1997). However, recent experiments have revealed that the reduction of CB_1 receptors occurs in advance of other receptor losses and even before the appearance of major HD symptomatology, when the incidence of cell death is still low (Glass et al. 2000). This suggests that losses of CB_1 receptors might be involved in the pathogenesis and/or progression of neurodegeneration in HD.

Studies with animal models of HD have validated the data obtained with post-mortem human tissues (see Lastres-Becker et al. 2003b for a review), and also indicate that these models may predominantly reflect partial aspects or specific phases of striatal degeneration. For instance, decreases of CB_1 receptors in the basal ganglia have also been found in various transgenic mouse models that express mutated forms of the human huntingtin gene (Denovan-Wright and Robertson 2000; Lastres-Becker et al. 2002c). In these genetic models, cell dysfunction rather than cell death is the major change that takes place, so the observation of reduced CB_1 receptors in these animals might be equivalent to the reductions of these receptors reported by Glass et al. (2000) in early stages of the human disease. CB_1 receptors were reduced to a greater extent in rat models of HD generated by selective lesions of striato-efferent GABAergic neurons caused by mitochondrial or excitotoxic toxins (Page et al. 2000; Lastres-Becker et al. 2001b, 2002a,b). These toxins, in particular 3-nitropropionic acid, reproduce in animals the same changes that have been proposed to be associated with the human disease, i.e., failure of energy metabolism, glutamate excitotoxicity, and, to a lesser extent, oxidative stress, leading to progressive neuronal death (for reviews see Alexi et al. 1998; Brouillet et al. 1999). However, they are more representative of the pattern of profound neuronal loss that occurs in advanced states of the human disease (Brouillet et al. 1999). In these conditions, the losses of CB_1 receptors might be a mere side effect caused by the progressive and selective destruction of striatal GABAergic projection neurons, neurons on which these receptors are located. In this rat model, the losses of CB_1 receptors were accompanied by a decrease in the content of both anandamide and 2-arachidonoylglycerol in the caudate-putamen (Lastres-Becker et al. 2001b). Therefore, all the data collected from humans and from animal models indicate that endocannabinoid transmission becomes progressively hypofunctional in the basal ganglia in HD. This might contribute to some extent to the hyperkinesia typical of this disorder and so support a therapeutic usefulness of cannabinoid agonists for alleviating motor deterioration, as will be described below.

2.2.2 Therapeutic Usefulness of Cannabinoids

Medicines used for the treatment of HD include mainly antidopaminergic drugs to reduce the hyperkinesia characteristic of the first phases of the disease (Factor and Firedman 1997) and antiglutamatergic agents to reduce excitotoxicity (Kieburtz 1999). However, the outcome of both strategies has been poor in terms of improving quality of life for HD patients, despite the progress in the elucidation of molecular events involved in the pathogenesis of HD (Cattaneo et al. 2001). In this context, cannabinoid agonists might be a reasonable alternative, since they combine both antihyperkinetic and neuroprotective effects (for review see Fernández-Ruiz et al. 2002; Lastres-Becker et al. 2003b). As mentioned above, we will not address here the neuroprotective potential of cannabinoids in HD, because this has been addressed in the chapter by Guzmán (this volume), but we will address the potential antihyperkinetic action of substances that can elevate endocannabinoid activity in

Table 2. Potential therapeutic effects of cannabinoid-related compounds in basal ganglia disorders (*continued on next page*)

Compound	Disease	Therapeutic application
Plant-derived cannabinoids		
$\triangle^9$-THC	Huntington's disease	Reduction of striatal injury in 3NP rat model (Lastres-Becker et al. 2004b)
		Divergent effects on striatal injury in the malonate rat model (Lastres-Becker et al. 2003c; Aroyo et al. 2005)
	Parkinson's disease	Reduction of dopaminergic injury in the 6-hydroxydopamine rat model (Lastres-Becker et al. 2004a)
		Failure to alleviate symptoms in PD patients (reviewed by Consroe 1998)
	Tourette's syndrome	Reduction of tics and obsessive-compulsive behaviors (reviewed by Müller-Vahl 2003)
Cannabidiol	Huntington's disease	Failure to reduce hyperkinetic movements in HD patients (reviewed by Consroe 1998)
		Poor neuroprotective action in the malonate rat model (Aroyo et al. 2005)
	Parkinson's disease	Reduction of dopaminergic injury in the 6-hydroxydopamine rat model (Lastres-Becker et al. 2004a)
Synthetic cannabinoids		
CP 55,940	Huntington's disease	Certain antihyperkinetic activity in 3NP-lesioned rats (Lastres-Becker et al. 2003a)
	Parkinson's disease	Potential reduction of tremor by reducing the overactivity of the subthalamic nucleus in the 6-hydroxydopamine rat model (Sañudo-Peña et al. 1998)
Nabilone	Huntington's disease	Increase of hyperkinesia (choreic movements) in HD patients (Müller-Vahl et al. 1999b)
	Parkinson's disease	Reduction of L-dopa-induced dyskinesia in PD patients (Sieradzan et al. 2001)
	Dystonia	No effects in patients with generalized and segmental primary dystonia (Fox et al. 2002b)
WIN 55,212-2	Parkinson's disease	Reduction of L-dopa-induced dyskinesia in rat models of PD (Segovia et al. 2003; Ferrer et al. 2003)
	Dystonia	Antidystonic effects in mutant dystonic hamsters (Richter and Löscher 1994, 2002)
HU308	Huntington's disease	Reduction of GABAergic injury in the malonate rat model; reversed by SR144528 (Aroyo et al. 2005)
Endogenous cannabinoids		
Anandamide	Huntington's disease	Certain antihyperkinetic activity in 3NP-lesioned rats (possibly VR1-mediated effect) (Lastres-Becker et al. 2002a)

Table 2. (*continued*)

Compound	Disease	Therapeutic application
Inhibitors of endocannabinoid inactivation		
AM404	Huntington's disease	Antihyperkinetic activity and recovery from neurochemical deficits in 3NP-lesioned rats (involvement of VR1 receptors) (Lastres-Becker et al. 2002a, 2003a)
	Parkinson's disease	Unable to reduce L-dopa-induced dyskinesia in the reserpine rat model (Segovia et al. 2003)
VDM11	Huntington's disease	Not effective in 3NP-lesioned rats (Lastres-Becker et al. 2003a)
UCM707	Huntington's disease	Certain antihyperkinetic activity in 3NP-lesioned rats (de Lago et al. 2004c)
AM374	Huntington's disease	Not effective in 3NP-lesioned rats (Lastres-Becker et al. 2003a)
Receptor antagonists		
SR141716 (CB1)	Huntington's disease	Increased striatal damage in the malonate rat model (Lastres-Becker et al. 2003c) Unable to reverse antihyperkinetic effects of AM404 in 3NP-lesioned rats (Lastres-Becker et al. 2003a) Unable to reduce late akinesia in 3NP-lesioned rats (Lastres-Becker et al. 2002b)
	Parkinson's disease	Effective to reduce L-dopa-induced dyskinesia in MPTP-treated marmosets and the reserpine rat model (Brotchie 1998, 2000; Segovia et al. 2003) Unable to reverse bradykinesia and rigidity in MPTP-treated primates (Meschler et al. 2001) Able to restore locomotion in the reserpine model of PD (Di Marzo et al. 2000a)
SR144528 (CB2)	Huntington's disease	Able to reverse neuroprotective effect of HU308 in the malonate rat model (Aroyo et al. 2005)
Capsazepine (VR1)	Huntington's disease	Able to reverse antihyperkinetic effects of AM404 in 3NP-lesioned rats (Lastres-Becker et al. 2003a)

3NP, 3-nitropropionic acid; HD, Huntington's disease; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease.

the basal ganglia. Thus, we have recently demonstrated that the endocannabinoid transporter inhibitor AM404 was able to reduce hyperkinesia and induce recovery from GABAergic and dopaminergic deficits in rats with striatal lesions caused by local application of 3-nitropropionic acid (Lastres-Becker et al. 2002a, 2003a), while direct agonists of CB_1 receptors, such as CP 55,940, only produced very modest effects (Lastres-Becker et al. 2003a). AM404 was also able to normalize motor activity in genetically hyperactive rats without causing overt cannabimimetic effects (Beltramo et al. 2000). However, in view of the fact that a progressive decrease of CB_1 receptors has been recorded in this disease, the efficacy of this compound might a priori be extended only to the early or intermediate hyperkinetic phases, when cell death is still moderate, but not to the late akinetic stages of the disease characterized by high neuronal death (see Lastres-Becker et al. 2003b for a review). These results, however, contrast with some clinical data that indicate that the administration of plant-derived cannabinoids (Consroe 1998), or some of their synthetic analogs (Müller-Vahl et al. 1999b), increased choreic movements in HD patients. It is possible that this is related to the lack of VR1 receptor activity of these cannabinoid agonists, since recent studies carried out in our laboratory (see details in Table 2) in rats with striatal lesions have revealed that only those cannabinoid-based compounds having an additional profile as VR1 receptor agonists were really effective in alleviating hyperkinetic signs (Lastres-Becker et al. 2003a). This was so for AM404, which, in addition to its ability to block the endocannabinoid transporter, also exhibits affinity for the VR1 receptor (Zygmunt et al. 2000). Interestingly, inhibitors of endocannabinoid inactivation that are not active at the VR1 receptor, such as VDM11 or AM374, did not have any antihyperkinetic action in HD rats (Lastres-Becker et al. 2003a), whereas UCM707, the most potent inhibitor to date, only produced modest effects (de Lago et al. 2004c) (see Table 2). Therefore, our data suggest that VR1 receptors alone, or better in combination with CB_1 receptors, might represent novel targets through which the hyperkinetic symptoms of HD could be alleviated. Possibly, the best option might be to develop "hybrid" compounds with the dual capability of activating both VR1 and CB_1 receptors, although the relative contribution made by each of these targets is likely to change during the course of the disease due to a progressive loss of CB_1 receptors without any concomitant loss of VR1 receptors (see Lastres-Becker et al. 2003b for a review).

2.3 Parkinson's Disease

PD is a progressive neurodegenerative disorder in which the capacity of executing voluntary movements is lost gradually. The major clinical symptomatology in PD includes tremor, rigidity, and bradykinesia (slowness of movement). The pathological hallmark of this disease is the degeneration of melanin-containing dopaminergic neurons of the substantia nigra pars compacta that leads to severe dopaminergic denervation of the striatum (for a recent review see Blandini et al. 2000).

2.3.1 Changes in the Endocannabinoid Transmission

Compared with HD, much less data exist on the status of CB_1 receptors in the postmortem basal ganglia of humans affected by PD. Only recently we have found that CB_1 receptor binding and the activation of G proteins by cannabinoid agonists were significantly increased in the basal ganglia as a consequence of the selective degeneration of nigrostriatal dopaminergic neurons (Lastres-Becker et al. 2001a). These increases were not related to the chronic dopaminergic replacement therapy with L-dopa that these patients were undergoing, since they were also seen in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated marmosets, a primate PD model, and disappeared after chronic L-dopa administration in these animals (Lastres-Becker et al. 2001a). It has also been found that endocannabinoid levels increase in a rat model of PD and that this increase can be reversed by L-dopa (Gubellini et al. 2002; Macarrone et al. 2003). This suggests the existence of an imbalance between dopamine and endocannabinoids in the basal ganglia in PD (see Fernández-Ruiz et al. 2002 for a review).

As in HD, a change in CB_1 receptor density might also be an early event in the pathogenesis of PD. This is supported by data obtained from individuals affected by incidental Lewy body disease, an early and presymptomatic phase of PD. These individuals, who did not receive any therapy as they presented Lewy bodies and a low degree of nigral pathology without any neurological symptoms, exhibited a trend towards an increase in CB_1 receptors in some basal ganglia structures (Lastres-Becker et al. 2001a). Moreover, preliminary experiments with a genetic model of PD, the parkin-2 knockout mouse (Itier et al. 2003), have yielded data showing an increase in CB_1 receptor binding in the substantia nigra of the knockout mice that occurs in the absence of neuronal death (González S, Lastres-Becker I, Ramos JA, Fernández-Ruiz J, unpublished results).

Overactivity of endocannabinoid transmission (as measured by increases in CB_1 receptor or endocannabinoid levels) has also been observed in the basal ganglia in different rat models of PD (Mailleux and Vanderhaeghen 1993; Romero et al. 2000; Di Marzo et al. 2000a; Gubellini et al. 2002), although the data are not consistent, with some authors reporting no changes (Herkenham et al. 1991b), reductions in CB_1 receptor levels (Silverdale et al 2001), or a dependency on chronic L-dopa co-treatment (Zeng et al. 1999). Despite these conflicts, we consider that most of the data indicate that endocannabinoid transmission becomes overactive in the basal ganglia in PD, a conclusion that is compatible with the hypokinesia that characterizes this disease. This would also support the suggestion that CB_1 receptor antagonists, rather than agonists, might be useful for alleviating motor deterioration in PD, or for reducing the development of dyskinesia caused by prolonged replacement therapy with L-dopa (Brotchie 2000).

2.3.2
Therapeutic Usefulness of Cannabinoids

Dopaminergic replacement therapy represents a useful remedy for rigidity and bradykinesia in PD patients (Carlsson 2002), at least in the early and middle phases of this disease. Later on, the chronic use of L-dopa therapy results in a loss of efficacy and even in the appearance of an irreversible dyskinetic state. Cannabinoid-based compounds might also be useful in PD. In this disorder, CB_1 receptor agonists or antagonists have both been proposed, for their use alone or as coadjuvants, against different signs of the complex motor pathology developed by PD patients (Brotchie 2000; Romero et al. 2000; Di Marzo et al. 2000a; Lastres-Becker et al. 2001a; Fox et al. 2002a; see Table 2). For instance, it has been reported that CB_1 receptor agonists: (1) are able to interact with dopaminergic agonists to improve motor impairments (Anderson et al. 1995; Maneuf et al. 1997; Brotchie 1998; Sañudo-Peña et al. 1998), (2) reduce tremor associated with an overactivity of the subthalamic nucleus (Sañudo-Peña et al. 1998, 1999), and (3) decrease and/or delay the occurrence of dyskinesia associated with long-term dopaminergic replacement (Sierazdan et al. 2001). Cannabinoids, particularly classical cannabinoids with antioxidant properties, have also been reported to provide protection against dopaminergic cell death (Lastres-Becker et al. 2004a; see Table 2).

However, because of the hypokinetic profile of cannabinoid agonists, it is unlikely that these compounds would be useful for alleviating bradykinesia in PD patients. This is confirmed by results obtained with humans or with MPTP-lesioned primates, as these indicated that the administration of plant-derived cannabinoid receptor agonists enhanced motor disability (for reviews see Consroe 1998; Müller-Vahl et al. 1999c). Indeed, it has been proposed that the blockade of CB_1 receptors may be a better strategy for reducing both bradykinesia (see Fernández-Ruiz et al. 2002 for review) and L-dopa-induced dyskinesia (Brotchie 2000, 2003) (see Table 2 for details). In support of this possibility, dysfunction of nigrostriatal dopaminergic neurons is associated with an overactivity of endocannabinoid transmission in the basal ganglia. Such overactivity has been observed after administration of reserpine (Di Marzo et al. 2000a) or dopaminergic antagonists (Mailleux and Vanderhaeghen 1993), or during degeneration of these neurons caused by the local application of 6-hydroxydopamine (Mailleux and Vanderhaeghen 1993; Romero et al. 2000; Gubellini et al. 2002; Fernández-Espejo et al. 2004) or MPTP (Lastres-Becker et al. 2001a). In theory, CB_1 receptor blockade would avoid the excessive inhibition of GABA uptake produced by the increased activation of CB_1 receptors in striatal projection neurons (Maneuf et al. 1996; Romero et al. 1998a), thus allowing a faster removal of this inhibitory neurotransmitter from the synaptic cleft, which would reduce hypokinesia. Despite this evidence, the first pharmacological studies that have examined the capability of rimonabant (SR141716) to reduce hypokinesia in animal models of PD have yielded conflicting resulted (Di Marzo et al. 2000a; Meschler et al. 2001; see Table 2 for more details). It is possible that the blockade of CB_1 receptors might be effective only at very advanced phases of the disease. Indeed, recent evidence obtained by Fernández-Espejo and coworkers (2004) is in favor of this option, which presents an additional advantage since it would make it

possible to give an antiparkinsonian compound at a stage of the disease at which classic dopaminergic therapy generally fails. In addition, in view of the recently demonstrated role of VR1 receptors in the regulation of dopamine release from nigral neurons (de Lago et al. 2004b), the potential of VR1 receptor ligands for the treatment of hypokinetic signs of this disease must also be considered.

2.4 Other Motor Disorders

To our knowledge, no data exist on the role(s) of cannabinoid receptors in other basal ganglia disorders in the human, such as tardive dyskinesia, Gilles de la Tourette's syndrome, dystonia, and others. Even so, cannabinoids might be of interest for the treatment of at least some of these diseases (for reviews see Consroe 1998; Fernández-Ruiz et al. 2002; Table 2 for more details). Thus, a relationship between cannabis use and the incidence of tardive dyskinesia has been described in psychiatric patients that were being chronically treated with neuroleptic drugs (Zarestky et al. 1993). A few studies have also addressed this issue for dystonia in humans (Fox et al. 2002b) or animal models (Richter and Löscher 1994, 2002), by demonstrating that cannabinoids have antidystonic effects (for reviews see Consroe 1998; Müller-Vahl et al. 1999c). In addition, plant-derived cannabinoids might have the potential to reduce tics and also to improve behavioral problems in patients with Tourette's syndrome (Hemming and Yellowlees 1993; Consroe 1998; Müller-Vahl et al. 1998, 1999a, 2002; for review see Müller-Vahl 2003). However, there are no data on the status of endocannabinoid signaling in patients or in animal models of this disease, and also no information on the neurochemical pathways mediating the beneficial effects of cannabinoids.

Another relevant disease in which cannabinoids might improve motor deterioration is multiple sclerosis. This is a disease of immune origin, but it progresses with neurological deterioration that affects mainly the motor system. Studies in laboratory animals have convincingly demonstrated that both direct and indirect cannabinoid receptor agonists are useful in this disease, in particular for the management of motor-related symptoms such as spasticity, tremor, dystonia, and others (for reviews see Pertwee 2002; Baker and Pryce 2003). These effects seem to be mediated by CB_1 and, to a lesser extent, CB_2 receptors (Baker et al. 2000). This pharmacological evidence explains previous anecdotal, uncontrolled, or preclinical data that suggested a beneficial effect of marijuana when smoked by multiple sclerosis patients to alleviate some of their symptoms, mainly spasticity and pain (for review see Consroe 1998). In line with these data, a clinical trial, recently completed in the UK, has demonstrated that although cannabis and Δ^9-THC did not have a beneficial effect on spasticity when this was measured objectively, these drugs did increase the patients' perception of improvement of different symptoms of this disease (Zajicek et al. 2003).

In contrast with the numerous pharmacological studies in this area of research, there are no data on possible changes in CB_1 and CB_2 receptors in the postmortem brains of patients with multiple sclerosis, and only a few studies have examined the

status of endocannabinoid transmission in animal models of this disease (Baker et al. 2001; Berrendero et al. 2001). Using a rat model of multiple sclerosis, we recently reported a decrease in central CB_1 receptors (Berrendero et al. 2001). This decrease was restricted to basal ganglia structures, which is consistent with the fact that motor deterioration is one of the most prominent neurological signs in these rats and also in the human disease (for review see Baker and Pryce 2003). This decrease was accompanied by a reduction in endocannabinoid levels that also occurred in brain structures other than the basal ganglia (Cabranes et al. 2005). This finding led us to hypothesize that the changes in CB_1 receptors and their ligands in the basal ganglia might be associated with disturbances in several neurotransmitter systems. If this were the case, it follows that the well-known effects of cannabinoid agonists on these systems might underlie their ability to ameliorate the motor symptoms of multiple sclerosis (see Fernández-Ruiz et al. 2002 for review). However, there is no support for this hypothesis. Thus, although we have detected reductions in CB_1 receptors (Berrendero et al. 2001) and endocannabinoid levels (Cabranes et al. 2005) in the basal ganglia of the lesioned rats, we were unable to detect any changes in dopamine, serotonin, GABA, or glutamate. Because of this finding, we recently tested the effects of various inhibitors of endocannabinoid transport that are capable of elevating endocannabinoid levels. We found that although these inhibitors were able to reduce the neurological decline typically exhibited by the lesioned rats, this reduction seemed to depend on the activation of VR1 receptors (Cabranes et al. 2005).

One other disorder worthy of mention is Alzheimer's disease, which, like multiple sclerosis, is not a disorder of the basal ganglia, and yet frequently gives rise to extrapyramidal signs and symptoms that are possibly caused by the degeneration of glutamatergic cortical afferents to the caudate-putamen (for review see Kurlan et al. 2000). Studies in postmortem brain regions of patients affected by this disease have revealed a significant loss of CB_1 receptors in the basal ganglia (Westlake et al. 1994). However, it is important to remark that the authors considered that their results related more to old age than to an effect selectively associated with the pathology characteristic of Alzheimer's disease (Westlake et al. 1994). Also using postmortem tissue from Alzheimer's patients, Benito et al. (2003) reported the induction of CB_2 receptors in activated microglia that surround senile plaques. This would suggest a role of this receptor subtype in the pathogenesis of this disease and a therapeutic potential for compounds that selectively target this receptor (see recent studies by Milton 2002; Iuvone et al. 2004).

3 Concluding Remarks and Future Perspectives

The studies reviewed here are all concordant with the view that control of movement is a key function for endocannabinoid transmission. We have collected the pharmacological and biochemical evidence that supports this hypothesis. We have also shown that endocannabinoid transmission is altered in motor disorders, in parallel with changes in classic neurotransmitters such as GABA, dopamine, or

glutamate. This provides the basis for the development of novel pharmacotherapies with compounds selective for the different target proteins that form the endocannabinoid system. However, only a few studies have examined, hitherto, the potential contribution these compounds might make to the management of motor disorders in the clinic. The importance of this novel system demands further investigation and the development of novel promising compounds for the symptomatic and/or neuroprotectant treatment of basal ganglia pathology.

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