Review

Modeling dyskinesia in animal models of Parkinson disease

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ABSTRACT

The treatment of motor symptoms of Parkinson disease (PD) with the dopamine (DA) precursor, L-3,4-dihydroxyphenylalanine (L-DOPA) introduced 50 years ago still remains a very effective medication. However, involuntary movements termed L-DOPA-induced dyskinesias (LID) appear in the vast majority of PD patients after chronic treatment and may become disabling. Once they appeared, the first dose after a several-weeks drug holiday will trigger them again, showing that L-DOPA has permanently or persistently modified the brain response to DA. LID are very difficult to manage and no drug is yet approved for dyskinesias, aside from a modest benefit with amantadine. New drugs are needed for PD to alleviate parkinsonian symptoms without inducing dyskinesias. Hence, animal models have been developed to seek the mechanisms involved in LID and new drug targets. The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was discovered as a contamination of a derivative of heroin taken by drug users and produced similar motor symptoms as idiopathic PD. Since then, MPTP is used extensively to model PD and LID in non-human primates and mice in addition to the classical PD model in rats with a 6-hydroxydopamine (6-OHDA) lesion. This article reviews rodent and non-human primate models of PD that reproduce motor complications induced by DA replacement therapy. Moreover, key biochemical changes in the brain of post-mortem PD patients with LID will be compared to those observed in animal models. Finally, the translational usefulness of drugs found to treat LID in animal models will be compared to their clinical activities.

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Abbreviations: 6-OHDA, 6-hydroxydopamine; AIMs, abnormal involuntary movements; AMPA, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid; DA, dopamine; DBS, deep brain stimulation; ERK1/2, extracellular signal-regulated kinase 1/2; GPe, external globus pallidus; GPi, internal globus pallidus; HFS, high frequency stimulation; L-DOPA, L-3,4-dihydroxyphenylalanine; LID, L-DOPA-induced dyskinesias; mGlu, metabotropic glutamate; MFB, medial forebrain bundle; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA, N-methyl-D-aspartate; PD, Parkinson disease; SNc, substantia nigra pars compacta; STN, subthalamic nucleus.

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**Introduction**

Parkinson disease (PD) is the most common neurodegenerative movement disorder and is likely to increase due to the aging population (Siderowf and Stern, 2003). PD involves principally the death of dopamine (DA) neurons in the substantia nigra pars compacta (SNc) but other neurotransmitters and neuromodulators are also affected.

Gene mutations in familial PD are reported but the cause for the majority of PD cases remains unknown (Olanow et al., 2009). There is currently no cure for PD. Neuroprotection or disease modification defined as an intervention that would protect or rescue vulnerable neurons, thereby slowing, stopping, or reversing disease progression, is not yet available for PD but laboratory studies are finding promising agents (Olanow et al., 2009).

Restoring deficient DA with its precursor L-3,4-dihydroxyphenylalanine (L-DOPA) is the most effective PD treatment, but remains a symptomatic treatment. Moreover, a majority of patients develop hard-to-manage abnormal involuntary movements called dyskinesias within the first 10 years of treatment (Mones et al., 1971; Olanow and Kollier, 1998). Motor fluctuations such as "wearing-off" are also common. Wearing-off is defined as a reduced duration of benefit from an individual L-DOPA dose and a recurrence of parkinsonian symptoms before the next normal dose of L-DOPA (Fahn et al., 2004).

Once dyskinesias appear, even if treatment is stopped for several weeks, the first dose will trigger them again, showing that L-DOPA has permanently or persistently modified the brain response to DA. Dopaminergic agonists have less potential to induce motor complications compared to L-DOPA but their symptomatic efficacy is generally inferior to L-DOPA (Olanow, 2004). Hence, most PD patients initiated with DA agonist monotherapy will eventually require L-DOPA as disease progresses and after 10–15 years their motor complications appear similar as would have if started initially on L-DOPA therapy (Katzenschläger et al., 2008; Parkinson Study Group, 2009). This suggests that disease progression plays the major role in the onset of dyskinesia rather than the type of dopaminergic drug treatment used.

No drug is yet available for dyskinesias, aside from a modest benefit with amantadine in some PD patients (Olanow et al., 2009).

Though investigated in numerous studies, the mechanisms involved in the occurrence of dyskinesias are still unknown. Moreover while L-DOPA and DA agonists, currently used in the pharmacological treatments of PD, are effective at reversing the motor symptoms of the disease little they do to combat the progressive underlying degeneration of DA neurons in the SNc.

Much emphasis has therefore been placed on finding alternative non-dopaminergic drugs that could circumvent some or all these problems. The design of novel agents to prevent dyskinesias requires elucidation of the adaptive changes produced in the parkinsonian brain by repeated administration of L-DOPA. An attractive strategy to treat L-DOPA-induced dyskinesias (LID) is to use adjunct drugs to modulate basal ganglia DA neurotransmission (Blanchet et al., 1999; Brotchie, 1998, 2003; Calon and Di Paolo, 2002; Grondon et al., 1999; Henry et al., 2001).

LID are typically observed at the peak of the effect of L-DOPA in PD patients. There is also diphasic dyskinesia at the beginning and at the end of the L-DOPA dosing cycle appearing with the rise and fall of DA levels in the brain (Luquin et al., 1992), and off-dystonia (Marsden et al., 1982). LID occur in 30–80% of PD patients treated with L-DOPA (Barbeau, 1980; Nutt, 1990). Two conditions are necessary for their appearance: 1) the loss of DA in the nigrostriatal pathway and 2) treatment with L-DOPA or DA agonists. Development of dyskinesias in man usually requires daily treatment for 3–5 years in idiopathic PD (Klawans et al., 1977) and for parkinsonism induced in man by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), it occurs after only weeks or months of treatment (Ballard et al., 1985). The same applies to MPTP monkeys where only weeks of L-DOPA therapy are enough before dyskinesias appear (Bedard et al., 1986; Falardau et al., 1988). MPTP primates respond to DA therapies in a similar manner than idiopathic PD patients (Jenner, 2003a,b) and are currently the best model for studying LID.

The rodent basal ganglia show some anatomical differences compared to the human and non-human primates. For instance, the caudate nucleus and putamen are the components of the striatum which are fused in rodents and undistinguishable, whereas they are separated by the internal capsule in primates (Martin and Bowden, 2000; Paxinos and Watson, 2007). Other structures of the basal ganglia also show species differences with an internal (GPI) and external (GPe) globus pallidus in primates compared to the structures termed entopeduncular nucleus and globus pallidus, respectively in rodents (Parent and Hazrati, 1995). Moreover, the segregation of the so-called direct (D1 receptor-related) and indirect (D2 receptor-related) pathways of the basal ganglia is well documented in rodents but their separation is less clear in primates (Parent et al., 2001). Hence, in primates both D1 and D2 receptor agonists can induce dyskinesias (Blanchet et al., 2004) whereas in rodents the contribution of the direct pathway with D1 receptors has been more associated with dyskinesias (Cenci et al., 2009). Nevertheless, the use of rodent models of PD and LID has clear advantages mainly their time- and cost-effectiveness.

Much remains to be learned from rodents and primates models of PD about the biochemical processes that underlie the development of dyskinesias, how dopaminergic and non-dopaminergic drugs can be used to avoid the initiation of dyskinesias in early PD, to prevent or inhibit their expression in later stages of the disease and to reverse the priming process through a normalization of the basal ganglia function. This review will present the current PD rodent and primate models to study dyskinesias with the associated behavioral and biochemical correlates. The translational values of the animal models will be discussed with salient examples of clinical results.

**Rodent models of L-DOPA-induced dyskinesias (LID)**

The 6-OHDA lesioned rat model

6-Hydroxydopamine (6-OHDA) is the oldest and the most widely used toxin animal model for PD and can induce degeneration of central monoamine neurons (Sachs and Jonsson, 1975; Ungerstedt, 1968). 6-OHDA has to be injected stereotactically in the brain since, unlike MPTP, it fails to cross the blood–brain barrier. This toxin can be delivered in various regions along the nigrostriatal tract, including the medial forebrain bundle (MFB), directly in the SNc or in the striatum resulting in an important decrease in DA in the ipsilateral striatum (Cenci et al., 2002; Schwarting and Huston, 1996; Ungerstedt, 1968; Winkler et al., 2002). When administered in the striatum, the 6-OHDA reveals a progressive and a partially lesioned model, where-as when injected in the SNc, it induces a more severe and rapid lesion. 6-OHDA has a similar chemical structure as DA, is uptaken into the catecholaminergic neurons by the DA transporter, retrogradely transported and promotes neurodegeneration through a combination of mechanisms such as oxidative stress and mitochondrial respiratory dysfunction leading to cell death (Glinka et al., 1997; Kunikowska and Jenner, 2001; Mazzio et al., 2004). The toxin is not specific and selective to the dopaminergic system. Due to its high affinity for the noradrenaline and the serotonin transporters, 6-OHDA may damage serotonin and noradrenergic neurons when injected in the MFB (Luthman et al., 1989). Specificity to the dopaminergic system can be achieved by sparing the noradrenergic neurons with inhibitors of the noradrenaline transporter, such as desipramine, imipramine and mirtazapine, administered before injections of 6-OHDA (Breese and Traylor, 1970; Jacks et al., 1972).

The toxin 6-OHDA is usually injected unilaterally and rats will show a characteristic contralateral turning behavior when the supersensitive receptors in the lesioned side of the brain are activated with L-DOPA or dopaminergic agonists such as apomorphine (Ungerstedt, 1971). Other...
drugs such as amphetamine produce an ipsilateral turning behavior. Severe bilateral lesions lead to high rates of death, high level of akinesia and disabling feeding issues such as adipsia and aphagia, which require postoperative healthcare treatments (Ungerstedt, 1971). Over the past years, several mechanisms have been proposed to explain the contralateral turning behavior, such as supersensitivity of postsynaptic striatal DA receptors ipsilateral to denervation (Deumens et al., 2002; Ungerstedt, 1971). Despite the fact that the exact mechanism of 6-OHDA toxic effects on striatal neurons and the pathophysiology of the turning behaviors are still unknown, the 6-OHDA-induced hemiparkinsonian rat model provides a good tool for preclinical drug studies for abnormal involuntary movements (AIMs) and neuroprotection. As observed in PD, the development of LID in rats is directly related to the level of striatal dopaminergic degeneration, the dose of 6-OHDA administered and the elapsed time since the onset of treatment (Lindgren et al., 2007; Nadjar et al., 2009; Paille et al., 2007). Moreover, the induction of the turning behavior requires a higher dose of 6-OHDA than to induce LID (Lindgren et al., 2007). Thus the turning behavior does not interfere the evaluation of LID and better reflects the clinical situation with similar doses used for PD patients.

The popularity of the hemiparkinsonian rat model is related to the fact that it is less expensive and simpler than the use of primates. Moreover, lesions obtained by the unilateral 6-OHDA lesions are highly reproducible among animals and administration of dopaminergic drug-inducing turning behaviors provides an easy, accurate and objective tool to measure motor behaviors and drug efficacy. Unilateral lesions also offer the advantage that the non-lesioned brain hemisphere or side of the body can be used as a control relative for biochemical and behavioral evaluations (Lundblad et al., 2002; Sachs and Jonsson, 1975). In spite of its usefulness, the hemiparkinsonian rat model shows limits. For instance, only some motor deficits are reproduced despite the fact that the 6-OHDA toxin has a relatively high specificity for the dopaminergic system and has also the ability to destroy the serotoninergic and noradrenergic fibers when injected in the MFB. Therefore, the model cannot mimic all stages of PD (Papa et al., 1994). Another weakness of the model is that the unilateral, as well as the bilateral 6-OHDA lesions do not induce any obvious parkinsonian symptoms or other similar motor dysfunctions as observed in non-human MPTP primate model. A dopaminergic therapy is needed in order to induce the turning behavior and dopaminergic priming is required to obtain a full antiparkinsonian effect (Di Chiara et al., 1992; Henry et al., 1998). Lastly, unilateral lesions affect only one side of the brain, whereas both hemispheres are depleted in striatal DA in PD.

The 6-OHDA lesioned-rat models do not display the same dyskinesias as those observed in primates and PD patients following a chronic dopaminergic treatment. For a long time, the only method used to study the motor effects of dopaminergic treatment was restricted to the turning behavior and it was generally considered that the animals did not display LID. Therefore, the behavioral assessment was considered to correlate with the antiparkinsonian activity of the drug tested (Fenu et al., 1997; Ungerstedt, 1976). More recently, the 6-OHDA-lesioned rat treated with 6-DOPA was reported to display LID, such as movements with dystonic or hyperkinetic features, which were observed in axial and orofacial muscles (Andersson et al., 1999; Cenci et al., 1998). Hence, this new concept was accepted since these 6-DOPA-induced abnormal movements interfered with the animal normal behavior and these were reduced with antidyskinetic drugs already used in non-human primates and in PD (Dekundy et al., 2007; Lundblad et al., 2002). The rotational response was suggested to be an equivalent of LID in rats (Papa et al., 1994) and a rating scale was created to evaluate and quantify the AIMs in parkinsonian rats, gradually replacing the contralateral rotation evaluations (Cenci et al., 1998). In fact, the rotational behavior did not always correlate with the development of dyskinesia in both rat and mouse models (Henry et al., 1998; Papa et al., 1994). A recent behavioral study demonstrated that the rotational behavior did not represent a complete antiparkinsonian response and that would probably be related to the 6-DOPA-induced motor response complication syndrome (Konitiotis and Tzronis, 2006). Moreover, it has been shown that some antiparkinsonian drugs with weak dyskinesiogenic potential, such as ropinirole and bromocriptine, can increase contralateral turning (Carta et al., 2008; Lindgren et al., 2009), while other antidyskinetic drugs that are well known for reducing LID and AIMs, such as amantadine and clozapine, did not prevent the contralateral turning behavior (Lundblad et al., 2002).

The AIMs rating scale is constituted of three main sections each representing a topographical area of the body: 1) limb dyskinesia characterized by repetitive and rhythmic movements or dystonic posturing of the forelimb on the side contralateral to the lesion; 2) axial dyskinesia characterized by lateral flexion and axial rotation/torsion affecting the neck and the upper trunk toward the side contralateral to the lesion; and (3) orolinguial dyskinesia affecting the orofacial musculature including chewing movements, tongue protrusions and jaw tremor (Cenci et al., 2002; Winkler et al., 2002). The AIMs scale is useful, valid and provides a precise evaluation of the intensity of LID for each animal (Dekundy et al., 2007). The 6-OHDA rat model for the study of LID in acute, sub-chronic or chronic study designs, has been largely used over the years for the validation of new pharmacological compounds. Many antidyskinetic treatments used in PD patients and non-human primates have been first tested in the 6-OHDA rat model and showed to reduce the AIMs score and to improve motor behavior (Bordia et al., 2012; Dekundy et al., 2007; Eskow et al., 2007; Kobylecki et al., 2010, 2011; Munoz et al., 2008; Quik et al., 2007; Rylander et al., 2010) (Table 1).

The 6-OHDA lesioned mouse model

The 6-OHDA lesioned mouse model is a recent model and LID have been reported for the first time in 2004 where the authors reported similar AIMs as those observed in rats (Lundblad et al., 2004). The toxin 6-OHDA can be administered by intracerebral injection to mice, but the rat model remains more practical to perform the lesion and to evaluate the motor behavior (Francardo et al., 2011, 2012; Nicholas, 2007; Smith et al., 2012). Compared to the MPTP-lesioned mouse model, the 6-OHDA mouse model is more convenient since the AIMs are easier to evaluate; the animals develop better dyskinesia with less inter-individual variability and biochemical variations (Sadler et al., 2000). Unilateral 6-OHDA lesions in mice lead to a stable and reproducible damage along the nigrostrial tract similar to those observed with the 6-OHDA rat model. Moreover, like in the rat model, it is possible to mimic different stages of PD by using different doses and different administration sites. The rating scales used for the motor behavioral evaluation and for detecting dyskinesia in mice are based on the rating scale used for the 6-OHDA rats. The scale used to evaluate the AIMs in mice also includes the frequency, the duration and the intensity of topographical limb, axial and orolinguial dyskinesias (Francardo et al., 2011, 2012). Although the 6-OHDA mouse model has been used for pharmacological validation against LID such as amantadine (Bido et al., 2011), the rat model is still more often used for all its advantages.

Other mouse models

Over the past 15 years, many knockout and transgenic mice models of PD have been developed to study genetic causes of PD, molecular pathways and targets for new pharmacological compounds (Dawson et al., 2010). The principal limitation of these models is that they do not reproduce the dopaminergic degeneration as observed in PD. Therefore, mouse models that have been developed to study overexpression of the genes implicated in some familial PD forms, such as α-synuclein (Cheeseth, 2008) and leucine-rich repeat kinase 2 (Li et al., 2010; Xu et al., 2012), do not develop LID following 6-DOPA treatment since there is no dopaminergic cell loss. However, a
Table 1

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Advantage</th>
<th>Inconvenient</th>
<th>Translational value</th>
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<tr>
<td>Rodent</td>
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<tr>
<td>6-OHDA rat model</td>
<td>Inexpensive</td>
<td>Fused components of the striatum</td>
<td>Excellent initial step for preclinical drug validation</td>
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<td></td>
<td>Time- and cost-effective</td>
<td>Segregation in the indirect and direct DA pathways 6-OHDA toxin is not specific/selective to DA system</td>
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<td></td>
<td>Widely used toxin animal model</td>
<td>Unilateral lesion</td>
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<td></td>
<td>Easily reproducible</td>
<td>Does not mimic all PD stages and is not progressive</td>
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<td></td>
<td>Excellent for preclinical drug validation</td>
<td>Dopaminergic priming is required for antiparkinsonian effect</td>
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<td></td>
<td>Different stage of PD can be produced</td>
<td>Displays different dyskinesia compared to human and non-human primates</td>
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<td>Turning behavior provides an objective evaluation tool for LID</td>
<td>Turning behavior may interfere with dyskinesia</td>
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<td>More recently an AIMs scale is available to measure LID</td>
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<tr>
<td>6-OHDA mouse model</td>
<td>Inexpensive</td>
<td>Model less well-known compared to rat and less suited to study fine motor behavior</td>
<td>Weak for LID</td>
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<td>Time- and cost-effectiveness</td>
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<td></td>
<td>Develops better LID than MPTP mouse/easier to evaluate</td>
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<tr>
<td>Genetic mouse model</td>
<td>Most of these mice model PD</td>
<td>Most of these models do not reproduce DA degeneration hence no LID</td>
<td>Weak for LID</td>
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<td>The aphasis mouse models PD and LID</td>
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<tr>
<td>MPTP mouse model</td>
<td></td>
<td>Requires large dose of l-DOPA to induced AIMs</td>
<td>Weak for LID</td>
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<td>Non-human primate</td>
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<tr>
<td>MPTP cymologus and rhesus macaque</td>
<td>Currently the best model to study LID</td>
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<td>Similar response to DA therapies as idiopathic PD</td>
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<td>Basal ganglia structures similar to humans</td>
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<td>Bilateral lesion (if systemic) as observed in PD</td>
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<td>Antiparkinsonian response at first dose of l-DOPA</td>
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<td>MPTP reproduces cognitive and gastro-intestinal impairments like in PD</td>
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<td>Allows to measure wearing-off</td>
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<td>Reappearance of LID after drug holiday</td>
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<td>Abundance of literature on PD and LID pathophysiology</td>
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<td>MPTP marmoset</td>
<td>Small size</td>
<td>Dystonic- and choreic-like movements are difficult to distinguish due to hyperkinesia</td>
<td>Excellent to test antiparkinsonian drugs both in acute and de novo studies</td>
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<td></td>
<td>Easy handling and housing</td>
<td>Limited literature on LID pathophysiology</td>
<td>Good to test surgical treatments</td>
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<td>Tends to be very active under l-DOPA</td>
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<td>Weak to test antidyskinetic drugs</td>
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<td>Good literature on PD pathophysiology</td>
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<tr>
<td>6-OHDA marmoset</td>
<td>Small size</td>
<td>Mainly unilateral lesion</td>
<td>Good to test antiparkinsonian drugs both in acute and de novo studies</td>
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<td>Easy handling and housing</td>
<td>Limited literature on LID pathophysiology</td>
<td>More studies are needed to validate the model</td>
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<td>Tends to be very active under l-DOPA</td>
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<td>Strong literature on PD pathophysiology</td>
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<tr>
<td>MPTP squirrel monkey</td>
<td>Small size</td>
<td>Can display LID under normal (unlesioned) conditions</td>
<td>No translational values</td>
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<td></td>
<td>Easy handling and housing</td>
<td>Limited literature on PD and LID pathophysiology</td>
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<td>Displays LID</td>
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Recent genetic model of PD, the aphasis mouse, showed AIMs after l-DOPA or dopaminergic agonist administrations (Ding et al., 2007). Following an amantadine treatment, the development of PD was reduced and some markers of LID were expressed similarly as those observed in 6-OHDA models such as the abnormal activation of extra-cellular signal-regulated Kinase 1/2 (ERK1/2) and the increased FosB-expression in the dorsal striatum (Ding et al., 2007, 2011).

Non-human primate models of LID

Similar etiology and functions of a particular human disease are the two must-have characteristics to model a disease. In order to avoid confusing and misleading results, the model has to replicate as many characteristics of the pathology as possible. The neurotoxin MPTP closely mimics both behavioral changes and cellular loss as seen in PD (Albanese et al., 1993). In fact, administration of MPTP in primates induces remarkable resemblance to the primary motor features of PD, including rigidity, bradykinesia and tremor. MPTP targets specifically cells expressing the DA transporter and induces neuronal death of dopaminergic cells through a cascade of intracellular reactions (Smeyne and Jackson-Lewis, 2005 and for more information, see corresponding article in the current issue). Moreover, MPTP-treated monkeys also display cognitive (Schneider, 1990) and gastrointestinal impairments similar to PD patients (Chaumette et al., 2009 and see corresponding articles in the current issue).

Prior to MPTP, lesions of the ventromedial mesencephalic tegmen-tament were performed in primates to induce tremor (Poirier, 1960) and administration of l-DOPA in these monkeys induced oro-facial dyskinesias similar to LID (Battista et al., 1971). MPTP was first used in monkeys (Burns et al., 1983) following the demonstration of its irreversible parkinsonian effects when taken by drug users as a contaminant of a derivative of heroin (Davis et al., 1979; Langston et al., 1983). Since then, it has been used extensively in rhesus and cynomolgus macaques (Macaca mulatta and Macaca fascicularis respectively), but is also used in African green monkeys (Wichmann et al., 1999), squirrel monkeys (Langston et al., 1984) and common marmosets for the study of PD (Jenner et al., 1984). Considering the above facts, MPTP-treated primates remain after nearly 30 years of the gold standard for the study of PD and LID, as well as to test compounds for their treatment.
Experimental paradigms

Two experimental approaches are reported to test new drugs as potential antiparkinsonian and/or antidyskinetic pharmacological agents. In the first experimental approach, animals are rendered parkinsonian and then chronically treated with L-DOPA for several weeks or months until they express stable and well-established LID. Then, acute (few doses) or chronic (generally protocols lasting less than a month) effects of new compounds are tested with the co-administration of L-DOPA (Bezard et al., 2004; Grégoire et al., 2009, 2011). This model is probably the most widely used since it allows rapid testing of new compounds and its tolerability, and animals may be used for several studies. In a second experimental approach, two or more groups of de novo animals are rendered parkinsonian and then treated with L-DOPA alone or in combination with the new agent. The advantages of the latter paradigm are to allow the study of the specific effects of the test compound on the development of LID and to assess if the effects diminish with long-term use, also called “wearing-off” (Grégoire et al., 2008; Hadj Tahar et al., 2004; Morin et al., 2012; Rylander et al., 2010; Samadi et al., 2006). Furthermore, measurements of biochemical changes are made possible if the animals are killed at the end of the protocol (Morin et al., 2012; Ouattara et al., 2010a; Samadi et al., 2008). However, such experiments are relatively expensive and the animals are not used in subsequent de novo studies since the test drug may have influenced permanently the development and expression of LID.

L-DOPA can be administered through several routes and may play a critical role in the behavioral assessment. Stereotactic L-DOPA administration was tried in PD patients and seemed successful when infused in the caudate nucleus (Velasco Suárez and Escobedo, 1970). However, leaking L-DOPA into the ventricles failed to achieve improvements in tremor and rigidity, induced dizziness and nausea, and was no longer investigated. Intraventricular administration of DA or DA agonists using implantable infusion pumps has been investigated in marmosets (de Yebenes et al., 1987, 1988). Hardware-related complications (mainly disconnection of the pump) and the poor stability and solubility of DA in water might explain why this technique was not replicated in other groups. Nowadays, there are two main routes of L-DOPA administration, namely orally or injected systemically. In the former case, L-DOPA is delivered by nasogastric gavage using human formulations of L-DOPA (per os route). In such protocols, all animals receive the same amount of L-DOPA. This route gives a shorter but stronger response compared to injected forms, allowing higher dyskinesias. It comes handy in studies focusing mainly on peak-dose LID (Hadj Tahar et al., 2004). In the systemic administration route, L-DOPA is given intravenously in primates, as sometimes performed in patients for research purpose (Richard et al., 2005; Stocchi et al., 1992), but is seldom used in primates for handling and restraining reasons. Subcutaneous (s.c.) injection of L-DOPA in its methylester form offers more stable and reproducible plasma levels since it avoids first-pass metabolism from the liver (Cooper et al., 1984). Subcutaneous injection of L-DOPA with oral administration of the investigational drugs also allows minimizing possible pharmacokinetic interactions between these drugs. Moreover, dyskinetic responses may vary less among the animals when s.c. doses are titrated. Subcutaneous L-DOPA methyl ester may, on the other hand, accumulate in the fat tissues. Consequently, peak dose LID may be lower than those obtained with per os administration, but will last longer with a smoother response.

The dose of L-DOPA may need to be adjusted according to the drug under investigation. For antidyskinetic drugs, L-DOPA should be administered at doses that offers the greatest improvement of the parkinsonian disability (optimal) or higher to elicit LID. For medications with potential antiparkinsonian activity, partial alleviation of parkinsonian symptoms by suboptimal doses of L-DOPA that elicit low dyskinesia may be needed to fully assess the new agent’s effects. If the dose of L-DOPA is kept too high, subtle effects may not be observed or missed and some monkeys may display stereotypies (Graybiel et al., 2000). Similar stereotyped behaviors are observed in PD humans with high doses of L-DOPA (Evans et al., 2004; Fernandez and Friedman, 1999).

In the latter case, when monkeys enter in a stereotypical state, they usually do not display dyskinesia and may have increased or decreased locomotor activity (Mones, 1973; Sassin, 1975). If not corrected, parkinsonian and dyskinetic scores may be interpreted as misleading results. Finally, adjusting the L-DOPA dose for each animal reflects better the clinical situation since each patient has its medication titrated for the best response. Therefore, L-DOPA titration for each animal allows a better assessment of the investigational drugs before moving to clinical trials.

Monkey models and LID

Squirrel monkeys and common marmosets are used for their small sizes and their convenience in handling and housing. Both species show sensitivity to MPTP and will develop PD symptoms. Squirrel monkeys have not been studied thoroughly since significant LID can be elicited in normal squirrel monkeys (Quik et al., 2002; Togasaki et al., 2001) at relatively low-doses of L-DOPA (15 mg/kg for a 2-day period). The underlying reason of this sensitivity of squirrel monkeys to L-DOPA without dopaminergic denervation remains to be addressed but questions its validity as an animal model for the study of LID. MPTP-treated marmosets will display behaviors similar to dyskinesia after 6 to 10 days of L-DOPA administration (Pearce et al., 1995). Under the influence of L-DOPA, marmosets will exhibit dyskinetic movements, including chorea-like (i.e. random flicking movements), dystonic-like (i.e. sustained postures) and repetitive aimless movements, but also tend to be very active and restless. However, choreic and dystonic components of LID in marmosets may be difficult to assess and to distinguish considering the pronounced hyperkinesia in these animals (Fox and Brodtchie, 2010). Hemiparkinsonism can also be achieved in marmoset by unilateral injection of 6-OHDA, but was used only in few studies (Pirkle et al., 2001; Svenningsson et al., 2000).

Bilateral parkinsonism by 2-stage injections of intracerebral 6-OHDA was developed in marmosets, but has not been used to study LID (Mitchell and Carroll, 1997; Mitchell et al., 1995). MPTP marmosets are good models for testing new antiparkinsonian drugs to be used as monotherapy or as adjunct treatments to L-DOPA in order to reduce non-specifically LID and/or to increase its antiparkinsonian response. On the other hand, drugs aiming to reduce more specific dyskinetic behaviors should be tested in other animal models considering the limited spectrum of dyskinesias in MPTP marmosets.

In contrast to marmosets, rhesus and cynomolgus macaques may show choreic-like, dystonic-like dyskinesias or the combination of both (Grégoire et al., 2011). As in PD patients (Rajput et al., 2009), each macaque will display its own pattern of parkinsonian symptoms. Dyskinesias involves one or more parts of the body and each of them should therefore be quantified separately (Hadj Tahar et al., 2000). Several scales are currently available to measure and quantify dyskinesia and were recently reviewed (Fox et al., 2012). Objective measures of bradykinesia with specific motor tasks are also important to separate the antidyskinetic from antiparkinsonian activity of compounds or surgeries (Jourdain et al., 2013). Moreover, MPTP monkeys display neuronal activity very similar to PD patients in the main targets for stereotactic surgery, that are the subthalamic nucleus (STN) and the GPi both “off-medication” (STN: (Bergman et al., 1994; Tachibana et al., 2011; Weinberger et al., 2006) and GPi: (Lee et al., 2007; Levy et al., 2001; Tachibana et al., 2011)) and “on-medication” (STN: (Gilmour et al., 2011; Levy et al., 2001) and GPi: (Heimer et al., 2002; Hutchison et al., 1997; Levy et al., 2001)). Finally, monkeys will tend to exhibit a worsening of motor symptoms before and after an acute L-DOPA challenge (Kuoppamäki et al., 2002), as seen in some PD patients (Evans et al., 2012). The evidence mentioned above...
demonstrates the efficacy of monkeys to replicate PD conditions and underlines their usefulness in the study of its treatment.

Despite the fact that animals are equally denervated (Guigoni et al., 2005), individual titration of L-DOPA is often needed to elicit the same amount of LID among the animals (Grégoire et al., 2011; Johnston et al., 2010), but it is generally accepted that there is a positive correlation between L-DOPA dose and the duration and the severity of LID (Kuoppamäki et al., 2007). One of the most interesting features of dyskinetic macaques is that administration of L-DOPA after drug holiday lasting few weeks will trigger the same LID as measured before. The same observation was made in PD patients in whom L-DOPA was stopped (Goetz et al., 1982; Mayeux et al., 1985). This observation supports the feasibility of many acute studies with the same animals therefore keeping the number needed (and consequently the costs) to a minimum. Furthermore, the reappearance of LID after a withdrawal indicates that permanent, or at least long-term changes are happening in the brain and these changes may be studied in post-mortem brain tissues. One of the other motor side effects of chronic L-DOPA is wearing-off, described as shortening in the duration of response to L-DOPA with gradual reappearance of parkinsonian symptoms. Patients usually experience such end-of-dose deterioration after several months or years of treatment (Palhwa and Lyons, 2009). Wearing-off is also modeled in de novo MPTP monkeys with a shortening of the antiparkinsonian effect of L-DOPA as reported after two weeks of treatment (Morin et al., 2012). This observation strongly suggests that this phenomenon is not due to a loss of presynaptic storage capacity for L-DOPA as the disease progresses.

**Dopaminergic denervation and LID**

Dopaminergic cell loss is generally required in order to elicit LID. Except for very high doses, chronic administration of L-DOPA does not seem to induce LID in non-PD humans (Rajput et al., 1997). Similar earlier results were observed in normal monkeys where acute administration of high doses of L-DOPA alone (100 to 400 mg/kg) did not induce LID (Mones, 1973), but rather displayed stereotyped behaviors (Sassin, 1975). More recently, L-DOPA doses of 80 mg/kg given for a three-month period induced LID in normal monkeys, whereas doses of 20 and 40 mg/kg did not (Pearce et al., 2001). LID generally appear rapidly in PD patients diagnosed in late stage (Varanese et al., 2011), young onset PD patients highly-denervated at diagnosis (Schrag et al., 1998) and MPTP exposed humans (Ballard et al., 1985). These observations indicate that a near complete DA depletion is needed to develop LID. This was further confirmed in primates where controlled dopaminergic lesions showed a correlation between the extent of DA denervation, the occurrence and severity of LID (Di Monte et al., 2000; Schneider, 1989). However, dopaminergic cell loss cannot be the sole explanation. For instance, some monkeys will never display LID independently of the nigral denervation (Aubert et al., 2005; Guigoni et al., 2005). A functional imaging study performed in PD patients came to similar conclusions (Linazasoro et al., 2009). A recent study showed that strictly unilateral hemiparkinsonian monkeys treated chronically with L-DOPA did not develop LID, suggesting compensatory mechanisms through interhemispheric crossover dopaminergic fibers (Lieu et al., 2011). Other individual factors (sex, weight, genetics) may contribute the occurrence or the absence of LID in patients and monkeys.

**Biochemical correlates of LID**

Denervation-induced supersensitivity of DA receptors is generally recognized as a plausible mechanism of LID. Post-mortem studies have shown that striatal DA receptors particularly of the D2 subtype were increased in PD patients (Bokobza et al., 1984; Guttman et al., 1986; Lee et al., 1978), while both D1 and D2 DA receptor subtypes were increased in MPTP-lesioned monkeys (Bedard et al., 1986; Falardeau et al., 1988; Gagnon et al., 1990; Graham et al., 1993). L-DOPA reverses this increase in humans (Guttman et al., 1986; Lee et al., 1978) and monkeys (Berretta et al., 1997; Falardeau et al., 1988; Gagnon et al., 1990). In MPTP monkeys D3 receptors are decreased; this is corrected with dopaminergic treatments (Morissette et al., 1998; Quik et al., 2000). D3 receptors were reported to be either decreased (Ryo et al., 1998) or unchanged in PD patients (Hurley et al., 1996). Dyskiniasias are clearly more complex than hypersensitivity due to a simple increase in the density of striatal DA receptors. Hence, changes were sought in the signaling pathways activated by DA receptors. DA receptors regulate cAMP-protein kinase A through G-protein mediated signaling (Beaulieu et al., 2007). The D1 class of receptors (D1 and D5) stimulates production of cAMP and activity of protein kinase A while the D2 class (D2, D3 and D4) regulates production of cAMP negatively and modulates intracellular Ca2+ levels (Greengard, 2001; Missale et al., 1998). ERK, a well-known player in the MAP kinase cascade signaling, is an important mediator of cAMP signaling involved in responses to DA drugs (Beaulieu et al., 2006; Valjent et al., 2005, 2006). DA receptors also exert their effect through Akt/GSK3 signaling (Beaulieu et al., 2007). Akt can phosphorylate GSK3β at Ser9 (pGSK3β Ser9) and inactivate it (Chong et al., 2005). GSK3β is at the crossroads of several pathways (Pelech and Charest, 1995; Salinas, 2008; Shaw et al., 1998). Prolonged stimulation of D2 receptors in rodents leads to specific dephosphorylation/inactivation of striatal Akt on Thr308 (pAkt[Thr308]), Ser473 (pAkt[Ser473]) remaining unaffected (Beaulieu et al., 2005). A significant positive correlation between LID AIMS scores in mice and extent of ERK1/2 phosphorylation was reported (Santini et al., 2007) but not in monkeys (Santini et al., 2014).
2010). L-DOPA-treated MPTP monkeys with dyskinasias display a positive correlation between dyskinesia scores and pAkt(Ser473) and pGSK3β(Ser9) levels in putamen (Morissette et al., 2010). Moreover, the metabotropic glutamate (mGlur) receptor 5 antagonist MTEP acutely inhibits LID and opposes L-DOPA-induced elevation of striatal p-ERK1/2 in the 6-OHDA lesioned rat model of PD (Rylander et al., 2009).

Glutamate is the most abundant excitatory neurotransmitter, mediating as much as 70% of brain synaptic transmission (Klockgether and Turski, 1993). The striatum receives two major inputs: massive excitatory glutamatergic projections from the cerebral cortex and the thalamus, as well as a dopaminergic projection from the SNC (Samadi et al., 2007). In PD, loss of striatal DA is associated with loss of the inhibitory DA control of corticostriatal glutamatergic drive with consequent increased glutamate release (Garcia et al., 2010). Glutamate activity is increased in the basal ganglia in PD (Klockgether and Turski, 1993) and is also believed to be involved in LID (Calon et al., 2003; Chase and Oh, 2000). Changes in ionotropic and metabotropic glutamate receptors are reported in the brain of PD patients with dyskinasias and dyskinetic MPTP monkeys (Calon et al., 2002, 2003; Carlsson, 1993; Ouattara et al., 2009, 2010a,b). GABA is the most abundant inhibitory neurotransmitter and its receptors are also changed in the brains of dyskinetic human and non-human primates (Calon and Di Paolo, 2002). Serotonin receptors (Huot et al., 2010), serotonin transporters (Rylander et al., 2010), adenosine A2A receptors (Calon et al., 2004) are also affected in LID, as well as the neuropeptides preproenkephalin and preprodynorphin (Tamim et al., 2010). Significant work has been published over the last few years on the role of serotonergic neurons in the appearance of LID both in rodents and primates and several compounds that increase brain extracellular serotonin levels have shown antidyskinetic efficacy in these models (Durif et al., 1995; Gomez-Mancilla and Bedard, 1993; Iravani et al., 2003). The mechanisms underlying the antidyskinetic effects of serotoninergic compounds remain unknown; but it is probably related to the activation of presynaptic 5-HT1A receptors, which reduces the synaptic release of glutamate (Barnes and Sharp, 1999; Meltzer et al., 2003) as seen with the 5-HT1A agonists sarizotan (Bara-Jimenez et al., 2005; Bibbiani et al., 2001; Grégoire et al., 2009; Olanow et al., 2003) and buspirone (Bonifati et al., 1994; Kleidorsfer et al., 1991). Moreover, it has been shown that the agonists of the 5-HT1A receptors were able to prevent the increase of extracellular DA levels in the striatum after the administration of L-DOPA (Kannari et al., 2001), which can also explain the reduction of LID. Furthermore, the blockade of the postsynaptic 5-HT1A-type receptors can also alleviate the severity of LID (Baron and Dalton, 2003; Oh et al., 2002), probably related to the ability of 5-HT2 antagonists to boost dopaminergic cellular responses in striatal neurons (Svenningsson et al., 2002), the serotonin transporter (SERT) and other serotonin receptor subtypes are also implicated in PD and in the development of LID (for review, see (Huot et al., 2011)). Hence, the mechanisms involved in the occurrence of LID are complex and involve numerous neurotransmitters.

LID models and surgical treatment

Lesion studies

Surgical therapy is one of the options offered to patients with disabling LID. STN deep brain stimulation (DBS) is currently the mainstream surgery, but other structures are also targets for stimulation, including the GPI and the ventralis intermedius nucleus of the thalamus (Fasano et al., 2012; Walter and Vitek, 2004). These three nuclei may also be lesioned and provide a reasonable alternative when DBS is unavailable or contraindicated (Hooper et al., 2008). Despite the tremendous efforts of these surgical treatments, few studies have been conducted on the interactions of L-DOPA and surgeries. Behavioral studies in rats showed that unilateral STN lesion, also called subthalamotomy reduced AIm when performed ipsilateral to 6-OHDA-lesioned side (Aristieta et al., 2012; Levandis et al., 2008). On the contrary, some authors observed no changes in AIsM with ipsilateral subthalamotomy, but contralateral or bilateral STN lesions induced repetitive flexo-extensive movements of the upper limbs and repetitive movements of the head (Marin et al., 2004). Surprisingly, STN lesions made contralateral to 6-OHDA or bilaterally corrected the wearing-off phenomenon, whereas no such change was seen with ipsilateral lesions (Marin et al., 2004). On the cellular level, unilateral subthalamotomy was shown to correct the L-DOPA-induced increase in FoS/AsFoS and pDARPP32/DARPP32 protein expression in the striatum (Aristieta et al., 2012; Levandis et al., 2008), as well as reduce the 6-OHDA-induced increases in striatal GAD67, preproenkephalin and cytochrome oxidase mRNAs (Périer et al., 2003). These neurochemical observations suggest attenuation in the molecular changes associated with LID and a return to normal striatal activity. Recently, the first study on the response to i-DOPA after subthalamic lesion was conducted in MPTP-treated monkeys (Jourdain et al., 2013). The authors demonstrated that subthalamotomy had potentiation effects on suboptimal doses of l-DOPA and its doses could be reduced by 40% after SN lesion to have the same beneficial antiparkinsonian response to the medication as with optimal doses pre-surgery. Subthalamotomy also increased LID when the dose of l-DOPA was maintained. These results closely resemble those obtained in patients undergoing unilateral subthalamotomy (Alvarez et al., 2001, 2009; Su et al., 2002). Unilateral lesion of the GPI, also called pallidotomy was performed in dyskinetic marmosets and showed a lesion-size-dependency reduction of LID, with better improvement in dystonia compared to chorea (Iravani et al., 2005). Lesions in the ventrolateral pars oralis nucleus of the thalamus were also shown to reduce l-DOPA-induced chorea in MPTP-treated monkeys, where dystonia remained unchanged (Page et al., 1993). This particular thalamic nucleus receives pallidal efference and its lesion would therefore mimic an indirect pallidotomy. Lesions in ventrolateral thalamus (but no longer used) and pallidotomies are also performed in patients with disabling LID or hemiballism (Hariz, 2009; Narabayashi and Kubota, 1966; Suarez et al., 1997). Overall, these studies in monkeys not only show that stereotactic lesions can be replicated in animals, but they also add to the evidence that MPTP-treated monkeys are definitively the best model currently available for the study of PD, LID and their respective treatments.

High frequency stimulation studies

High frequency stimulation (HFS) via an implantable electrode is the closest model of DBS for animal models (Quintana et al., 2012). When applied in rats, STN-HFS reverses the striatal hyperactivity observed in 6-OHDA rats treated with saline or l-DOPA in both 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propionic acid (AMPA) and N-methyl-d-aspartate (NMDA) receptors as measured by patch clamp (Gubellini et al., 2006). This reduction in glutamatergic transmission from the corticostriatal pathway paralleled with an improvement in akinesia (Gubellini et al., 2006). In partially DA-denervated rats, ipsilateral STN-HFS elevated striatal concentration of DA and its metabolite DOPAC compared to parkinsonian rats receiving l-DOPA only during a one-hour stimulation and remained significantly higher 2.5 h post-stimulation (Lacombe et al., 2007). This latter increase in DA may explain in part the effects on the time spent “off” in patients with STN DBS (Deuschl et al., 2006), but also the decrease in l-DOPA requirements in PD patients (Follett et al., 2010). More recently, l-DOPA alone or STN-HFS alone decreased similarly serotonin levels in the prefrontal cortex and hippocampus compared to 6-OHDA rats receiving vehicle and sham stimulation, but no synergic effects were observed when l-DOPA and STN-HFS were combined (Navailles et al., 2010). On the other hand, DA levels were increased in these structures when l-DOPA was administered and further increased when STN-HFS was applied (Navailles et al., 2010). Finally, addition of STN-HFS to l-DOPA potentiated the
l-DOPA-induced striatal increases in Foα/ΔFoα, glial glutamate transporter type 1, as well as levels of preproenkephalin and preprodynorphin mRNAs (Ouellet et al., 2007). The latter findings contrast with those obtained with unilateral subthalamicotomy (Aristieti et al., 2012; Levandis et al., 2008; Périer et al., 2003) and suggests that although clinical outcomes are similar (Merello et al., 2008), lesions and DBS have different cellular mechanisms. To our knowledge, no studies using DBS have been conducted in dyskinetic primates yet. The high costs related to DBS implants (McIntosh, 2011) and feasibility in dyskinetic MPTP-primates may explain partially the absence of such studies. Nevertheless, interactions between surgery and LID animal models are only beginning to be explored and open new and fascinating fields of research on the pathophysiology of LID and their treatments.

Translational values of animal models

The rodent and non-human primate models of PD reproduce well the responsiveness of the motor symptoms to dopaminergic medications known to be effective in PD (Duty and Jenner, 2011; Jenner, 2009). Dissociating antidykinetic from an antiparkinsonian activity is not an easy task. Much recent research emphasis has been placed on finding non-dopaminergic drugs to treat dyskinesias while maintaining the antiparkinsonian activity of the dopaminergic drugs. This may require additional complexities from the animal models to reproduce more closely the non-dopaminergic pathological changes in PD in the search for non-dopaminergic targets to treat dyskinesias.

As described in the previous section glutamate is an important neurotransmitter in PD and LID and is therefore a primary target for antidykinetic drug development. Amantadine, a weak non-competitive antagonist of the ionotropic NMDA glutamate receptor has antidykinetic activity in rat (Dekundy et al., 2007; Kobylicki et al., 2011), mouse (Lundblad et al., 2005) and monkey (Blanchet et al., 1998) models of PD. These results in animal models translate well in PD patients. Amantadine is currently the only available efficacious medication for the pharmacological management of LID as add-on to l-DOPA in patients with PD (Fox et al., 2011), although the duration of benefit is reportedly to be short (Thomas et al., 2004).

Compounds targeting mGlu receptors are presently the objects of intense research for dyskinesias. The mGlu5 receptor subtype shows relatively selective distribution in the brain with high density in the striatum (Ouattara et al., 2011). Several mGlu5 receptor negative allosteric modulators (more commonly called antagonists) are shown to reduce the severity of dyskinesias in rats (Levandis et al., 2008; Marin et al., 2011; Mela et al., 2007; Rylander et al., 2009) and macaques (Johnston et al., 2010; Morin et al., 2010, 2012; Rylander et al., 2010). More specifically the translational value of the models for testing mGlu5 receptor antagonists is well demonstrated with AFQ056 (mavoglurant), an mGlu5 receptor antagonist, that is shown to reduce LID in MPTP monkeys (Grégoire et al., 2011) and also in PD patients (Berg et al., 2011).

Sarizotan, a serotonin 5-HT1A agonist was tested in MPTP primates (Grégoire et al., 2009) and was shown at low doses to reduce dyskinesias while maintaining the antiparkinsonian efficacy of L-DOPA whereas at higher doses it reduced the L-DOPA-induced locomotor response. Another study in 6-OHDA rats showed that LID were improved acutely by sarizotan 2.5 mg/kg and in MPTP monkeys at 2 mg/kg (Bibbiani et al., 2001). In PD patients, sarizotan was shown to reduce the duration and severity of dyskinesias (UPDRS Items 32 + 33) at 2 mg/kg with a trend at 10 mg/kg but not on diary-based measures of dyskinesia or the Abnormal Involuntary Movement Scale (Goetz et al., 2007). At higher doses, sarizotan’s dopaminergic antagonist property appears causing a deterioration of the antiparkinsonian response and could partly explain the inconsistent results obtained. Dyskinesias are highly sensitive to placebo effect and in a large double-blind placebo controlled clinical trial all effects in the sarizotan group were statistical- ly explained by the placebo-effect regression model (Goetz et al., 2008).

The present models in rodents and primate were designed to reproduce the nigrostriatal pathology and the main dopaminergic loss and do not reflect the overall pathological picture occurring in PD. These models have been very useful to investigate motor complications in PD. Dyskinesias in MPTP primates model closely this motor symptom in humans but monkeys with severe dyskinesias may alter their pattern of movement to prevent the appearance of involuntary movements. Monkeys are observed to gasp bars of their cage to avoid bucco-lingual dyskinesias or sit on their hand to avoid limb dyskinesias (personal observations). In addition, pharmacological agents can induce hypotension, muscle relaxation or sedation that reduces movement.

It is increasingly recognized that nonmotor symptoms are common in PD and have yet to be modeled properly in animals and require future attention. Nonmotor symptoms are of neuropsychiatric nature such as anxiety, depression, hallucinations, impulse control disorders, and cognitive impairment, as well as autonomic, such as gastrointestinal, urinary, and sexual disturbances (Lyons and Palwa, 2011). Excessive sweating, orthostatic hypotension, and sleep disturbances are also nonmotor symptoms observed in PD (Lyons and Palwa, 2011). Do the antidykinetic drugs presently under development improve nonmotor symptoms of PD? This has yet to be fully investigated. Animal models combining MPTP-induced loss of nigrostriatal DA neurons with other toxins to mimic more closely the PD pathological condition would be beneficial to widen the applicability of the models and find better drug treatments.

In conclusion, the MPTP lesioned monkey continues to be the best model of dyskinesias in humans and has brought significant advances for the treatment of dyskinesias and will continue to do so. With the rodent models that are less expensive, initial screening of numerous compounds can be performed. Moreover, the mouse models of PD and dyskinesias can be developed with genetically modified animals that will provide additional tools to understand the mechanisms involved in the development of dyskinesias.

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