Neuroscience 211 (2012) 13–27

REVIEW

ANIMAL MODELS OF L-DOPA–INDUCED DYSKINESIA: AN UPDATE ON THE CURRENT OPTIONS

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Abstract—Major limitations to the pharmacotherapy of Parkinson's disease (PD) are the motor complications resulting from L-DOPA treatment. Abnormal involuntary movements (dyskinesia) affect a majority of the patients after a few years of L-DOPA treatment and can become troublesome and debilitating. Once dyskinesia has debuted, an irreversible process seems to have occurred, and the movement disorder becomes almost impossible to eliminate with adjustments in peroral pharmacotherapy. There is a great need to find new pharmacological interventions for PD that will alleviate parkinsonian symptoms without inducing dyskinesia. The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned non-human primate model is an excellent symptomatic model of PD and was the first model used to reproduce L-DOPA-induced dyskinesia experimentally. As it recapitulates the motor features of human dyskinesia, that is, chorea and dystonia, it is considered a reliable animal model to define novel therapies. Over the last decade, rodent models of L-DOPA-induced dyskinesia have been developed, having both face validity and predictive validity. These models have now become the first-line experimental tool for therapeutic screening purposes. The application of classical 6-hydroxydopamine (6-OHDA) lesion procedures to produce rodent models of dyskinesia has provided the field with more dynamic tools, since the versatility of toxin doses and injection coordinates allows for mimicking different stages of PD. This article will review models developed in non-human primate and rodents to reproduce motor complications induced by dopamine replacement therapy. The recent breakthroughs represented by mouse models and the relevance of rodents in relation to non-human primate models will be discussed.

This article is part of a Special Issue entitled: Neuroscience Disease Models.

Key words: L-DOPA-induced dyskinesia, 6-OHDA, MPTP, animal models, abnormal involuntary movements, Parkinson's disease.

Contents

Motor fluctuations and dyskinesia (abnormal involuntary movements) are major problems in the standard treatment of Parkinson's disease (PD) with L-DOPA, the precursor of dopamine (DA). Motor fluctuations are characterized by rapid transitions between periods of normal motor function and periods of akinesia and immobility (referred to as "on" or "off" states, respectively). Fluctuations first appear as a "wearing-off phenomenon" that consists in a shortening of duration of a single L-DOPA dose. The wearing-off phenomenon requires an augmentation in number of doses of L-DOPA per day, which subsequently increases the risk for dyskinesia. L-DOPA-induced dyskinesia (LID) appears in a majority of PD patients after a few years of treatment with L-DOPA (Ahlskog and Muenter, 2001). The term applies to a large variety of abnormal involuntary movements (AIMs), including movements with dystonic, choreiform, ballistic, or stereotypic features. Risk factors consistently correlated with dyskinesia are young age at disease onset, severity of parkinsonism and L-DOPA treatment duration and dosage (Sharma et al., 2010; Prashanth et al., 2011). The clinical definitions of LID subtypes include peak-dose dyskinesia, appearing when L-DOPA and DA brain levels are highest (hence producing maximal anti-parkinsonian efficacy); diphasic dyskinesia, which coincides with the rise and fall of DA levels in the brain, during the beginning or end of the L-DOPA dosing cycle (Luquin et al., 1992); and off-dystonia (Marsden et al., 1982). The topographic and phenomenological features of LID vary greatly among PD patients suggesting heterogeneity in the contributing mechanisms. Nevertheless, peak-dose dyskinesia typically includes choreiform movements of the upper limbs, hands/fingers, trunk, and orofacial muscles, in contrast to diphasic dyskinesia, which has more distinct stereotypic and dystonic features and more frequently affects the lower limbs (Luquin et al., 1992). Off-dystonia normally occurs mostly in the morning and primarily involves the feet (Melamed, 1979). Until now, only the peak-dose variant of LID has been reproduced in the preclinical models described later in the text.

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Abbreviations: AIMs, abnormal involuntary movements; LID, L-DOPA-induced dyskinesia; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MFB, medial forebrain bundle; PD, Parkinson's disease; s.c., subcutaneous; TH, tyrosine hydroxylase; 5-HT, serotonin; 6-OHDA, 6-hydroxydopamine.

0306-4522/12 $36.00
doi:10.1016/j.neuroscience.2012.03.023

Table 1. Current options for modeling L-DOPA-induced dyskinesia in animal model

Animal model	Pros	Cons	Ideal usage	Pharmacological validation
MPTP-lesioned cynomolgus and rhesus macaque	Similarity to human in behavioral repertoire Extensive literature on the PD pathophysiology	Infrastructure	Final proof of concept of a new entity for anti-dyskinetic effect before clinical trial	Optimal—virtually all drugs and surgical therapies tested in this model
MPTP-lesioned marmoset	Small size Convenient housing Literature on the PD pathophysiology	Very difficult to separate dystonic and choreic components during dyskinesia	De novo designs (ability of a strategy to delay or prevent LID appearance)	Good validation, especially for de novo designs
MPTP-lesioned squirrel monkey	Small size Convenient housing	LID in normal animals Lack of literature	No specific advantage	
Rat 6-OHDA	Cost-effective Easy to study large number of behavioral methods Mechanistic studies	Acute lesion model not reproducing the progressive nature of nigrostriatal DA degeneration in PD	Pharmacological validation of both de novo and acute anti-dyskinetic efficacy; Mechanistic studies	Optimal—virtually all drugs and surgical therapies tested in this model
Mouse 6-OHDA	Time- and cost-effective Mechanistic studies Genetic studies	More difficult to study detailed fine motor behavior than in the rat.	Possibility to study sophisticated genetic manipulations	Suboptimal—not a model of choice for rodent POC
Mouse MPTP	Progressive denervation	Aged mice and large doses of L-DOPA required to induce AIMs. All subtypes of AIMs are not represented.	Mechanistic studies	none
Mouse aphakia	Bilateral milder denervation	Lack of non-dyskinetic animals. Different AIMs phenomenology than in the toxin models	Mechanistic studies	none

Dopamine agonists are good treatment alternatives to L-DOPA, since they normally are more long acting thus giving a more continuous DA stimulation (Stocchi, 2009). Long-acting DA agonists have been shown to produce less dyskinesia than L-DOPA when given as early monotherapy (Rascol et al., 2000). Their symptomatic efficacy is, however, inferior to that of L-DOPA, and most patients eventually need to be started on L-DOPA during the course of the disease (reviewed in Cenci et al., 2011). Also non-pharmacological DA replacement therapy options are under development, but it is yet unclear whether these will be free of dyskinetic complications. For example, the transplantation of fetal ventral mesencephalic tissue into the putamen of PD patients was successful in alleviating rigidity and akinesia in clinical trials but unfortunately led to the development of severe dyskinesia in a significant portion of the patients (Freed et al., 2001; Hagell and Cenci, 2005; Lane et al., 2010).

Trying to relieve parkinsonian symptoms without inducing dyskinesia is still a therapeutic unmet need. To achieve this goal, more knowledge is needed concerning the mechanisms through which anti-parkinsonian therapies induce dyskinesia. Moreover, a better understanding of the genesis and the pathophysiology of dyskinesia will give opportunities to find appropriate targets for its effective management. In order to devise new treatments and study disease mechanisms, it is extremely important to develop clinically relevant animal models that mimic key features of the dyskinesias seen in PD patients.

Several animal models are currently used to study LID of which a summary is supplied in Table 1. Toxin-induced models of PD in both rodents and non-human primates promptly develop AIMs when treated with L-DOPA. Being the first model to be introduced, the non-human primate model of LID has been extensively used to study system-level pathophysiology on which the metabolic or electrophysiological correlates of LID is based (Bezard et al., 2001a; Jenner, 2008). Non-human primate models of LID show remarkable phenomenological similarities to peak-dose LID in PD patients and are, therefore, considered very reliable for pathophysiological and pharmacological investigations. However, the use of rodents is advantageous because of their time- and cost-effectiveness. Rodents allow for performing complex mechanistic studies at the cellular and molecular level, and the use of genetically modified mice allows for identifying therapeutic targets when pharmacological tools are absent or insufficiently validated. In addition to the large degree of genetic homologies between rodents and humans, the basal ganglia of rodents share essential anatomical and neurochemical features with the human basal ganglia (Reiner et al., 1998). These considerations further justify the use of the rodent species to model extrapyramidal movement disorders. Neurotoxic-based models of PD often represent the late stage of the human disease where DA denervation in the putamen exceeds 90%. These models allow for an induction of dyskinesias within a very compressed time frame, since dyskinesia normally appears in a later stage of PD progression.

NON-HUMAN PRIMATE MODELS OF LID

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned non-human primates treated chronically with

L-DOPA can provide excellent models to mimic dyskinesia in PD. These models include the two conditions needed for LID to appear: loss of DA in the nigrostriatal pathway, which is the basic biochemical alteration in PD (but not the sole) and development of dyskinesia after treatment with L-DOPA.

The neurotoxin MPTP was first discovered in the early 80s, when young heroin users developed severe symptoms of PD after injection of a derivative of heroin contaminated by MPTP (Langston et al., 1983). The remarkable clinical resemblance to PD led to the development of an animal model of PD using chronic administration of MPTP. In the non-human primate MPTP model, the dopaminergic neurons residing in the substantia nigra pars compacta degenerate that leads to a dopaminergic depletion in the putamen and the nigrostriatal tract in similarity to PD (Burns et al., 1983; Jenner et al., 1984; Bezard et al., 2001b; Jan et al., 2003; Guigoni et al., 2005). The noradrenergic and serotonergic system are also affected in some models (Pifl et al., 1991; Rylander et al., 2010b). Four species have been frequently used, namely the squirrel (*Saimiri sciureus*), but only by Langston's group (Langston et al., 2000; Hsu et al., 2004), the marmoset (*Callithrix jacchus*), the cynomolgus (*Macaca fascicularis*), and rhesus macaque (*Macaca mulatta*) monkeys. The MPTP-lesioned macaque monkeys show all of the major behavioral attributes of human PD, including bradykinesia, rigidity and postural abnormality (Langston et al., 2000; Bezard and Przedborski, 2011) as well as several non-motor symptoms such as cognitive impairment (Schneider, 1990; Schneider and Kovelowski, 1990), chronobiological alterations (Almirall et al., 2001) with sleep/wake disorders (Barraud et al., 2009) and gastro-intestinal perturbations (Chaumette et al., 2009). While such validations are known for the macaque species, it is much less clear whether these symptoms exist in other species.

Even if the heterogeneity of the MPTP non-human primate model of PD is beyond the scope of this review, it is worth briefly mentioning its intricacies(Porras et al., 2012). The number/frequency/schedule of administration can range from a few days (Bezard et al., 1997, 2001b) to a few months (Schneider, 1990; Schneider and Kovelowski, 1990). Also, to achieve a bilateral lesion, different routes have been used: intravenous (i.v.) (Bezard et al., 1997, 2001b), subcutaneous (s.c.), intramuscular (i.m.), and through osmotic mini-pump (Bélange et al., 2003; Hadj Tahar et al., 2004). All these regimens of intoxication differ between laboratories and can produce varying degrees of dopamine loss. In addition, different species are exposed to this variety of intoxication regimens. A careful reading of the literature is needed to evaluate the pros and cons of the methods used in each specific study.

The MPTP-lesioned marmoset

In addition to its small size and convenience in housing and handling, the MPTP marmoset monkey shows a parkinsonian state that is reversible upon administration of L-DOPA and other dopamine agonist compounds (Jenner et al., 1984). After chronic administration of L-DOPA, the MPTP marmoset monkey exhibits dyskinetic-like behaviors. Behavioral assessments are made post hoc on video-recordings of animals freely behaving in an observation cage. Such ratings are performed by trained experimenters blinded to the treatment (Pearce et al., 1998; Maratos et al., 2001; Hill et al., 2004), on which regular check of inter-observer reliability is needed (Pearce et al., 1995). Hence, the anti-parkinsonian effect of L-DOPA is assessed following rating scales deriving from the United Parkinson's disease Rating Scale (UPDRS) (Imbert et al., 2000; Bezard and Przedborski, 2011). The parkinsonian disability is assessed by a combination of mobility, bradykinesia, and posture scores. The severity of dyskinesia is commonly rated using the Dyskinesia Disability Scale (Pearce et al., 1995): 0, dyskinesia absent; 1, mild, fleeting, and rare dyskinetic postures and movements; 2, moderate, more prominent abnormal movements, but not interfering significantly with normal behavior; 3, marked, frequent and, at times, continuous dyskinesia intruding on the normal repertoire of activity; or, 4, severe, virtually continuous dyskinetic activity replacing normal behavior and disabling to the animal. The dyskinesia score assesses both the severity and duration of the dyskinesia. Besides the subjective analysis of the videos, an automated measurement of locomotor activity is commonly performed. Chronic L-DOPA administration produces a marked and continuous hyperkinesia (without episodes of rest) during the L-DOPA peak time. The animals are restless and driven to move. Marmosets exhibit dyskinetic movements including random flicking movements (chorea-like), sustained posturing (dystonia-like), and repetitive purposeless movements (Pearce et al., 1995). However, the pronounced hyperkinetic component of the marmoset dyskinesia makes it difficult to separately assess choreic and dystonic components (Fox and Brotchie, 2010). The marmoset model has been used to study novel treatment entities using both drug-naïve animals, that is, in a de novo design (Pearce et al., 1998; Maratos et al., 2001; Hill et al., 2004) and in L-DOPA-exposed animals (Huot et al., 2011; Kobylecki et al., 2011).

The robust locomotor activity in response to L-DOPA administration provides a simple quantitative way to assess both alleviation of anti-parkinsonian symptoms and induction of dyskinesia by the tested therapeutic agent. The marmoset model is often used to select anti-parkinsonian compounds given as monotherapy or adjuncts to L-DOPA on the basis of a greater/longer reduction of the motor disability and/or of a lower propensity to induce dyskinesia compared with the gold-standard L-DOPA treatment. However, the limited behavioral repertoire of the marmoset model called for further efforts in modeling LID in species that would allow researchers to distinguish and rate the severity of both choreic-like and dystonic-like disabling movements. Since the pathophysiology of both manifestations differs, new therapeutic interventions are likely to differentially affect them, therefore requiring a detailed analysis for grounding development decisions.

MPTP-lesioned macaques (cynomolgus and rhesus)

The macaque model basically takes advantage of the same experimental setting, design and scoring system described in the marmoset section except that chorea and dystonia can be assessed separately. The rhesus and cynomolgus macaques readily show various combinations of choreic, dystonic, and even ballistic movements (Clarke et al., 1987; Boyce et al., 1990; Bézard et al., 2003; Gold et al., 2007; Berton et al., 2009; Fasano et al., 2010). Dyskinetic patterns of activity induced by L-DOPA are highly idiosyncratic for each animal. The macaque model of LID presents a repertoire and severity of dyskinesia similar to the one seen in PD patients. Moreover, after being established by chronic administration of L-DOPA, the dyskinesias in the MPTP macaque model are stable and reproducible. Even if the L-DOPA treatment is stopped for a few weeks, restoration of L-DOPA at the first dose will trigger the same dyskinesias as observed before. This allows repeated drug testing on acute expression of LID (Bezard et al., 2004; Rylander et al., 2010a).

There are two schools for the L-DOPA administration. One administers the same dose of methyl L-DOPA via a s.c. route to a group of MPTP macaques involved in the study (Grégoire et al., 2009, 2011; Ouattara et al., 2009). The s.c. route by-passes the digestive system and thus the absorption and metabolism of L-DOPA at this level. The plasma concentration of L-DOPA will be constant and homogeneous for the animal group and can mimic intravenous L-DOPA therapy (although this practice is not routinely used in patients). However, this administrative route is far from what happens in clinic where each patient responds differently to L-DOPA and thus receives different doses. The other school tailors the dose of human formulation of L-DOPA (per os route) for each animal to obtain an optimal improvement of the disability score (Bézard et al., 2003; Gold et al., 2007; Ahmed et al., 2010; Fasano et al., 2010; Rylander et al., 2010a). Even if the doses are individually different, the anti-parkinsonian behavioral response to L-DOPA will be constant and homogeneous for the group of MPTP macaques, which is similar to the common practice of treating patients. Testing new anti-dyskinetic drugs in these conditions, thus, constitutes a valid proof of concept before moving on to clinical trials. Furthermore, it appears that plasma concentrations of L-DOPA are quite homogenous with such administration procedure, suggesting that variability in doses is mostly due to absorption differences.

In conclusion, the similarity to human symptoms makes the MPTP-lesioned macaque a valuable animal model of LID. In addition, L-DOPA replacement therapy has also been associated with cognitive disorders (Decamp and Schneider, 2009), calling for specific assessment using quantitative neuropsychological tests. Among those, an object retrieval task (Schneider and Pope-Coleman, 1995), a spatial delayed response task (Decamp and Schneider, 2009), a reaction time task (Bezard et al., 2001b) can be used and introduced to complete the behavioral analysis in a given animal to maximize the level of information gathered in such complex models. L-DOPA-induced psychosis-like behaviors (Fox et al., 2006; Visanji et al., 2006) have been described as well. The latter do not seem to correlate to dyskinesia and are sensitive to other pharmacological treatments than LID.

RODENT MODELS OF LID

The 6-OHDA rat model

To induce a parkinsonian state in rodents, the neurotoxin 6-hydroxydopamine (6-OHDA) (Ungerstedt, 1968) can be injected virtually anywhere along the nigrostriatal tract, where it induces a varying degree of DA denervation (Cenci et al., 2002). The toxin is taken up by catecholaminergic neurons in which it causes oxidative stress and mitochondrial damage ultimately leading to cell death. 6-OHDA is only a relatively selective toxin, since it has the ability to destroy also serotonergic and noradrenergic fibres, especially when injected in the medial forebrain bundle (MFB), which includes ascending fiber systems from the raphe pontine nucleus and locus coeruleus, respectively. However, noradrenergic fibers can be spared if an inhibitor of the noradrenaline transporter (desipramine) is injected before the 6-OHDA lesion. However, desipramine is ineffective when large toxin concentrations are injected into the MFB (Iderberg, unpublished observations). Depending on the site of injection, different lesion extents can be obtained. With the toxin concentrations commonly used in the literature, 6-OHDA injection in the MFB leads to a close to complete nigrostriatal lesion, with up to 100% loss of dopaminergic terminals in the striatum (Winkler et al., 2002). The toxin is generally injected unilaterally, as a severe bilateral lesion leads to a severe phenotype where animals require particular postoperative nursing protocols. In addition, a major practical advantage offered by unilateral lesion models is that motor performance on the non-impaired side of the body can serve as a control relative to the impaired side in all tests assessing lateralized behavior, for example, rotation, sensorimotor integration, and forelimb use (Lundblad et al., 2002).

In the literature, it was long assumed that the responsiveness to L-DOPA merely could be measured with tests of contralateral rotation and that actual dyskinetic movements would be impossible to evaluate. However, in 1998 a rating scale to quantify AIMs in rats was first published by Cenci and collaborators (Cenci et al., 1998). Since then, this method for scoring AIMs has gradually replaced measures of contralateral rotation in most rodent studies of LID. A landmark toward this development was the demonstration that L-DOPA-induced rotations, and AIMs show different responses to anti-parkinsonian and anti-dyskinetic interventions (Lundblad et al., 2002). Although contralateral rotations has been used as a measure of dyskinesia in both rats and mice (Papa et al., 1994; Henry et al., 1998), it has become increasingly recognized that this parameter not always correlates with the development of dyskinesia. Indeed, contralateral turning can be induced also by a number of anti-parkinsonian drugs that have very low dyskinesiogenic potential, such as bro-

mocriptine (Lundblad et al., 2002; Lindgren et al., 2009), and ropinirole (Ravenscroft et al., 2004; Carta et al., 2008). Moreover, drugs that reduce dyskinesia do not necessarily reduce the animal's contralateral rotational behavior (Lundblad et al., 2002).

Treatment of 6-OHDA-lesioned rats with therapeutic doses of L-DOPA induces a clear improvement in many commonly used behavioral tests of akinesia, such as the cylinder test and the rotarod test (Lundblad et al., 2002, 2003). However, L-DOPA-induced AIMs can interfere with these goal-directed behaviors (Lee et al., 2000; Lundblad et al., 2002; Picconi et al., 2003; Dekundy et al., 2007), which attests that the AIMs are purposeless and potentially disabling. Using larger doses of L-DOPA results in an increased incidence and earlier development of severe dyskinesia (Lindgren et al., 2007), making it difficult to evaluate the effects of L-DOPA on goal-directed behaviors.

Assessing AIMs is quite feasible in rodents with unilateral lesions since side-biased dyskinetic movements, which clearly depart from the animal's normal behavioral repertoire, are easy to recognize. There is, however, no absolute requirement for the lesion to be unilateral in order for L-DOPA to induce dyskinesia. Indeed, L-DOPA treatment induces AIMs also in bilateral 6-OHDA rat models of PD (Paillé et al., 2007). The rodent AIMs are rated on scales based on their topographical distribution, duration, and amplitude (Winkler et al., 2002; Cenci and Lundblad, 2007). A combined application of amplitude and time-based scales gives the AIMs test a large dynamic range and allows for a careful and precise evaluation of the profile of the dyskinesia in each subject. Three main AIM subtypes are included in the ratings, each representative of a certain topographical area of the body: (I) Limb dyskinesia, affecting the forelimb contralateral to the lesion, (II) axial dyskinesia, affecting the neck and upper trunk with twisting movements toward the side contralateral to the lesion and (III) orolingual dyskinesia affecting the orofacial musculature. The AIMs has been described in detailed with illustrative pictures and representative video-sequences in previous publications (Cenci et al., 2002; Winkler et al., 2002; Cenci and Lundblad, 2005). Importantly, the rating scale only takes into account movements that are qualitatively different from an increased manifestation of normal rodent behaviors, such as grooming, exploratory sniffing, or goal-directed licking or gnawing. These normal behaviors can be readily distinguished from the AIMs as they engage both sides of the body, and they are superimposed to a pattern of general behavioral activation. The occurrence of LID in the rat is highly dependent on the degree of striatal denervation (Winkler et al., 2002; Paillé et al., 2007; Nadjar et al., 2009) and the dose of L-DOPA given (Lindgren et al., 2007). In 2002, it was reported that also rats with intrastriatal 6-OHDA-lesions, which mimics a partial denervation in early PD, develop dyskinetic movements following chronic L-DOPA administration (Winkler et al., 2002). However, at the same dose of L-DOPA, the overall AIMs severity was lower in this model than in rats with complete lesions (Winkler et al., 2002). The threshold dose of L-DOPA for inducing contralateral turning in a DA-denervated rat is generally higher than the threshold for inducing LID (Lindgren et al., 2007), which can be considered a positive feature of the model because the lower drug doses sufficient to induce AIMs are more clinically relevant and reflect the daily L-DOPA doses given to advanced PD patients. At low-therapeutic doses of L-DOPA, the range of dyskinesia severities will vary greatly within a group of 6-OHDA-lesioned animals, thus mimicking the variable susceptibility to LID in PD patients. This is advantageous for experimental research given that the severity of dyskinesia can be correlated to molecular changes in the brain, facilitating the identification of critical mechanisms in the pathophysiology of LID (Cenci et al., 1998; Andersson et al., 1999). The large surges of extracellular DA in the striatum after L-DOPA administration (Meissner et al., 2006; Lindgren et al., 2010) act on supersensitive DA receptors in DA-denervated neurons, causing upregulation of immediate early genes and neurotransmitter-related genes (reviewed in Cenci and Konradi, 2010). Using immunohistochemical detection methods, the degree of upregulation of several of these genes and signaling molecules downstream of the DA receptors has been correlated to the severity of dyskinesia (Cenci et al., 1998; Andersson et al., 1999; Sgambato-Faure et al., 2005; Pavón et al., 2006; Santini et al., 2007; Westin et al., 2007). Recently, also microvascular plasticity in the basal ganglia has been reported to correlate positively to dyskinesia severity in the rat model of LID (Westin et al., 2006; Lindgren et al., 2009). This microvascular plasticity is largely modulated by vascular endothelial growth factor (VEGF), the main angiogenic cytokine that also increases the permeability of the blood–brain barrier (Ohlin et al., 2011). Following observations made in the rat model, angiogenic activity and upregulation of VEGF mRNA was revealed also in postmortem basal ganglia tissue from dyskinetic PD patients (Ohlin et al., 2011).

The rat model of LID has been the subject of extensive pharmacological validation studies. These have demonstrated that many agents that reduce LID in PD patients and non-human primates also significantly reduce the AIMs scores in the rat (Lundblad et al., 2002; Dekundy et al., 2007; Eskow et al., 2007; Quik et al., 2007; Muñoz et al., 2008; Kobylecki et al., 2010; Rylander et al., 2010a; Bordia et al., 2012; Kobylecki et al., 2011). Furthermore, anti-parkinsonian medications that have low dyskinesiogenic potential do not induce significant AIMs in the rat (Lundblad et al., 2002, 2003), further confirming the model's predictive validity.

A recently appreciated intricacy of the rat model of LID is the degree of damage that 6-OHDA lesions potentially cause to the serotonergic and noradrenergic systems in the brain. Depending on the injection paradigm used, these systems are differentially damaged. Likewise, the extent of neurodegeneration affecting these systems can vary significantly between PD patients, possibly depending on age, disease duration, and genetic predispositions. The importance of these systems to the pathophysiology and treatment of LID has been brought forward by several recent publications (Carta et al., 2007; Rylander et al.,

2010b; Dupre et al., 2011; Miguelez et al., 2011; Ostock et al., 2011; Rylander, 2012). Of particular interest, the density of striatal serotonin (5-HT) innervation is higher in dyskinetic subjects in rat and monkey PD models (Rylander et al., 2010b; Zeng et al., 2010), which is congruent with findings in the postmortem striatum from dyskinetic PD patients (Rylander et al., 2010b). Intriguingly, the 5-HT system plays an important role in the presynaptic control of DA release after L-DOPA administration, and agonists of the 5-HT autoreceptors, 5-HT_{1A} and 5-HT_{1B} reduce DA efflux from 5-HT neurons as well as dyskinesia (Carta et al., 2007; Lindgren et al., 2010). This category of compounds represents a therapeutic strategy that is currently under clinical evaluation. The previously mentioned considerations indicate the importance of considering the degree of lesion affecting all monoaminergic systems when comparing results from different laboratories. Moreover, a lesion of the MFB causing noradrenergic and serotonergic denervation in rodents is not necessarily a disadvantage in modeling the human disease as a loss of the latter is an important aspect of the pathology of PD.

In addition to LID and motor symptoms, rodents with 6-OHDA lesions can be used to model non-motor aspects of PD, particularly within the domains of cognitive and autonomic dysfunction (reviewed in Fleming, 2011; Lelos and Dunnett, 2011). Thus far, the possibilities offered by these more complex behavioral tests do not seem to have been exploited for the sake of therapeutic discovery.

The 6-OHDA mouse model

Among the rodent species, the rat is the most convenient to use for surgical manipulation and behavioral analysis. Nevertheless, the vast availability of genetically engineered mouse strains has raised a great interest toward using the mouse for studies of LID. Damage to the midbrain DA neurons in mice can be induced both by systemic administration of MPTP and by intracerebral injection of 6-OHDA. The MPTP model, however, presents some drawbacks due to its strain dependency (Jackson-Lewis and Przedborski, 2007) and its variable degree of behavioral and biochemical impairments (Date et al., 1990; Mitsumoto et al., 1998; Sedelis et al., 2000). Moreover, the induction of LID in MPTP mice has been described to require aged mice and very large doses of L-DOPA (200 mg/kg), and it does not present all the dyskinetic subtypes observed in human PD, parkinsonian non-human primates, or 6-OHDA-lesioned rats (Nicholas, 2007). Thus, 6-OHDA lesions currently represents the procedure of choice to obtain mouse models of LID (Santini et al., 2007; Darmopil et al., 2008; Francardo et al., 2011; Smith et al., 2012). Indeed, the unilateral 6-OHDA lesion procedure presents many advantages, inducing a stable and reproducible damage to the nigrostriatal system, as well as a high predictability in the degree and temporal course of DA degeneration. Choosing the appropriate toxin concentration and injection site makes it possible to obtain different models of PD, mimicking either the early or late stages of the disease (Blandini et al., 2008). In our hands, mice with 6-OHDA lesions in the MFB do not show biochemical evidence of 5-HT damage (Francardo et al., 2011). However, this may depend on the fact that we use a minimally invasive lesion procedure, that is, a low toxin concentration (3.2 μg/μl) that is injected with a very thin glass capillary (tip diameter $\sim$20 μm). In another recent study on MFB-lesioned mice, the use of a higher toxin concentration (6 μg/μl) and a normal syringe needle indeed caused some degree of 5-HT depletion (Smith et al., 2012).

The first evidence that 6-OHDA lesioned mice can develop dyskinesia was published in 2004, when Lundblad et al. reported the presence of AIMs with dystonic and hyperkinetic features in mice, similar to those previously characterized in the rat (Lundblad et al., 2004). The rating scale used for mouse AIMs follows the same principles as that used for the rats, and reflects the topographic distribution, frequency, and duration of the dyskinetic behavior affecting orofacial, trunk, and limb muscles (Lundblad et al., 2004; Darmopil et al., 2008; Francardo et al., 2011; Smith et al., 2012). The mouse model of LID has been pharmacologically validated to some extent, showing that the severity of AIMs can be reduced by acute administration of compounds like amantadine and buspirone, which alleviate LID in other animal models of PD (Lundblad et al., 2005) and in PD patients (Jankovic and Stacy, 2007). However, for therapeutic screening purposes, the rat is to prefer over the mouse model. Indeed, AIMs are easier to quantify in rats, they have been more extensively validated, and they display a large degree of stability and reproducibility over prolonged treatment periods (unpublished observations from Iderberg and Francardo).

An important issue raised by the first studies performing 6-OHDA lesions in mice was the high degree of postoperative mortality, particularly when using MFB lesions (82%), but also intrastriatal lesions (30%) (Lundblad et al., 2004). More recently, Francardo et al. (2011) showed that such a large mortality is not an inherent feature of the 6-OHDA model in mice, and that it can be prevented using adequate postoperative nursing protocols. Indeed, Francardo et al. (2011) managed to completely eliminate any postoperative mortality even after complete MFB lesions thanks to intensive, daily postoperative care and food supplementation during 3 weeks postlesion (Francardo et al., 2011). This same study showed that lesions in the MFB or the striatum result in different patterns of DA denervation, different extents of postsynaptic supersensitivity to L-DOPA, and largely different susceptibilities to dyskinesia. The MFB lesion, yielding a severe and uniform DA depletion in both lateral and medial striatum, provides a model of maximal molecular supersensitivity to L-DOPA. On the contrary, striatal 6-OHDA lesions cause a comparably large denervation only in the lateral striatum. The large amount of residual DA innervation explains why mice with striatal 6-OHDA lesions show some degree of spontaneous recovery if observed over several weeks (Alvarez-Fischer et al., 2008), being associated with compensatory DA fiber sprouting (Mitsumoto et al., 1998). In the latter model, the severity of axial, limb, and orolingual AIMs varies markedly among animals, and some of them remain totally free from dyskinesia, when treated with low thera-

peutic doses of L-DOPA (6 mg/kg). The presence of non-dyskinetic animals and the high interindividual variability of AIMs severity in the striatal 6-OHDA model affords the possibility to investigate potential susceptibility factors to dyskinesia. By contrast, all mice with MFB lesions develop severe dyskinesia when treated with standard, low doses of L-DOPA (6 mg/kg) (Fasano et al., 2010; Francardo et al., 2011). With the latter model, a differentiation between dyskinetic and non-dyskinetic subjects only can be achieved by using different doses of L-DOPA. In both lesion models described previously, as already observed in rats, L-DOPA induces contralateral rotations, more pronouncedly in dyskinetic than in non-dyskinetic mice (Francardo et al., 2011).

The striatal and MFB lesion paradigms differ also in the expression pattern of postsynaptic markers of dyskinesia. As described in other animal models of PD, each L-DOPA dose transiently induces phosphorylated (active) forms of extracellular signal regulated kinase 1 and 2 (pERK1/2) in striatal neurons (Westin et al., 2007) and provides an early marker of aberrant neuroplasticity and postsynaptic D1 receptor supersensitivity (reviewed in Cenci and Konradi, 2010). It was recently shown that the expression pattern of pERK1/2 following an acute administration of L-DOPA in mice with striatal 6-OHDA lesions provides a mirror image of the density of tyrosine hydroxylase (TH) immunoreactivity (Francardo et al., 2011). More specifically, pERK1/2 is expressed only in the lateral most TH-depleted striatal regions, whereas medial areas with more than 60% residual TH fibers do not show any ERK activation. In contrast, MFB-lesioned mice, having pronounced and uniform loss of striatal TH fibers, exhibit a widespread upregulation of pERK1/2 throughout the striatum (Francardo et al., 2011). Intranigral injection of 6-OHDA was recently described as a possible alternative lesion model of PD in mice (Grealish et al., 2010). However, our observations using this type of lesion show very low levels of ERK activation after an acute L-DOPA injection also in the most denervated striatal regions, indicating that nigral 6-OHDA lesions are not suitable for studies aiming at reproducing LID in the mouse (Francardo et al., 2011).

In rats (Andersson et al., 1999), non-human primates (Berton et al., 2009; Fasano et al., 2010), and mice (Lundblad et al., 2004; Pavón et al., 2006; Fasano et al., 2010; Francardo et al., 2011), a robust molecular correlate of dyskinesia is provided by the striatal expression of ΔFosB, a stable transcription factor that accumulates in the brain after chronic perturbations (Hope et al., 1994). Interestingly, upregulation of ΔFosB has recently been demonstrated also in postmortem putamen from PD patients with dyskinesia (Lindgren et al., 2011). The expression pattern of ΔFosB is similar to the one described for pERK1/2, being widely upregulated throughout the striatum in the MFB lesion model and restricted to the most denervated lateral regions in the striatal lesion model (Pavón et al., 2006; Francardo et al., 2011). As described in the rat (Andersson et al., 1999; Cao et al., 2010) and in the non-human primate models (Berton et al., 2009), also in the mouse the involvement of pERK1/2 and ΔFosB in the dyskinetic mouse is further demonstrated by the important reduction of dyskinesia obtained by targeting upstream components of the Ras-ERK-ΔFosB signaling cascade (Fasano et al., 2010).

An interesting observation in the mouse 6-OHDA lesion model is the presence of dopaminergic neurons in the striatum (Darmopil et al., 2008; Francardo et al., 2011; Masuda et al., 2011; Smith et al., 2012). TH-positive neural bodies in the striatum were first observed in the rat striatum by Tashiro et al. (1989) (Tashiro et al., 1989) and later by other groups both in rats (Meredith et al., 1999; Jollivet et al., 2004), non-human primates (Dubach et al., 1987; Palfi et al., 2002), and in PD patients (Huot and Parent, 2007). These neurons have been described as GABAergic interneurons regulated by 6-OHDA lesion and L-DOPA treatment (Darmopil et al., 2008). Compared with the corresponding rat model, MFB-lesioned mice show a much larger number of TH-positive cell bodies in the striatum (Iderberg and Francardo; unpublished observations). Following L-DOPA treatment, the number of these cells increases greatly in the mouse, correlating both with dyskinesia severity and with the expression levels of ΔFosB (Francardo et al., 2011). However, the functional importance of these neurons is yet to be clarified.

Potential strain differences in the sensitivity to L-DOPA ought to be considered when setting up a mouse model of LID. A recent study from Thiele et al. (2011) compared rotational behavior and AIMs following a chronic L-DOPA treatment in pure FVB and FVB/C57BL6 mice, and a higher sensitivity to develop dyskinetic behavior was observed in these latter ones (Thiele et al., 2011). Except for this study, no other strains comparisons have been done, and to our knowledge only the C57BL6 strain has been utilized thus far to generate mouse models of LID (Lundblad et al., 2004; Santini et al., 2007; Darmopil et al., 2008; Grealish et al., 2010; Francardo et al., 2011; Smith et al., 2012).

The relative ease of genetic manipulation in the mouse has led to a recent development of many genetic models of PD in this species (Dawson et al., 2010). Although only about 10% of PD cases are clearly due to genetic causes, the study of knockout and transgenic mice for PD-related genes is very helpful to investigate molecular pathways of neurodegeneration and devise biomarkers or targets for therapeutic intervention. Several interesting mouse strains have been generated to overexpress the genes involved in autosomal-dominant PD, that is, α-synuclein (Chesselet, 2008; Chesselet et al., 2008) and leucine-rich repeat kinase 2 (LRRK2) (Li et al., 2009, 2010). Models to study autosomal-recessive PD have been generated through knockout, or knockdown, of Parkin (Itier et al., 2003; Perez and Palmiter, 2005), DJ-1 (Goldberg et al., 2005), and phosphatase and tensin homolog (PTEN)-induced novel kinase 1 (PINK1) (Kitada et al., 2007; Gautier et al., 2008; Gispert et al., 2009). However, none of these models accurately reproduces PD pathology, since nigral DA neurons do not degenerate. Indeed, the lack of nigrostriatal pathology may depend on compensatory mechanisms occurring during development (Dawson et al., 2010). Since

the DA denervation is strictly required for the development of LID, the use of genetic mouse models of PD for reproducing LID has thus far been very limited. To the best of our knowledge, the only genetic model of PD in which dyskinetic movements have been observed following the administration of L-DOPA is the aphakia mouse (Ding et al., 2007). This mouse shows a bilateral DA depletion occurring selectively in the nigrostriatal system. In aphakia mice, bilateral AIMs (particularly prominent in the hind limbs) were induced by L-DOPA and DA receptor agonists, attenuated by anti-dyskinetic agents (amantadine and buspirone), and were accompanied by the expression of postsynaptic markers of dyskinesia, similarly to that observed in the 6-OHDA model (Ding et al., 2007, 2011).

The advances made in the last years in lesion procedure, postoperative care and experimental protocols for behavioral testing in 6-OHDA-lesioned mice have smoothed some of the disadvantages previously associated with this animal model. These technical improvements will certainly facilitate a larger application of mice to dissect mechanisms and investigate pathways at the basis of LID.

VALIDATION OF THE MODELS: THE THERAPEUTIC APPROACH

Animal models are tools of primary importance in the search for new pharmacological options to treat LID. Over the last years, the knowledge acquired studying animal models allowed for the discovery of several new targets and development of new drugs that are now in different phases of clinical trials (Cenci et al., 2011 and Meissner, 2011 #297).

The glutamate system is a primary target for anti-dyskinetic therapeutic, since it has been showed to be strongly implicated in the mechanisms behind LID. A dysregulated corticostriatal glutamatergic transmission giving rise to increased glutamate levels in the striatum and the substantia nigra pars reticulata have been shown to be associated with LID in the rat (Sgambato-Faure and Cenci, 2012). Amantadine, which is a weak non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, has been shown to achieve significant anti-dyskinetic effects in the rat (Lundblad et al., 2002; Dekundy et al., 2007; Kobylecki et al., 2011), mouse (Lundblad et al., 2005), macaque (Blanchet et al., 1998), and the marmoset model of LID (Hill et al., 2004; Kobylecki et al., 2011). Amantadine is currently the only available efficacious medication for the treatment of dyskinesia (Verhagen Metman et al., 1998; Luginger et al., 2000; da Silva-Junior et al., 2005; Wolf et al., 2010). The effect magnitude of amantadine found in the animal models translates quite well with that seen in patients.

Metabotropic glutamate receptors (mGluR) are emerging as a hot topic in therapeutic PD research, due to their modulatory role in synaptic transmission and relatively selective distribution in the brain. Specific antagonists of metabotropic glutamate receptor 5 (mGluR5) have been shown to reduce the severity of dyskinesia in rats (Mela et al., 2007; Levandis et al., 2008; Rylander et al., 2009; Marin et al., 2011), in macaques (Rylander et al., 2010a; Grégoire et al., 2011), and recently also in a double-blind randomized placebo-controlled phase II clinical trial (Berg et al., 2011).

Another system that deserves particular attention is the serotonergic system. The importance of this system in the development of LID has evoked interest for its modulators as potential treatment strategies. Agonists of the 5-HT_{1A} and 5-HT_{1B} receptors has proven to be efficacious in reducing LID in rats (Carta et al., 2007; Lindgren et al., 2010; Gerlach et al., 2011) monkeys (Muñoz et al., 2008; Grégoire et al., 2009) and importantly also in patients (reviewed in Cenci et al., 2011). Buspirone, an anxiolytic agent with primarily 5-HT_{1A} agonist activity, was shown to improve dyskinesia in PD patients already in 1994 (Bonifati et al., 1994).

Also, a growing body of research points to the possibility of targeting either the adenosine, endocannabinoid, or opioid receptors pharmacologically to treat LID. Among these, a main candidate is the adenosine 2A (A2A) receptor, abundantly expressed in striatal medium spiny neurons of the indirect pathway, with projections to the external globus pallidus (Schiffmann et al., 1991; Augood and Emson, 1994). Activation of these receptors would ultimately counteract parkinsonian symptoms induced by DA deficiency, modulating the striatopallidal GABA transmission that in the parkinsonian state is decreased. Accordingly, antagonists of A2A receptor have demonstrated anti-akinetic efficiency in both rodents (Hauber et al., 2001) and non-human primates (Grondin et al., 1999). However, these antagonists have proven efficacious in alleviating dyskinesia only to a minor extent in MPTP-treated non-human primates (Bibbiani et al., 2003) and MPTP-treated mice (Xiao et al., 2006). Following clinical assessment in double-blind randomized clinical trials, it is more likely that A2A antagonists will best be used as an adjunct to L-DOPA in early treatment due to their DOPA-sparing activity (Hauser et al., 2011). Combinatory treatment may allow for usage of lower L-DOPA doses, preventing or delaying the development of dyskinesia. Also, opioid transmission is of major importance for basal ganglia function in terms of motor control. Accordingly, the aberrant transmission of certain opioid receptors has been correlated to the expression of LID in PD patients (Piccini et al., 1997b) and 6-OHDA-lesioned rats (Johansson et al., 2001a), However, non-specific opioid receptor antagonists have had no effect on dyskinesia in clinical trials (Rascol et al., 1994; Fox et al., 2004). Conversely, a selective antagonist to the Mu-Opioid receptor was recently shown to reduce LID in the MPTP-lesioned macaque model (Henry et al., 2001; Koprich et al., 2011), which is promising for future clinical studies.

The extensive use of the available animal models to screen for new potential treatments has provided evidence of great drug response variability between subjects. This fact highlights the need for individually tailored pharmacological strategies in the future. A plausible explanation to this phenomenon is the heterogeneity in plastic changes in

the brain following DA degeneration and chronic L-DOPA treatment. In clinical studies, the age of the patient, the progression of the disease and the duration of the L-DOPA treatment should, thus, be used as important parameters in the choice of the treatment. For example, agonists of 5-HT autoreceptors could be proposed as treatment for young patients that do not present a pronounced degeneration of the 5-HT system.

Unfortunately, despite promising anti-dyskinetic effects in animal models, some drugs, for example sarizotan, a 5-HT_{1A} agonist, have failed in larger doubled-blind placebo controlled clinical trials (Goetz et al., 2007). These inconsistent results can be explained by the fact that dyskinesia is highly sensitive to placebo effect (Goetz et al., 2008). Hence, to increase the success rate of clinical trials, further investigations in the available animal models are needed in order to determine which receptors or targets and which associated compounds represent the most interesting and promising approaches for the future treatment of LID.

Moreover, one should bear in mind that the most common endpoints in phase II and III clinical trials for LID therapeutics are the time spent ON without disabling LID and the quality of life. These two features are reported in the patient's home diary, which is highly subjective and of subject to interferences. As reliable as the models can be, we still face this issue in adapting the analysis of the animal models to this crude observation. In an attempt to approach the clinical situation, researchers now provide estimates of the time spent by dyskinetic monkeys with or without disabling dyskinesia during the testing sessions-(Koprich et al., 2011), thereby providing an easily translational index, that is, time instead of severity per se. Whether this measure will increase the predictive validity of the animal data will have to be demonstrated by upcoming clinical trials.

CONCLUDING REMARKS

The current status of preclinical research on LID includes different animal models such as non-human primates, rats, and mice. The development of these animal models has led to progress in the understanding of the molecular mechanisms at the basis of this movement disorder. As our tools develop further we will be able to unveil the complexity of the systems that induce dyskinetic movements. A major concern to justify the use of a certain animal model is to be able to ascertain its face validity and its translational applicability (both toward the other models and to the clinic). Face validity implies the animal model's ability to model the disease in a way that it, in fact, looks like the human disorder. Dyskinesia in PD patients is defined as movements that are abnormal and involuntary and interfere with physiological motor activities, and they consist of both dystonic and hyperkinetic components. Indeed, the AIMs seen in the animal models described herein all fulfil this definition.

The term construct validity reflects the working hypothesis that underlies the model, and whether the model is measuring what is intended. These aspects have been validated in mechanistic studies. Presently there is a unified view that LID is caused by large surges in striatal extracellular levels of DA following the administration of L-DOPA combined with a state of postsynaptic DA receptor supersensitivity. Large changes in DA release post–L-DOPA administration have been shown in PD patients using PET-raclopride binding (de la Fuente-Fernández et al., 2004), non-human primates (Carta and Bezard, 2011), and in rats using in vivo microdialysis (Carta et al., 2006; Meissner et al., 2006; Lindgren et al., 2010). A large part of this exacerbated release most likely originates from serotonergic neurons (Carta et al., 2007; Lindgren et al., 2010), a notion confirmed by a recent study where PET-raclopride binding was increased and extracellular levels of DA decreased after treatment with the 5-HT_{1A} agonist 8-OH-DPAT in rats with complete DA lesions (Nahimi et al., 2012). On the postsynaptic side, both rodent and non-human primate models of LID show a reduced density of opioid receptor binding in the striatum and other basal ganglia nuclei (Johansson et al., 2001b; Aubert et al., 2007), which is also seen in human dyskinetic patients (Piccini et al., 1997a). In addition, a striatal upregulation of opioid precursor genes (like prodynorphin), and immediate early genes (like ΔFosB) has been shown to occur in both rats (Henry et al., 2003), non-human primates (Fasano et al., 2010), and human subjects affected by LID (Lindgren et al., 2011). Recent microdialysis studies in rats and mice have provided mechanistic information implying that LID also is associated to large surges in GABA in the substantia nigra. Anti-dyskinetic treatment with amantadine has been shown to blunt this GABA surge (Bido et al., 2011), strengthening its importance in the mechanisms behind LID. Additionally, a D1 antagonist locally infused into the striatum will both reduce LID and the accompanying GABA surge (Mela et al., 2012).

Regarding predictive validity, the animal models of LID have been validated through their response to pharmacological agents that are already in use for the treatment of PD, such as amantadine, clozapine, and DA receptor agonists (Lundblad et al., 2002; Dekundy et al., 2007; Kobylecki et al., 2011). Other drugs that reduce LID in the animal models have produced anti-dyskinetic effects in proof-of-concept clinical trials (Cenci et al., 2011). In addition, rodent LID is worsened by higher doses of L-DOPA, just like in patients. Rodent dyskinesias are negligible when animals are treated with long-acting DA agonists in comparison with L-DOPA. Taken together, these data provide sufficient predictive validity for using the described animal models in order to devise new potential treatments.

The most recent contribution to the field has been the development of LID models in mice. This development lays the ground for using genetically modified animals in the study of LID, which may have potentially revolutionary effects on understanding the molecular pathways through which L-DOPA induces dyskinetic motor responses.

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(Accepted 16 March 2012)
(Available online 21 March 2012)