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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.

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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.

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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