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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.

Contents

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 Koller, 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 they would have if started initially on L-DOPA therapy (Katzenschlager 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; Grondin 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 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; Falardeau 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, whereas 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