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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

# Non-human primate models of PD to test novel therapies

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**Abstract** Non-human primate (NHP) models of Parkinson disease show many similarities with the human disease. They are very useful to test novel pharmacotherapies as reviewed here. The various NHP models of this disease are described with their characteristics including the macaque, the marmoset, and the squirrel monkey models. Lesion-induced and genetic models are described. There is no drug to slow, delay, stop, or cure Parkinson disease; available treatments are symptomatic. The dopamine precursor, L-3,4-dihydroxyphenylalanine (L-Dopa) still remains the gold standard symptomatic treatment of Parkinson. However, involuntary movements termed L-Dopa-induced dyskinesias appear in most patients after chronic treatment and may become disabling. Dyskinesias are very difficult to manage and there is only amantadine approved providing only a modest benefit. In this respect, NHP models have been useful to seek new drug targets, since they reproduce motor complications observed in parkinsonian patients. Therapies to treat motor symptoms in NHP models are reviewed with a discussion of their translational value to humans. Disease-modifying treatments tested in NHP are reviewed as well as surgical treatments. Many biochemical changes in the brain of post-mortem Parkinson disease patients with dyskinesias are reviewed and compare well with those observed in NHP models. Non-motor symptoms can be categorized into psychiatric, autonomic, and sensory symptoms. These symptoms are present in most parkinsonian patients and are already installed many years before the pre-motor phase of the disease. The translational usefulness of NHP models of Parkinson is discussed for non-motor symptoms.

**Keywords** Non-human primate · Parkinson · Levodopa · Dyskinesia · Pharmacotherapy · MPTP

## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide after Alzheimer's disease (Ascherio and Schwarzschild 2016; Dorsey et al. 2007; Pringsheim et al. 2014). The incidence and prevalence of PD increase with age and are estimated at about 0.3% in the general population and about 3% among people over 65 years of age (Pringsheim et al. 2014). PD is a chronic and progressive movement disorder characterized by motor symptoms consisting of a combination of resting tremor, rigidity, bradykinesia, and postural abnormalities (Siderowf and Stern 2003; Stacy 2009). Furthermore, non-motor symptoms are also observed in most of the parkinsonian patients including cognitive impairment such as dementia, behavioral symptoms, neuropsychiatric disorders including depression and anxiety, autonomic dysfunctions such as bladder dysfunction, sensory symptoms, pain, sleep disturbances and fatigue which persist despite treatment, reducing their quality of life (Martinez-Fernandez et al. 2016).

The pivotal pathological hallmarks of PD is loss of dopamine (DA) neurons in the substantia nigra *pars compacta* (SN*pc*) and presence of intracytoplasmatic and intraneuritic inclusions named Lewy bodies (LB) and

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Lewy neurites, respectively, mainly containing abnormal aggregates of α-synuclein (Dickson et al. 2009; Spillantini et al. 1998). Other brain neurotransmitters are also involved in PD such as noradrenergic neurons of the locus coeruleus (Chan-Palay 1991; Gesi et al. 2000), cholinergic neurons of the nucleus basalis of Meynert (Bohnen and Albin 2011; Korczyn 2001; Whitehouse et al. 1983) and pedunculopontine nucleus (Bensaid et al. 2016; Hirsch et al. 1987; Jellinger 1988), serotoninergic neurons of the raphe nucleus (Politis et al. 2012), glutamatergic neurons in the thalamus centromedian/parafascicular nucleus (Halliday 2009; Henderson et al. 2000), and hypocretin (orexin) neurons in the hypothalamus (Fronczek et al. 2007; Thannickal et al. 2007). Several studies have shown that the presence of LB in some PD patients is not restricted to SN*pc* DA neurons but is also observed in amygdala, hippocampus, olfactory nucleus, brainstem and neocortex neurons as well as in the peripheral nervous system such as the enteric, sympathic, and parasympathic ganglia (Braak et al. 2004; Jellinger 2015). Disturbances in non-dopaminergic systems observed in peripheral and central nervous systems of PD could explain, at least in part, appearance of several non-motor symptoms mainly autonomic, enteric, and neuropsychiatric disorders.

Pathological studies have shown that 50–60% of SN*pc* perikarya and up to 80–85% of striatal nerve terminals are degenerated before appearance of motor symptoms and no treatment is yet available to slow or stop progression of neuronal degeneration (Bernheimer et al. 1973; Cheng et al. 2010; Riederer and Wuketich 1976; Wirdefeldt et al. 2011). However, some non-motor features commonly associated with PD can be detected from prodromal to early stages of the disease before motor impairment. Therefore, the preclinical and prodromal stages of PD provide a good window of opportunity to identify early markers and to initiate strategic neuroprotective or disease-modifying treatments (Berg et al. 2014; Gaenslen et al. 2011; Kalia et al. 2015; Kalia and Lang 2015, 2016; Lindholm et al. 2016; Siderowf and Lang 2012).

There is no cure for PD, but treatment of motor symptoms with the DA precursor, L-3,4-dihydroxyphenylalanine (L-Dopa), introduced 50 years ago still remains the gold standard treatment and the most effective in early stages of the disease (Mercuri and Bernardi 2005). However, after 4–6 years of L-Dopa treatment, about 40% of patients develop various motor complications including L-Dopa-induced dyskinesias (LIDs) and motor fluctuations (wearing-off), which limit the quality of life in PD patients and are difficult to manage with available medication (Fabbri et al. 2016; Fabbrini et al. 2007).

Given the longer life expectancy in industrialized countries, the number of people suffering of PD will inevitably increase. Therefore, it is imperative to develop more effective treatments in the near future. In this review, we report recent advances of preclinical studies in the treatment of non-motor and motor symptoms in non-human primate (NHP) models of PD.

## NHP models of PD

Extensive knowledge on the etiology, pathogenesis, and pathophysiology of PD has been gained thanks to animal models of PD. The animal models most commonly used in preclinical studies can be categorized as neurotoxic- and genetic-based models.

### Lesion-induced NHP models of PD

The neurotoxic-based models mimic most of the pathological and behavioral features of PD in human and are very useful for the development of new therapies. The synthetic neurotoxins 6-hydroxydopamine (6-OHDA) and 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine (MPTP) inducing selective degeneration of nigrostriatal neurones in rodents and primates are the most often used for modeling PD in animals (Jagmag et al. 2016). The majority of preclinical studies using neurotoxic-based models of PD are performed in rats (6-OHDA) and mice (MPTP). Nevertheless, there are a significant amount of studies that use the NHP neutotoxic-based model. The species most commonly used as experimental model are the species of Old World monkeys, namely, African green monkey (also called the vervet monkey, *Chlorocebus sabaeus*), rhesus and cynomolgus macaques (*Macaca mulatta* and *Macaca fascicularis* respectively), and the species of the New World monkeys, the common marmosets (*Callithrix jacchus*), and the squirrel monkeys (*Saimiri sciureus*) (Morin et al. 2014; Potts et al. 2014). One of the most relevant benefits of using NHP to study PD is the great similarities with man in respect to neuroanatomical, neurophysiological, immunological, and genetic features (Grow et al. 2016) allowing translational studies in etiopathophysiology, surgical procedures, and drug treatments in PD. Moreover, although PD has not been described in monkeys, they show several similarities with human regarding age-related dysfunction of the nigrostriatal system that is correlated with motor impairments (Emborg et al. 1998; Zhang et al. 2000).

Ungerstedt (1968) was the first to use 6-OHDA to lesion the rat nigrostriatal dopaminergic pathway by stereotaxic bilateral intracerebral injections into the SN or the medial forebrain bundle (MFB) (Ungerstedt 1968). However, the bilateral lesion with 6-OHDA caused a high degree of morbidity and mortality in animals and its administration was modified to a unilateral intracerebral injection to

induce unilateral PD symptoms (Ungerstedt 1976). Depending on animal species used, the rate of the lesion formation and magnitude of the lesion will depend on the amount of 6-OHDA injected and the site of injection chosen (Przedborski et al. 1995).

Although the rat is the preferred species used for the 6-OHDA model of PD, a few studies attempted to replicate this model in NHPs. Unilateral (Annett et al. 1992) or a two-stage bilateral (Mitchell et al. 1995) stereotaxic injections of 6-OHDA into the nigrostriatal bundle of marmosets or into the SN of baboon (*Papio papio*) (Apicella et al. 1990) replicate parkinsonian features such as striatal DA depletion, nigral DA cell loss, and a marked motor impairment of limbs contralateral to the injected hemisphere. More recently, new methods for behavioral assessment of PD symptoms in a two-stage bilateral 6-OHDA lesioned common marmoset have been developed using manual scoring of PD symptoms according to an adapted PD motor rating scale, and automated movement tracking procedures based on digital video recording (Santana et al. 2015). Furthermore, especially, when testing the neuroprotective efficacy of potential neuroprotective molecules, a partial lesion animal model is a prerequisite (Blandini et al. 2008; Boix et al. 2015; Truong et al. 2006). Therefore, Eslamboli et al. (2003a) characterized the behavioral effects of intrastriatal injection of 6-OHDA in the common marmoset. These lesioning procedures led to a progressive and partial lesion of nigrostriatal dopaminergic neurons and provide an excellent therapeutic window for studying the effects of treatments to slow or stop progression of dopaminergic degeneration (Eslamboli et al. 2003a). An interesting feature of the unilateral 6-OHDA model is that the unlesioned hemisphere could be used as an internal control for each animal. However, functional and compensatory interdependence between the nigrostriatal systems in both hemispheres has been demonstrated (Blesa et al. 2011; Lieu and Subramanian 2012). It is, therefore, crucial to take into account this compensatory mechanism when interpreting the behavioral and biochemical results from studies using animals with unilateral lesions of the nigrostiatal neurons.

This neurotoxic-based model does not replicate all of the clinical features of PD, since it does not induce proteinaceous aggregates or typical LB, that is one of the cardinal hallmarks of the pathophysiology of PD, and does not affect other neuronal neurotransmitter systems such as noradrenergic neurons of the locus coeruleus, cholinergic neurons of the nucleus basalis of Meynert, or serotoninergic neurons of the raphe nucleus (Jellinger 2015). An important drawback of this animal model is that multiple stereotaxic injections of 6-OHDA into the primate striatum are required to reduce spontaneous recovery (Eslamboli et al. 2003a, 2005). In addition, intracerebral injection of 6-OHDA requires sophisticated surgical procedures performed by highly qualified personnel and proper care of animals the days following surgery.

Exposure of drug users to the neurotoxin MPTP contained in an illicit meperidine synthesis induced both behavioral changes and cellular losses that closely mimic motor symptoms in idiopathic PD (Davis et al. 1979; Langston and Ballard 1984; Langston et al. 1983). This provided a rare opportunity of having a toxin taken by humans to be used thereafter to model PD. Administration of MPTP in primates induces a parkinsonian syndrome showing a remarkable resemblance with all primary motor features of PD (Albanese et al. 1993; Bédard et al. 1992). Systemic administration of MPTP induces degeneration of DA neurons in the SN*pc* resulting in a depletion of DA in the caudate nucleus and the putamen (Bezard et al. 2001b; Burns et al. 1983; Jenner et al. 1984; Langston et al. 1984a; Smeyne and Jackson-Lewis 2005). Neuronal loss after MPTP intoxication is also observed, but to a lesser extent than for DA neurons, for noradrenergic and serotonergic neurons in the locus coeruleus and the raphe nucleus, respectively, as observed in PD (Engeln et al. 2015; Masilamoni et al. 2011; Mitchell et al. 1985; Pifl et al. 1991; Rylander et al. 2010b). Dyskinesias, the most common form of motor complications triggered by chronic treatment with L-Dopa, is also faithfully replicated in monkeys treated with MPTP (Bastide et al. 2015; Morin et al. 2014).

Furthermore, monkeys lesioned with MPTP display non-motor symptoms similar to those observed in PD such as neuropsychiatric behavior, cognitive impairment, sleep disorders, and disturbances of enteric functions (Aron Badin et al. 2015; Chaumette et al. 2009; Decamp and Schneider 2004; Duong 2010; Fifel et al. 2014; Johnston and Fox 2015; Roeltgen and Schneider 1994; Schneider and Kovelowski 1990; Schneider and Pope-Coleman 1995; Schneider and Roeltgen 1993; Tereshchenko et al. 2015).

Considering the numerous similarities described above, the NHP model of PD is still the most useful model to study the pathophysiology of PD, as well as motor and non-motor complications related to chronic treatment with L-Dopa. However, the presence of typical LB has not been observed so far in the MPTP-treated monkeys albeit accumulation of α-synuclein and phosphorylated α-synuclein immunoreactivity was identified in nigral neurons and other non-dopaminergic brain structures (Forno et al. 1986; Halliday et al. 2009; Kowall et al. 2000; McCormack et al. 2008; Purisai et al. 2005; Vermilyea and Emborg 2015).

Among various species of NHP used to model PD, the Old World monkeys, rhesus, and cynomolgus macaques (*Macaca mulatta* and *Macaca fascicularis,* respectively) are shown to be superior in modeling PD phenomenology but are expensive (Burns et al. 1983; Mitchell et al. 1985).

The New World monkeys, namely, the common marmosets (*Callithrix jacchus*) and the squirrel monkeys (*Saimiri sciureus*), of smaller size are cheaper, easier to care for but display not as clear motor symptoms (Jenner et al. 1984; Langston et al. 1984b). MPTP can also induce a parkinsonian syndrome in the baboon (Old World monkey species), but because of their large size (15–37 kg), these animals are seldom used in preclinical studies (Hantraye et al. 1993; Varastet et al. 1994). The vervet monkey (Africal green monkey, *Chlorocebus Sabaeus*) also used to model PD is the only NHP displaying a validated rest tremor (Raz et al. 2000).

Different regimens and doses of MPTP administration to macaques produce various outcomes of interest for the pathophysiology of PD. A critical analysis of 108 macaques including rhesus and cymomolgus (*Macaca mulata and fascicularis*) with a bilateral lesion following intravenous MPTP injections was reported to model PD for translational studies (Potts et al. 2014). This study showed that the MPTP-treated macaque offers a good model reproducing marked parkinsonism and LID as seen in patients with moderate/advanced PD. However, modeling PD in monkeys for translational studies relies critically on customized systemic MPTP treatment to the sensitivity of individual animals for consistency of stable parkinsonian features. It is also important to produce stable parkinsonism in macaques that critically depends on reaching "marked" motor disability. Mildly parkinsonian monkeys have a higher risk of spontaneous recovery thus providing an inconsistent model (Elsworth et al. 2000); they may be inadequate for studies of pharmacotherapies for LID but a useful model to test neuroprotective strategies (Bezard et al. 2001b, c). A more a chronic delivery of MPTP of lower doses over 2–3 weeks has been reported as well as longer treatment schedules over weeks or months and slow delivery of MPTP through osmotic mini-pumps (see reviews: Fox and Brotchie 2010; Morin et al. 2013a). Hemiparkinsonism in monkeys can also be induced with an intracarotid infusion of MPTP, but necrotic lesions were observed with this procedure limiting its use (Bankiewicz et al. 1986; Emborg et al. 2006).

Following treatment with L-Dopa, MPTP-treated macaques will exhibit dyskinetic movements including choreic-athetoid (random and constant writhing and flicking movements), dystonic (slow repetitive movements or abnormal postures), and sometimes, ballistic movements (high amplitude flailing of the limbs on one side of the body) (Ahmed et al. 2010; Bastide et al. 2015; Bezard et al. 2001a; 2003; Gregoire et al. 2011; Johnston et al. 2010; 2013; Koprich et al. 2011; Langston et al. 2000; Morin et al. 2013a, 2014; Porras et al. 2012). However, when MPTP animals are denervated to the same extent, doses of L-Dopa must be adjusted individually to produce a full antiparkinsonian effect and to develop LID to the same degree, but in general, there is a positive correlation between L-Dopa dose and the duration and the severity of LID (Gregoire et al. 2011; Guigoni et al. 2005; Johnston et al. 2010; Kuoppamaki et al. 2007). Furthermore, each macaque will display its own pattern of parkinsonian symptoms and dyskinetic movements as observed in PD patients (Rajput et al. 2009). Several rating scales exist to quantify LID and were reviewed and criticized with a focus on macaques (Fox et al. 2012). Another motor side effect induced by chronic L-Dopa administration that can be modeled in MPTP treated macaque is the wearing-off phenomenon that is described by a shorter antiparkinsonian effect of L-Dopa response followed by a gradual reappearance of parkinsonian symptoms (Morin et al. 2013a; Pahwa and Lyons 2009). Another very interesting characteristic of dyskinesias in macaque monkeys is that when L-Dopa is withdrawn for a few weeks, the next dose of L-Dopa will induce dyskinesias with the same duration and severity as measured before (Goetz et al. 1982; Mayeux et al. 1985). Moreover, treatments with dopaminergic agonists reverse motor deficit induced by MPTP and induce little or no dyskinesias before the first exposure to L-Dopa (see section on symptomatic treatments below). Adaptation of the brain to long-term DA loss and chronic L-Dopa treatment is documented in MPTP-lesioned monkeys and models changes observed in brain of PD patients. This adds to the translational value of this model that is useful in the investigation of novel drug targets.

Marmosets treated with MPTP are also frequently used to model parkinsonian syndromes and LIDs and they show physiological and behavioral effects characteristic of this species (Yun et al. 2015). The common marmoset has the advantage of their small size (about 250 g), which makes handling and housing facilities more convenient compared to the macaque (Yun et al. 2015). Systemic administration of MPTP to marmoset was first described by (Jenner et al. 1984). Acute administration of MPTP (1–3 mg/kg) with 1–5 doses administered during 4–8 days to give a bilateral DA loss is the favoured regimen (Eslamboli 2005; Yun et al. 2015). Chronic administration of MPTP (0.25–4.5 mg/kg) to marmosets over a period of weeks or months to model the slow progression of PD was shown to induce a gradual onset of behavioral deficits but with spontaneous recovery upon cessation of MPTP delivery thus limiting it use (Eslamboli 2005). Administration of L-Dopa to MPTP-treated marmosets can induce dyskinetic-like movements characterized mainly by choreic-like, dystonic-like, and repetitive aimless movements (Pearce et al. 1995). It also induces continuous and pronounced hyperlocomotion making choreic-like and dystonic-like abnormal movements difficult to assess and to distinguish (Ando et al. 2014; Bastide et al. 2015; Fox and Brotchie

2010; Iderberg et al. 2012; Morin et al. 2014). This feature of dyskinetic-like movements in MPTP-treated marmosets is not representative of the clinical pattern of dyskinesias observed in humans in which dyskinetic movements are more acutely discriminated (Bastide et al. 2015; Morin et al. 2014). In this context, this model is not privileged to test new medications intended to reduce dyskinetic movements or specific segments of the latter, but it could be more useful to test neuroprotective/neurorestorative and antiparkinsonian treatments as well as non-motor associated symptoms. In the later case, several studies in MPTP-treated common marmoset have clearly shown non-motor symptoms including constipation, bladder hyper-reflexia, excessive salivation, and sleep disturbance (Albanese et al. 1988; Barraud et al. 2009; Yoshimura et al. 1993, 1998).

Just like the macaque and the common marmoset, the squirrel monkeys intoxicated with MPTP develop a parkinsonian-like syndrome including akinesia, rigidity, and bradykinesia (Langston et al. 1984a). Administration of L-Dopa to MPTP-treated squirrel monkeys elicits dyskinetic-like abnormal movements with a prevalence of choreic-like compared to dystonic-like components (Bastide et al. 2015; Boyce et al. 1990b; Di Monte et al. 2000). Curiously, significant LID can be elicited in normal unlesioned squirrel monkeys even at therapeutic doses of L-Dopa (15 mg/kg + carbidopa, per os for 2 weeks) (Togasaki et al. 2005b; 2001). This phenomenon is also observed in other non-lesioned primate species but at very high doses of L-Dopa and over a very long period of time (Sassin et al. 1972; Pearce 1999; Pearce et al. 2001). Hence, the squirrel monkey may not be an adequate model to study this motor complication; they do not accurately model the abnormal movements of PD patients. In contrast, several studies using aged and MPTP-treated squirrel monkeys have shown the propensity of this species to accumulate α-synuclein in various brain regions as well as nitrated and phosphorylated forms of α-synuclein and also proteinase K-resistant (insoluble) α-synuclein aggregates which suggest possible development of LB in the later stages of the disease or at advanced age (Forno et al. 1986; McCormack et al. 2008; Purisai et al. 2005).

In MPTP-lesioned monkeys, a loss of striatal membrane DA transporter (DAT) is observed as in human PD (Calon et al. 2003a; Morin et al. 2013b). Striatal DA receptors particularly the D2 subtypes are reported to be increased in PD patients (Bokobza et al. 1984; Guttman et al. 1986; Lee et al. 1978); this is also observed for D1 an D2 receptors in MPTP-lesioned monkeys (Bedard et al. 1986; Falardeau et al. 1988; Gagnon et al. 1990; Graham et al. 1993). L-Dopa treatment is reported to reverse 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); in PD, these receptors were reported to be either decreased (Ryoo et al. 1998) or unchanged (Hurley et al. 1996).

Glutamate is the most abundant excitatory neurotransmitter, mediating as much as 70% of brain synaptic transmission (Klockgether and Turski 1993). 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. 2003b; Chase and Oh 2000). Changes in ionotropic (NMDA, AMPA) and metabotropic (mGlu2/3,m Glu5) glutamate receptors are reported in the brain of PD patients with dyskinesias and this is modeled in dyskinetic MPTP-lesioned monkeys (Calon et al. 2002b, 2003b; 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 PD patients and MPTP-lesioned monkeys (Calon and Di Paolo 2002).

Striatal serotonin content is decreased in MPTP-lesioned monkeys but to a lesser extent that DA (Riahi et al. 2011); this loss is also observed in the striatum of PD patients (Hornykiewicz 1975; Kish 2003; Kish et al. 2008). The serotonin transporter (SERT) and several serotonin receptor subtypes are implicated in PD and LID (Ballanger et al. 2016; Huot et al. 2011) and these transporter and receptor changes are modeled in MPTP-lesioned monkeys. (Agid et al. 1989; Chen et al. 1998; Huot et al. 2012b; Morin et al. 2015a, b; Riahi et al. 2012; 2011; Rylander et al. 2010b).

Other receptors in the brain such as adenosine $A_{2A}$ (Calon et al. 2004; Morin and Di Paolo 2014; Morissette et al. 2006a), and α7 nicotinic acetylcholine receptors (Morissette et al. 2016) as well as the neuropeptide preproenkephalin have shown similar changes in the brain associated with LID in MPTP-lesioned monkeys and human PD (Calon et al. 2002a; Morissette et al. 2006b; Tamim et al. 2010).

## Genetic-based NHP models of PD

The majority of PD cases are sporadic with unknown etiology, while approximately 5–10% of patients have monogenic Mendelian inheritance form of the disease (Tysnes and Storstein 2017). The mutated genes associated with early- or late-onset familial PD include autosomal dominant mutations in the α-synuclein, leucine-rich repeat kinase 2 (LRRK2) and the vacuolar protein sorting 35 homolog (VPS35) genes, and autosomal recessive mutations in the genes encoding for Parkin, DJ-1, and PINK-1

(Kalinderi et al. 2016). This discovery has prompted the development of various transgenic rodent lines to replicate inherited PD forms (Jagmag et al. 2016). α-Synuclein being recognized to play a key role in the sporadic and hereditary forms of PD, several transgenic models overexpressing the native or mutated form of α-synuclein have been developed (reviewed in: Jagmag et al. 2016).

Development of transgenic NHP models of PD has proven to be more difficult than in rodents (Izpisua Belmonte et al. 2015; Jennings et al. 2016). Nevertheless, genetic manipulation to create transgenic monkeys has been reported (Chan et al. 2001; Chen et al. 2015; Liu et al. 2014; Niu et al. 2010, 2014; Sasaki et al. 2009; Seita et al. 2016; Yang et al. 2008). Niu et al. (2015) created transgenic PD rhesus monkeys that express mutant α-synuclein (A53T missense mutation) that developed age-dependent (around 2.5 years of age) non-motor symptoms, including cognitive defects and anxiety phenotype, without detectable sleeping disorders (Niu et al. 2015). These authors suggest that expression of mutant α-synuclein at the early stage of the disease is more likely to affect mood behavior rather than sleep disorders. These transgenic monkeys did not demonstrate motor PD phenotypes probably due to their young age. This new model seems very promising, but a more extensive evaluation will be necessary to validate and demonstrate its usefulness and translational value especially in the pre-motor phase of PD.

The lack of transgenic models with strong genotypes and phenotypes of PD is mainly to be imputed to the limited expression of the transgene in the transgenic animal. Several studies have attempted to circumvent these problems using the viral modeling approach. A benefit of this approach is that the amount of injected viral particles can be adjusted to obtain much higher levels of transgene expression than those obtained in transgenic animals. Furthermore, the intracerebral injection of the viral particles containing the transgene of interest or a combination of different transgenes may be restricted to specific brain structures such as the striatum and SN*pc* (Fiandaca and Federoff 2014; Low and Aebischer 2012; Van der Perren et al. 2015). These models are widely used in rodents, but as observed in transgenic models, most of them do not faithfully replicate all of the etiopathological characteristics of PD (Fiandaca and Federoff 2014; Low and Aebischer 2012; Van der Perren et al. 2015).

The first NHP model using a viral gene expression system was performed on common marmosets (Eslamboli et al. 2007; Kirik et al. 2003). The recombinant adeno-associated viral vector serotype 2/2 (rAAV2/2) or rAAV2/5 vectors expressing the wild type and mutated forms of α-synuclein were injected unilaterally in the SN (Eslamboli et al. 2007; Kirik et al. 2003). Although these NHP models display some features of the PD phenotype, progression of this phenotype is slow and loss of DA neurons is low to moderate and a high degree of variability is observed between animals. The development of new viral vectors able to deliver α-synuclein or mutated α-synuclein in larger amounts would be advisable to produce a more robust degeneration of DA neurons in the SN*pc*.

Clinical and preclinical studies clearly show that high levels of α-synuclein in nigrostriatal DA neurons are associated with greater susceptibility to degeneration. Thus, a reduction or suppression of neuronal α-synuclein expression should induce a neuroprotective effect for these neurons (Collier et al. 2016). rAAV expressing α-synuclein short hairpin RNA (shRNA) to knock down α-synuclein expression was generated and injected into the SN of vervet monkeys, where it led to a significant degeneration of TH-positive neurons (Collier et al. 2016). The loss of TH-positive fibers was much more important in the putamen than the caudate nucleus and the presence of TH-negative neuromelanin-positive neurons was detected (Collier et al. 2016). This demonstrates that expression of α-synuclein is crucial for maintenance and survival of DA neurons and that α-synuclein loss-of-function could play a significant role in the etiopathology of PD (Chu and Kordower 2007; Collier et al. 2016; Kanaan and Manfredsson 2012).

Numerous experimental approaches are used to reduce overexpression of natural and pathological forms of α-synuclein and most of these new treatments are in clinical trials (Wong and Krainc 2017). The majority of the preclinical studies that led to clinical trials were performed in rodents. It would be very useful to conduct similar studies in NHPs to better understand the mechanisms of action involved in their therapeutic effects.

## NHP for treatment studies of PD

### *Symptomatic treatment*

*Pharmacotherapies to test motor symptoms* The MPTP cynomolgus macaque with an extensive loss of striatal DA (of about 95%) is often used to model advanced PD. This model is widely used to test compounds for antiparkinsonian activity, it is rapid, and animals may be used for several studies. It provides an invaluable model to study Parkinsonism and treatment-related complications. Thus, pharmacologically MPTP-lesioned NHPs have proven most useful. The nature of dyskinesias developed in NHPs is almost indistinguishable from those occurring in human PD consisting of chorea, dystonia, and athetosis, which can be assessed using semi-quantitative rating scales akin to those used in man (Langston et al. 2000). Various dyskinesias rating scales for MPTP monkeys have been

developed and were critically compared (Imbert et al. 2000). These scales are based on those used to assess dyskinesias in PD patients such as the Abnormal Involuntary Movement Scales (AIMS) and the Unified Parkinson's disease rating scale (UPDRS) and have good translational value to humans. The NHP scales include assessment of severity and range of movement, bradykinesia, posture, altertness, and tremor. These scales can be complemented with measures of motor activity using various activity monitors or video analysis systems to provide additional objective measures of overall motor activity (Campos-Romo et al. 2009; Liu et al. 2009; Togasaki et al. 2005a). Through the years, these motor scales have been revised and refined to model better the human condition such as reporting good ON time (by contrast to bad ON time) that is time with good antiparkinsonian activity of L-Dopa without disabling dyskinesias. Dyskinesias have been categorized as disabling or troublesome compared to non-disabling or mild dyskinesias (for example: Huot et al. 2015). This is to model in NHPs measures such as ON time and ON time with troublesome dyskinesias used in clinical studies (Fox et al. 2012; Rascol et al. 2005).

*L-Dopa* L-Dopa is the gold standard symptomatic treatment for PD, but after years of treatment, the majority of PD patients develop LIDs that are troublesome and difficult to treat (Fabbrini et al. 2007). The MPTP-lesioned macaque model is also valuable to investigate LID. Macaques are first rendered parkinsonian with MPTP and then chronically treated with L-Dopa for several weeks or months until they express stable and well-established LID both choreic and dystonic similar to those that develop in human PD (reviewed in: Morin et al. 2014). As in MPTP-exposed drug addicts, MPTP-lesioned NHPs repeatedly administered L-Dopa develop LID rapidly after initiation of L-Dopa therapy (Bedard et al. 1986; Clarke et al. 1987; Langston and Ballard 1984; Langston et al. 2000). The rapidity of onset differs from idiopathic PD where LIDs generally take years to emerge; this reflects the high degree of nigral denervation in these NHPs that lower the extent and duration of L-Dopa exposure required for the appearance of involuntary movements (Kuoppamaki et al. 2007; Smith et al. 2003).

The doses of L-Dopa to investigate LID in MPTP-lesioned macaques are generally higher than those used to treat PD patients (Huot et al. 2012a). Nevertheless, an L-Dopa pharmacokinetic study showed that a high dose of 30 mg/kg L-Dopa administered to MPTP monkeys leads to similar maximal plasma concentrations than with 200 mg L-Dopa in PD patients with a similar half-life and time at maximal plasma levels (Huot et al. 2012a). This thus supports the validity of the MPTP-lesioned macaque to investigate pharmacotherapies for LID.

Acute dose–responses or chronic (generally for less than a month) treatments of new compounds are investigated co-administered with L-Dopa (for example: Bezard et al. 2004; Gregoire et al. 2011, 2009) to potentiate the antiparkinsonian activity of L-DOPA and inhibit and/or delay the development of LID.

Another experimental approach uses two groups of de novo macaques rendered parkinsonian with MPTP and then treated with L-Dopa alone or in combination with a compound under investigation. The latter paradigm allows studying specific effects of the test compound on the development of LID and assessing if the effects diminish with long-term use, that is "wearing-off" (Gregoire et al. 2008; Hadj Tahar et al. 2004; Morin et al. 2013a; Rylander et al. 2010a; Samadi et al. 2006). Furthermore, measures of the long-term biochemical changes associated with LID and their prevention (and/or inhibition) are made possible if the animals are killed at the end of the protocol along with controls and MPTP-lesioned untreated macaques (Morin et al. 2013a; Ouattara et al. 2010a; Samadi et al. 2008). Alternatively, a crossover design is possible to decipher if the adjunct treatment with L-Dopa inhibited the expression of LID or inhibited their development (Rylander et al. 2010a).

In pharmacotherapeutic investigations using MPTP-lesioned primates, L-Dopa is mainly administered orally or injected systemically. In the former case, L-Dopa is delivered by nasogastric gavage using human formulations of L-Dopa (*per os* route). This route gives a shorter but stronger response compared to injected forms, allowing higher dyskinesias that are useful in studies investigating peak-dose LID (Hadj Tahar et al. 2004). Subcutaneous administration of L-Dopa in its methylester form offers more stable and reproducible plasma levels, since it avoids first-pass liver metabolism (Cooper et al. 1984). A subcutaneous injection of L-Dopa with oral administration of the investigational compound also allows minimizing possible pharmacokinetic interactions between these drugs. However, L-Dopa methyl ester administered subcutaneous may accumulate in fat tissues, and consequently, peak dose LID may be lower than those obtained with *per os* administration, but will last longer with a smoother response.

Moreover, in pharmacotherapeutic investigations using MPTP-lesioned primates, the dose of L-Dopa will also be adjusted depending on the compound investigated. For compounds with expected antidyskinetic activity, high doses of L-Dopa with optimal antiparkinsonian activity but also inducing dyskinesias will be administered. Compounds with potential antiparkinsonian activity will be tested alone but will likely be less effective than L-Dopa and will also be tested combined with L-Dopa to investigate possible additive or synergistic effect. Indeed, since LIDs are considered dose dependent, reducing the L-Dopa dose

with the addition of an adjunct treatment could maintain the antiparkinsonian activity of L-Dopa with less dyskinesias. Thus, to avoid a celling effect, a suboptimal dose of L-Dopa giving partial alleviation of parkinsonian symptoms should be used to combine with the new agent under investigation.

In addition to LID, MPTP-lesioned primates treated in the long-term with L-Dopa also display a reduction in the duration of the antiparkinsonian effect of L-Dopa, wearing-off (Fox et al. 2010; Jenner 2003b).

Care should be taken in pharmacotherapeutic investigations using MPTP-lesioned primates to administer doses L-Dopa not too high that could induce stereotypies (Graybiel et al. 2000). In PD patients, stereotyped behaviors can be observed with high doses of L-Dopa (Evans et al. 2012; Fernandez and Friedman 1999). Monkeys displaying stereotypies will usually do not display dyskinesias and this will be associated with increased or decreased locomotor activity (Mones 1973; Sassin 1975); hence, the parkinsonian and dyskinetic scores may not be representative. Finally, in pharmacotherapeutic investigations, the dose of L-Dopa should be adjusted for each MPTP-lesioned primate modeling the clinical situation, where each patient has its medication titrated for an optimal response. Therefore, L-Dopa titration for each animal allows a better assessment of the investigational drugs before moving to clinical trials.

*Dopamine receptor agonist* Such as PD patients, MPTP-lesioned NHPs respond well to DA receptor agonists, for example, bromocriptine, pergolide, cabergoline, apomorphine, ropinirole, pramipexole, and piribedil (Close et al. 1990; Fukuzaki et al. 2000; Jenner 2003a, 2008a). It is well documented that the DA receptor agonists have a lower efficacy than L-Dopa in controlling motor symptoms but induce less dyskinesias (Oertel and Schulz 2016). The long-acting DA agonists ropinirole, pergolide, and cabergoline improve motor behavior with low dyskinesias in drug naïve MPTP-lesioned NHPs (Grondin et al. 1996; Hadj Tahar et al. 2000; Maratos et al. 2001) and in *de novo* PD patients (Korczyn et al. 1999; Rascol et al. 1998; 2000; Rinne et al. 1997, 1998a). Since these agonists show more affinity for the D2 and D3 receptor subtypes, it was initially proposed that D1 receptor activation was responsible for the development of dyskinesias. Hence, bromocriptine, a D2 receptor agonist, given to *de novo* PD patients (Lees et al. 1978; Lees and Stern 1981; Rascol et al. 1979) and to MPTP-lesioned NHPs (Bedard et al. 1986; Falardeau et al. 1988; Pearce et al. 1998), is less likely to induce significant dyskinesias compared to L-Dopa, activating all DA receptors. MPTP-lesioned NHPs treated with selective D1 receptor agonists, such as SKF 82958, relieves parkinsonism but induces dyskinesias (Blanchet et al. 1996); the selective D2 receptor agonists quinpirole and (+)-PHNO also rapidly induce dyskinesias to drug naïve MPTP-lesioned NHPs (Bedard et al. 1992; Gomez-Mancilla and Bedard 1992; Luquin et al. 1992). Taken together, these results suggest in human PD and this is well modeled in NHPs that the DA receptor subtype selectivity cannot be related simply to the propensity to induce dyskinesias.

A common feature of many DA agonists that induce modest or no dyskinesias is their relatively long half-life compared to L-Dopa. Based on MPTP-lesioned NHPs and clinical data, the short half-life of L-Dopa giving fluctuating striatal DA levels was proposed to be an important contributing factor to the priming of the basal ganglia for dyskinesias (Nutt et al. 2000; Olanow and Obeso 2000; Stocchi 1998). Once primed, all dopaminergic therapies will produce dyskinesias similar in MPTP-lesioned NHPs and in PD patients (Jenner 2002). The importance of continuous dopaminergic stimulation to avoid LID is well illustrated in our earlier study comparing the behavioral effect of repeated subcutaneous injection and continuous subcutaneous infusion of the same short-acting D2 selective DA agonist in MPTP-lesioned NHPs. Repeated injection of U-91356A produced marked dyskinesias, whereas they were mild with the continuous infusion via an osmotic mini-pump (Blanchet et al. 1995; Morissette et al. 1997). Continuous dopaminergic stimulation to avoid LID has also been developed using transdermal patches such as for the D3/D2/D1 DA receptor agonist rotigotine (Loschmann et al. 1989; Stockwell et al. 2009). In parkinsonian NHPs, the continuous delivery of apomorphine, ropinirole or rotigotine from osmotic mini pumps or subcutaneous depots was shown to produce less dyskinesias than by oral administration or with repeated subcutaneous injections (Bibbiani et al. 2005; Stockwell et al. 2008, 2009). Hence, this suggests that more continuous drug delivery should be used in the treatment of PD. Indeed, continuous delivery of apomorphine by subcutaneous infusion and L-Dopa by intraduodenal infusion in late stage PD improves motor function over oral therapy and reduces dyskinesias (Manson et al. 2002; Stocchi et al. 2005).

D1 agonists, such as ABT-431and CY 208–243, all show effectiveness in animal models of PD, but none has yet been generally been used clinically (Gnanalingham et al. 1995a, b; Kebabian et al. 1992; Loschmann et al. 1992; Nomoto et al. 1988; Shiosaki et al. 1996; Temlett et al. 1988, 1989).

In MPTP-lesioned NHPs, repeated administration of ropinirole or piribedil was reported to induce little or no dyskinesias but on first exposure to L-Dopa intense dyskinesias appears (Jackson et al. 2007; Smith et al. 2006). Similarly, PD started on a DA agonist in the long-term, as disease progresses, are supplemented with L-Dopa because of the lower efficacy of DA agonists to control motor

symptoms; they develop troublesome dyskinesias as PD patients initially started on L-DOPA (Katzenschlager 2008; Parkinson Study Group 2000). Hence, while DA agonists give less dyskinesias than L-Dopa, they prime the basal ganglia for LID and this long-term adaptation observed in PD patients is modeled well in MPTP-lesioned NHPs. This could be because most DA agonists used in the clinic are D2/D3 receptor agonists, whereas L-Dopa has a wider range of activities such as stimulating all five DA receptors, metabolized into noradrenaline, displace 5-HT from serotoninergic neurons, and altering glutamate release.

*Catechol-O-methyl transferase (COMT) inhibitor* Inhibition of metabolism of L-Dopa with COMT inhibitors is used to extend the half-life of L-Dopa and to deliver L-Dopa more continuously. For example, administration of entacapone with L-Dopa enhanced intensity and duration of the locomotor response in MPTP-lesioned marmosets (Smith et al. 1997) and in PD patients (Ruottinen and Rinne 1996). Extensive clinical studies confirm the NHP findings, showing that entacapone added to L-Dopa enhances motor control in PD patients (Parkinson Study Group 1997) and (Rinne et al. 1998b) but with increased L-Dopa plasma concentrations LID occur (Smith et al. 2003). The COMT inhibitors tolcapone was also shown to potentiate the actions of L-DOPA (see, e.g., (Smith et al. 1997)).

*Monoamine oxidase (MAO) inhibitor* MAO-B is an enzyme metabolizing DA. Its inhibition conserves the depleted synaptic levels of DA, as shown with the MAO–B irreversible inhibitors rasagiline and selegiline in MPTP NHPs (Kupsch et al. 2001). They thus can be used to delay LD treatment in patients with early-stage PD. MAO-B inhibition can also potentiate and prolong the effect of L-Dopa thus allowing to use a lower dose (Riederer and Laux 2011). The reversible MAO-B inhibitor, safinamide, was found efficacious used alone or with L-Dopa to treat PD (Riederer and Laux 2011) and its efficacy was demonstrated in MPTP-lesioned NHPs (Gregoire et al. 2013). Hence, parkinsonian NHPs also show good translational value for MAO-B inhibitors.

*Monoamine uptake inhibitor* The non-specific inhibitors of monoamine reuptake brasofensine, tesofensine, and BTS 74–398 were reported to be effective in reversing motor disability in MPTP-treated marmosets (Hansard et al. 2002a, b, 2004; Pearce et al. 2002) but to be inactive in PD patients (Bara-Jimenez et al. 2004; Hauser et al. 2007; Rascol 2008). The lack of specificity for DA neurons of these drugs may possibly explain these discrepancies. Differences between the model and PD in the loss of brain noradrenergic and serotoninergic neurons could be implicated. These monoamine reuptake blockers could activate limbic or cortical neurons that could lead to the increased motor activity observed.

*Aromatic Amino Acid Decarboxylase* As described above, LID in PD patients could be caused by a pulsatile activation of striatal DA receptors, since more sustained delivery of DA prevents the development of dyskinesias (Cenci and Lundblad 2006; Jenner 2008c; Lang and Lozano 1998; Olanow et al. 2006). Aromatic amino acid decarboxylase (AADC) is an enzyme that converts L-Dopa to DA (Daubner et al. 2011; Hadjiconstantinou and Neff 2008). As disease progresses, PD patients require increasing doses of L-Dopa with the associated motor side effects. AADC activity is postulated to be depleted in PD (Bankiewicz et al. 2000). Thus, increasing or restoring the activity of AADC with a gene delivery system could provide a continuous ectopic production of DA in the striatum for advanced PD patients thereby reducing the symptoms and the effective dose of L-Dopa. Indeed, in MPTP hemiparkinsonian rhesus monkeys, injection of AAV2-AADC vector in the caudate nucleus and putamen induced an increase of AADC activity and immunostaining for AADC, improvement in clinical rating scores, and in L-Dopa responsiveness as well as a decrease of L-Dopa-associated side effects (Bankiewicz et al. 2000, 2006; Daadi et al. 2006; Forsayeth et al. 2006). Interestingly, all of these positive outcome persisted up to 8 years in hemiparkinsonian monkeys with no signs of adverse effects and postmortem analysis revealed no signs of neuroinflammation or reactive gliosis (Hadaczek et al. 2010). In a phase I clinical trial (Christine et al. 2009; Eberling et al. 2008), bilateral intraputaminal injection of either a low or a high dose of AAV2-AADC vector in moderately advanced PD patients was shown to be safe and well tolerated and to produce clinical improvements mainly characterized by increased on time and reduced off time without increased "on" time dyskinesias (Christine et al. 2009). Interestingly, a long-term follow-up of these subjects showed that the PET scans using the AADC tracer [$^{18}$F]fluoro-*L*-m-tyrosine were elevated in the first 12 months and persisted over 4 years in both dose groups (Mittermeyer et al. 2012). In addition, the off medication UPDRS score improved during the first 12 months in all patients and showed a slow deterioration in subsequent years likely due to ongoing neurodegeneration (Mittermeyer et al. 2012). The results of this clinical study have showed promising outcomes, but higher doses should be considered in the upcoming clinical studies to reproduce behavioral improvements in L-Dopa response seen in AAV2-AADC-injected monkeys. Another independent clinical study conducted in Japan showed similar results following intraputaminal injection of AAV-AADC (Muramatsu et al. 2010).

*Tyrosine hydroxylase, Aromatic Amino Acid Decarboxylase, guanosine 5-triphosphate cyclohydrolase 1* Another strategy to achieve a sustained tonic activation of DA receptors in the motor region of the striatum is to inject the three enzymes required for biosynthesis of DA, namely, tyrosine hydroxylase (TH), AADC, and guanosine 5-triphosphate cyclohydrolase-1 (GCH-1, a rate limiting enzyme in the synthesis of a cofactor for TH called tetrahydrobiopterin). Thus, mixtures of three separate AAV vectors expressing human TH, human AADC, and human GCH-1, respectively, were unilaterally injected into the putamen of MPTP-treated rhesus monkeys (Muramatsu et al. 2002). Co-expression of the enzymes in the unilateral putamen resulted in restoration of motor functions and increased DA levels in the injected putamen compared to the control side (Muramatsu et al. 2002). A tricistronic lentiviral vector derived from the equine infectious anemia virus (EIAV) encoding human TH, human AADC, and human GCH-1 in a single vector (Lenti-TH-AADC-CH1, ProSavin) was generated and tested in MPTP-treated rhesus monkeys (Jarraya et al. 2009). Bilateral injection of this tricistronic lentiviral vector into the motor postcommissural putamen safely restored extracellular concentrations of DA and corrected the motor deficits for 12 months without dyskinesias (Jarraya et al. 2009). The motor improvements were associated with restoration of the firing rate and pattern of neurons within the basal ganglia and reduced metabolic activity within the subthalamic nucleus (STN) (Jarraya et al. 2009). ProSavin was further evaluated in an open label phase I/II clinical trials in patients with moderate to severe PD that received a bilateral injection of vector in the striatum (ClinicalTrials.gov Identifier: NCT00627588 and NCT01856439). Injection of the lentiviral vector in humans was safe and modest improvements in motor responses as assessed with UPDRS part III (off medication) scores were observed 6 months after vector administration (Palfi et al. 2014). Low levels of transgene expression may explain the lack of clear and robust effects observed in these studies.

*Glutamic acid decarboxylase* Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme that catalyzes the decarboxylation of glutamate to the inhibitory neurotransmitter GABA (Erlander et al. 1991). It is now well known that PD is associated with pathological hyperactivity of the STN mainly caused by a reduced GABAergic input from the globus pallidus (Bergman et al. 1990; Hamani et al. 2004; Rodriguez et al. 1998). In PD patients, subthalamotomy, high-frequency stimulation, or topical administration of GABAergic agonists has been shown to alleviate signs of advanced PD (Hamani et al. 2004; Obeso et al. 2000). A novel strategy to reduce overexcitation of the basal ganglia output neurons is to inject an AAV2-GAD vector into the STN to promote local production and release of GABA with glutamate in the internal globus pallidus (GPi). Using hemiparkinsonian MPTP-treated rhesus monkey, Emborg et al. (2007) showed that injection of AAV2-GAD vector in the ipsilateral STN produced a significant improvement of the clinical rating scores and an increase in glucose utilization in the ipsilateral motor cortex compared to AAV2-GFP controls over 56 weeks after AAV2-GAD injection (Emborg et al. 2007). Based on preclinical results in rodents and rhesus monkeys and positive outcome from an open phase I trial (ClinicalTrials.gov: NCT00195143) (Kaplitt et al. 2007), a phase II double-blind, randomized, sham-controlled trial was conducted to assess the safety and efficacy of bilateral surgical infusion of AAV2-GAD65/67 into the STN in advanced PD patients (ClinicalTrials.gov: NCT00643890) (LeWitt et al. 2011). A significant improvement in the UPDRS-III score in the off state (the primary endpoint) was observed 6 month post procedure for the AAV2-GAD65/67-treated group compared with the sham group (LeWitt et al. 2011). Despite modest but positive outcomes from this study, the subsequent long-term follow-up study was terminated. Compared to DBS, the most favored approach to date, the injection of AAV-GAD shows an advantage, it does not require a permanent implantation of electrodes in the brain, and can restore neuronal activity of the basal ganglia in a more physiological way.

*Non-dopaminergic therapies* The MPTP-lesioned NHP has also been used to examine the potential of non-dopaminergic therapies to treat motor symptoms of PD and LID (reviewed in Brotchie 2005; Fox et al. 2006, 2008). Since other neurotransmitters other than DA are implicated in PD pathology, a strategy receiving much research attention has been to combine non-dopaminergic compounds with L-Dopa to reduce dyskinesias while maintaining its antiparkinsonian activity. Numerous targets such as glutamate, serotonin, nicotine, and cannabinoid have been investigated with tests in MPTP-lesioned NHPs of agonists and antagonists at specific receptor subtypes as well as positive and negative allosteric modulators leading to new and emerging therapies (Lotia and Jankovic 2016).

Amantadine, a non-competitive antagonist at N-methyl-D-aspartate (NMDA) receptors, to a lesser extent clozapine, is the only pharmacological therapies available to treat LID (Fox et al. 2011). The antidyskinetic effect of amantadine has been modeled in the MPTP-lesioned macaque (Blanchet et al. 1998; Gregoire et al. 2013; Rylander et al. 2010b). However, in PD, the beneficial effect of amantadine for dyskinesias is often transient and high doses may cause cognitive impairment (Fox et al. 2011); a new long-acting extended-release formulation of amantadine HCl is also hampered with side effects (Pahwa et al. 2015). More

recently, selective metabotropic glutamate receptor drugs are being evaluated (see section below on translational values of primate models).

Acetylcholine (ACh) is a neurotransmitter playing a pivotal role in neurotransmission in the central nervous system. Cholinergic degeneration is a major feature of PD and may contribute to gait and cognitive impairments, psychosis, and REM-sleep disturbances observed in this disease (reviewed in (Perez-Lloret et al. 2016). Antagonists of the muscarinic acetylcholine receptors, derived from *Atropa belladonna*, were used to treat akinetorigid disorders before the use of dopaminergic drugs to treat PD (Katzenschlager et al. 2003). Presently, anticholinergic drugs are recognized as clinically useful for the treatment of motor symptoms in monotherapy or in conjunction with L-Dopa (Fox et al. 2011). They have shown efficacy for motor symptoms such as gait and tremor. Nevertheless, their clinical efficacy is mild-to-moderate and tolerability is often poor. MPTP-lesioned NHPs also respond to muscarinic drugs such as trihexyphenidyl and benztropine (Close et al. 1990; Fukuzaki et al. 2000; Jenner 2003a, 2008b) and reviewed in (Duty and Jenner 2011).

The largest area of potential use for non-dopaminergic drugs is as add-on therapy for motor fluctuations. Numerous drug classes have been tested in NHP such as adenosine $A_{2A}$ receptor antagonists, antiepileptic agents, β-adrenergic antagonists, 5-$HT_{2A}$ antagonists, antidepressant such as mirtazapine, and 5-$HT_{1A}$ agonists (reviewed in Fox 2013). The translational value of NHP pakrinsonian model is discussed in a latter section.

*Surgical treatments*

It is now well accepted that abnormal oscillations in the basal ganglia network are a key feature of PD (Bergman et al. 1994; Dejean et al. 2008; Filion and Tremblay 1991; Heimer et al. 2006; Mallet et al. 2008; Mitchell et al. 1987; Nini et al. 1995; Raz et al. 2000). Thus, changes in synaptic connectivity and disruption of normal synchronization in motor networks observed in DA-depleted rodent and NHP as well as in PD patients might be implicated in the motor symptoms of the disease (reviewed in: Benazzouz et al. 2014). According to the classical model of the anatomo-functional organization of the basal ganglia in PD, DA depletion leads to increased activity of striatal neurons of the indirect pathway, resulting in inhibition of the external globus pallidus (GPe) and subsequent disinhibition of STN and GPi/SN *pars reticulata* (Albin et al. 1989; DeLong 1990). This pathological neuronal activity in the basal ganglia was reported to be corrected by lesions of the STN that reversed PD symptoms in MPTP-lesioned NHPs (Aziz et al. 1991).

While drugs are generally tested in rodent and NHP models of PD to later move up to clinical trials, effectiveness of deep brain stimulation (DBS) was first observed in humans (Benabid et al. 2009). During a thalamotomy for essential tremor, an electrical stimulation was used to probe the site of the lesion and Benabid's group observed an acute and reversible modification of tremor (Benabid et al. 1987). Moreover, high-frequency stimulation of the STN, instead of lesioning, alleviated PD symptoms in MPTP-lesioned NHPs (Benazzouz et al. 1993). The first attempt of high-frequency stimulation of the STN in PD patients was soon after performed successfully, bilateral STN stimulation improved akinesia and rigidity in three PD patients (Limousin et al. 1995).

Since then, several thousand PD patients worldwide have benefited from this surgical method. The STN and the GPi are the main structures of the basal ganglia targeted for DBS (Miocinovic et al. 2013). STN or GPi DBS is reported to be equally effective to improve rigidity, bradykinesia, and tremor (Follett et al. 2010). Interestingly, a significant reduction in dopaminergic medication in the post-operative phase is usually observed with STN DBS but not with GPi DBS (Follett et al. 2010). GPi DBS allows a direct antidyskinetic effect and represents a better option in patients who do not require medication reduction (Sankar and Lozano 2011). Finally, when patients present cognitive and psychiatric symptoms, the GPi is the favoured target (Okun et al. 2009).

In advanced stages of PD, when medications no longer adequately control motor symptoms, surgical treatments offer therapeutic alternatives for patients including lesions and more generally nowadays DBS (Hickey and Stacy 2016). NHP models of PD are also useful to study lesion and DBS taking advantage of the larger size of their brain compared to rodents and the more similar anatomy of their basal ganglia compared to humans.

A study on the response to L-Dopa after subthalamic lesion in MPTP-lesioned macaque monkeys (Jourdain et al. 2013) showed that subthalamotomy potentiated the antiparkinsonian effects of L-Dopa; its doses could be reduced by 40% after STN lesion to have the same beneficial antiparkinsonian response as with an optimal L-Dopa dose pre-surgery. These results closely resemble those obtained in PD patients undergoing unilateral subthalamotomy (Alvarez et al. 2001, 2009). In L-Dopa-primed MPTP marmosets, an unilateral lesion of the GPi gave 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-lesioned monkeys, where dystonia remained unchanged (Page et al. 1993). These studies show that stereotaxic lesions performed in humans can be

replicated in monkeys and further support this model to study PD and its treatments.

Publications up to now have reported the effect of DBS in a limited number (one or two) intact or MPTP monkeys in each study and show motor behavior effects as in humans (Baker et al. 2011; Johnson et al. 2015; Rosenbaum et al. 2014; Santaniello et al. 2010; Xu et al. 2011; Zitella et al. 2015). To our knowledge, no studies using DBS have been conducted in dyskinetic primates yet and no study has compared pharmacological antiparkinsonian drug response before and with DBS. Since DBS is currently offered in PD patients that previously received antiparkinsonian dopaminergic treatments and many that developed dyskinesias it will be important to model the adaptations of the brain to these drug treatments in the response to DBS in NHPs.

*Disease-modifying treatments*

PD is a complex disease with multiple neurotoxic pathways that contribute to its aetiology and finally, death of DA, and other neurons (Dickson et al. 2009; Kalia and Lang 2015; Lang 2007). To address this multiplicity in the pathologic process, compounds targeting more than one pathological event in cell-death cascades need to be designed and investigated (Youdim et al. 2007). Compounds with neuroprotective, neurorestorative, and neurorescuing properties are investigated. A neuroprotective drug is defined as a drug that prevents or slows down neuronal death; a neurorestorative drug is a drug that replaces dying or dead neuronal cells with viable cells and a neurorescuing drug is a drug that rescues cell where neuronal cell death has already started (Youdim et al. 2007). Alternatively, there are compounds with 'disease modifying' activity implying a modification of the clinical course of the disease without implicating mechanism (Lang 2010). Some active compounds were discovered through serendipity, while others were the products of active drug design projects. Hence, numerous compounds of various chemical classes were reported with neuroprotective-neurorescue properties such as rasagiline (n-propargyl-1R-aminoindan) and selegiline MAO-B inhibitors, adenosine $A_{2A}$ receptor antagonists, NMDA antagonism by calcium channel blockers, green tea polyphenols, docosahexaenoic acid (DHA), and estrogens (Bourque et al. 2009; Bousquet et al. 2008; Youdim et al. 2007). There are many studies reporting beneficial neuroprotective effects in rodent models of PD, whereas in NHP, they are much less abundant and clinical studies in this respect have yet been inconclusive (Schapira 2009). Clinical studies up to now have failed to report disease-modifying activity of the compounds tested in phase III trials including the use of co-enzyme Q10, creatine monohydrate, pioglitazone, and neurturin (reviewed in: Oertel and Schulz 2016). A recent review of current disease modifying approaches to treat PD lists examples of on-going clinical trials showing a focus on trophic factors and compounds with efficacy on DA neurons in preclinical animal models (Lindholm et al. 2016). Nevertheless, NHP studies of disease-modifying therapies are still worthwhile and useful to improve symptomatic therapy of motor and non-motor symptoms especially in the later stages of the disease. For example, serotoninergic and glutamatergic activity is implicated in LID and drugs affecting these neurotransmission can have antidyskinetic activity in addition to disease-modifying activity.

In cynomolgus monkeys, the serotonin 5-$HT_{1A}$ agonists BAY639044 and repinotan were shown to oppose MPTP-induced excitotoxicity-mediated cell death (Bezard et al. 2006). Both compounds delayed the appearance of motor symptoms. These treatments were initiated 8 days after starting MPTP administration for 17 days to model early symptomatic PD patients when they would possibly receive such treatments. The delay in appearance of motor abnormalities in the MPTP-treated monkeys treated with BAY639044 was a consequence of partial neuroprotection of nigrostriatal DA neurons both at neuronal and terminal levels as shown with, respectively, TH-immunohistochemistry and DAT binding.

MPTP-lesioned monkeys chronically treated with the metabotropic receptor 5 negative allosteric modulator MTEP were shown to have a decrease of MPTP-induced toxicity towards DA in the SN*pc* and ventral tegmental area and noradrenergic neurons in the locus coeruleus and the adjoining A5 and A7 noradrenaline cell groups (Masilamoni et al. 2011). This neuroprotection of DA neurons could be because of a reduction of glutamate overactivity observed in the parkinsonian state.

In marmosets, the antiglutamatergic compound riluzole treatment started 1 week before MPTP and pursued during 2 weeks of MPTP administration and for 1 week after was used to model early stages of PD (Verhave et al. 2012). This treatment led to a relatively mild decline of 50% of DA neurons in the SN. Riluzole improved clinical scores but not abnormal involuntary movements (AIMs). It improved hand–eye coordination, turning ability, sleep architecture, and rapid eye movement (REM) behavioral disorder and increased the number of surviving DA neurons. This is in agreement with an other study in marmosets (Obinu et al. 2002), where riluzole was administered starting 1 h after the first of two MPTP injections for 4 weeks and preserved a better motor function and spared TH-stained nigral neurons and terminals in the striatum. Moreover, this agrees with an earlier pilot study in two rhesus monkeys, where parkinsonian motor symptoms were prevented with a treatment with riluzole started before MPTP administration (Benazzouz et al. 1995).

However, in PD patients, clinical trials with riluzole showed no beneficial effect (Bensimon 2009; Jankovic and Hunter 2002) perhaps because of the multiplicity of pathologic processes in PD and the need for treatment at earlier non-symptomatic stages of the disease. Moreover, there is disease heterogeneity in PD causing difficulty in designing trials of disease-modifying therapy particularly at an early stage of disease when intervention is likely to be most effective but when there is less diagnostic confidence. However, as prodromal PD markers improve (Postuma and Berg 2016), testing of disease-modifying therapies will improve.

Considering the implication of mitochondrial and inflammatory processes in PD leading to oxidative injury, a logical approach would be to test compounds with antioxidant activity. In this respect, the fullrene compound $C_3$ was tested in MPTP-treated macaques starting 1 week after MPTP for 2 months (Dugan et al. 2014). After 2 months, $C_3-$ treated monkeys had improved motor ratings and higher striatal DA levels.

Photobiomodulation is a novel approach for PD recently reviewed (Hamblin 2016). Various mechanisms of action have been reported including increased adenosine triphosphate (ATP) content, decreased of oxidative stress, increased blood flow, activation of neuroprotective signalling mediators, and transcription factors (Hamblin 2016). Near-infrared light (NIR) was used for neuroprotection against MPTP toxicity in macaques with light on during the 57 day period of MPTP injections and for the following 3 weeks (Darlot et al. 2016). MPTP monkeys treated with NIR light had less motor behavior impairment and less $TH^+$ nigral cell and striatal terminal loss. Motor symptoms in these MPTP monkeys were improved at low compared to high doses of light (Moro et al. 2016). Moreover, these investigators just reported in MPTP monkeys that NIR treatment reduced markedly astrogliosis in the SN*pc* and striatum (El Massri et al. 2016); NIR reduced dramatically by about 75% glial fibrillary acidic protein levels (to label astrocytes; GFAP). A more limited impact was observed on ionised calcium-binding adaptor molecule 1 (to label microglia; IBA1) in both nuclei; they were no change in the number of microglia, although they were reduced in size. No clinical study has yet been published on the use of NIR for PD except an abstract (Maloney et al. 2010), discussed in (Hamblin 2016; Johnstone et al. 2015) reporting an improvement of gait, freezing, difficulty of speech, and cognitive function. The main zone of pathology in PD is deep in the brain and more invasive intracranial NIR light delivery systems will be required (Johnstone et al. 2015). Nevertheless, this would be compatible for PD patients selected for DBS that could have an NIR optical fiber implanted surgically at the same time to possibly protect remaining DA neurons (Johnstone et al. 2015).

*Neurotrophic factors: Glial-derived neurotrophic factors and neurturin* The glial cell line-derived neurotrophic factor (GDNF) and neurturin (NTRN) are a member of the transforming growth factor (TGF)-β superfamily known to promote with high efficiency and specificity survival of DA neurons in vitro and in vivo in animal and cellular models of PD (Salvatore et al. 2004; Staudt et al. 2016; Tomac et al. 1995; Yang et al. 2009). Indeed, intracerebroventricular (ICV) infusion of GDNF into MPTP-treated and aged rhesus monkeys as well as in MPTP-treated marmoset showed significant improvement of motor disabilities and nigral DA neurons regeneration associated with a reduced occurrence of LID (Costa et al. 2001; Gash et al. 1996; Gerhardt et al. 1999; Grondin et al. 2002, 2003; Miyoshi et al. 1997). However, in a phase I–II, randomized, double-blinded clinical trial, monthly injections of GDNF via an implanted ICV catheter in PD patients did not improve their conditions and many developed strong adverse effects (Nutt et al. 2003). The negative outcomes of this study have been attributed to a limited diffusion of GDNF in target tissues from the injection catheters into the brain parenchyma (Gash et al. 2005; Lang et al. 2006).

It is now well documented that neurotrophic factors are released by target tissues and transported retrogradely to cell bodies to achieve their survival promoting activities (Harrington and Ginty 2013; Ito and Enomoto 2016; Zweifel et al. 2005). In PD, axonal degeneration is observed before death of neurons and some remaining nerve endings are required for effective treatment with neurotrophic factors (Cheng et al. 2010; Grosch et al. 2016; Kurowska et al. 2016; Lingor et al. 2012; Tagliaferro and Burke 2016). Therefore, infusion of GDNF or NTRN directly into the putamen of MPTP-treated or aged monkeys induced major improvements of motor performance and nigral DA neurons regeneration (Ai et al. 2003; Garbayo et al. 2016; Grondin et al. 2008; Maswood et al. 2002; Oiwa et al. 2006). Although this route of administration of GDNF demonstrated beneficial neuroprotective effects in simian models, results of subsequent clinical studies have been inconclusive (Gill et al. 2003; Lang et al. 2006; Love et al. 2005; Patel et al. 2005; Slevin et al. 2005).

The negative outcomes from clinical studies have prompted use of a new delivery approach consisting of in vivo viral vector gene delivery to improve the safety and the therapeutic efficacy of GDNF or NTRN treatments (Bartus and Johnson 2016a, b). Controlled release of GDNF and NRTN has been carried out with striatal and/or nigral injection of AAV2-GDNF and AAV2-NTRN (CERE-120) vectors, respectively, in aged monkeys or in 6-OHDA- and MPTP-lesioned monkeys. The results of

these studies showed a robust and long-lasting dopaminergic neuroprotective effect of viral vector delivery of GDNF or NRTN in NHP (Bartus et al. 2011; Eberling et al. 2009; Eslamboli et al. 2003b, 2005; Herzog et al. 2007, 2008, 2009; Johnston et al. 2009; Kells et al. 2010; Kordower et al. 2000, 2006; Su et al. 2009). Interestingly, the presence of GDNF in the SN of rhesus monkeys with extensive DA depletion suggests anterograde transport of AAV2-GDNF vector particles via striatonigral connections and anticipates a possible use of this treatment in the more advanced stages of the disease (Kells et al. 2010). In this context, a phase I open label study is ongoing in a dose escalation safety study to test the safety and effectiveness of AAV2-GDNF gene transfer for advanced PD (ClinicalTrials.gov Identifier: NCT01621581). In addition, given the efficiency, safety, and tolerability of CERE-120 in rhesus monkeys, clinical trials have been designed to assess the feasibility, safety, tolerability, biologic activity, and therapeutic efficacy of intraputaminal (ClinicalTrials.gov Identifiers:NCT00252850 and NCT00400634) or combined intraputaminal with intranigral (ClinicalTrials.gov Identifier: NCT00985517) injections of CERE-120 in idiopathic PD subjects. Unfortunately, no significant therapeutic efficacy of CERE-120 delivery was observed (Bartus et al. 2011; Marks et al. 2010, 2008; Olanow et al. 2015). This lack of therapeutic efficacy of CERE-120 in these clinical studies has been attributed to the recruitment of PD patients in advanced stage of the disease that could impair the anterograde transport of the NRTN (Bartus and Johnson 2016a, b; Bartus et al. 2015; Hickey and Stacy 2013; Kirik et al. 2016; Olanow et al. 2015).

*Parkin* Gene mutations in PARK2, which encodes parkin, are the most common causes of autosomal recessive juvenile PD (Kitada et al. 1998; Puschmann 2013). Experiments using human brains suggest a possible interaction between parkin and α-synuclein, where parkin mitigates α-synuclein-induced neuronal cell death in vivo and in vitro (Choi et al. 2001; Hasegawa et al. 2002; Imaizumi et al. 2012; Lo Bianco et al. 2004; Schlossmacher et al. 2002; Yamada et al. 2005). In this context, injection of a rAAV1-α-synuclein vector unilaterally in the striatum of rhesus monkeys was shown to decrease striatal TH-positive terminals compared with the contralateral side injected with a combination of rAAV1-α-synuclein and rAAV1-parkin vectors (Yasuda et al. 2007). In addition, overexpression of parkin in striatonigral GABAergic neurons reduced accumulation of α-synuclein and phosphorylated α-synuclein at Serine 129 (Yasuda et al. 2007). Although the small number of animals used represents a significant limitation of this study, these results support a new neuroprotective therapeutic option for PARK2 linked as well as for idiopathic PD.

*Stem cells transplantation* PD being characterized by loss of DA neurons, a cell replacement therapy could be an effective treatment option. Since the first attempts of intracerebral transplants in humans performed by the team of Backlund et al. (1985) who grafted adrenal medullary tissue into the caudate nucleus or putamen of PD patients, tremendous progress has been made in this research field (Backlund et al. 1985) (reviewed in: Barker et al. 2015). However, the use of foetal ventral mesencephalic DA cells or other types of embryonic stem cells (ESC) raises ethical issues and several immunological drawbacks such as rejection of specific cells derived from allogenic human ESCs after transplantation (Shen et al. 2016). In 2006, Yamanaka's group reported that the combination of transcription factors, OCT4, SOX2, KLF4, and c-Myc, could generate ES-like pluripotent stem cells from somatic fibroblasts, called induced pluripotent stem cells (iPSCs) (Takahashi and Yamanaka 2006). Since this discovery, iPSCs were generated from a wide variety of tissues sources, including skin, liver, and stomach cells, neural stem cells, and adipose and peripheral blood cells; these cells have the capacity to differentiate into any tissue in the body (Aasen and Izpisua Belmonte 2010; Haase et al. 2009; Loh et al. 2009; Utikal et al. 2009; Xiao et al. 2016; Xu et al. 2016). These great innovations in the field of stem cells are very attractive for possible cell replacement therapy in PD, since iPSCs are able to differentiate to DA neurons (Xiao et al. 2016).

Results of several studies in monkeys are so far very promising. For instance, bilateral transplantation of DA neurons, generated from monkey neural ESCs, into the putamen of MPTP-treated cynomolgus monkeys improved motor deficits and transplanted cells act as DA neurons (Takagi et al. 2005). Behavioral recovery was also observed in MPTP-treated African green monkeys that received injections of human neural ESC (taken from the ventricular germinal zone of a 13-week-old human foetal cadaver) or foetal ventral mesencephalic tissue in the SN, caudate nucleus, and/or putamen (Redmond et al. 2007, 2008). In MPTP-treated rhesus monkeys, injection of DA cells derived from human or monkey iPSC-derived neural pluripotent cells can efficiently survive and function as DA neurons (Kikuchi et al. 2011; Kriks et al. 2011). Furthermore, the primate iPSC-derived neural cells survived in the striatum of MPTP-treated cynomolgus macaque for at least 1 year after autologous transplantation (Sundberg et al. 2013) and can differentiate into neurons, astrocytes, and myelinating oligodendrocytes with a minimal presence of inflammatory cells and reactive glia (Emborg et al. 2013). Transplantation of cynomolgus monkey iPSC-derived midbrain DA neurons in MPTP-lesioned cynomolgus monkeys can survive up to 2 years following autologous transplantation; in one animal,

unilateral engraftment of these iPSCs induced a gradual onset of functional motor improvement contralateral to the side of DA neuron transplantation without a need for immunosuppression (Hallett et al. 2015). Finally, Morizane et al. (2013) demonstrated that autologous transplantation of iPSC-derived neurons in normal rhesus monkeys resulted in a higher number of DA neurons that survived in the autografts with a minimal immune response in the brain compared to allografts that caused an acquired immune response with the activation of microglia and infiltration of leukocytes (Morizane et al. 2013).

Overall, results from these studies demonstrate the utility of the NHP models of PD to evaluate safety and efficacy of transplanted iPSCs and human ESC-derived DA neurons. Furthermore, the possibility of studying the immune system reactions involved in graft rejection makes this model even more attractive (Morizane et al. 2013). The NHP, mainly those of the New World monkey family, represents the best models for transplantation studies with iPSCs and human ESCs owing to neuroanatomical similarities and the high degree of sequence similarity in the major histocompatibility complex (MHC) with human. Although results in NHP models of PD are extremely promising, there is still much to do for the development and validation of a reliable model for evaluating SC-based therapies for PD (Grow et al. 2016).

*NHP and non-motor symptom treatment*

It is now well documented that non-motor symptoms are present in most PD patients and that they are already installed 20 years or even more before the appearance of motor impairment and worsen with disease progression (Sauerbier et al. 2016; Sveinbjornsdottir 2016). Some of these symptoms are very detrimental and affect significantly the quality of life of PD patients. Non-motor symptoms in PD patients are numerous and diverse and include olfactory deficits, pain, parasthesia, orthostatic hypotension, gastrointestinal and bladder dysfunctions, dysphagia, sexual dysfunctions, increased sweating, depression, anxiety, apathy, psychosis, cognitive impairments, excessive daytime somnolence, dementia, and REM sleep behavior disorder (Jellinger 2015). It is obvious that midbrain DA neuron degeneration is not the unique physiological factor that would explain all of these symptoms, but a generalized effect of the LB pathology in the brain and the periphery is strongly suspected (Jellinger 2015; Sauerbier et al. 2016; Todorova et al. 2014). In fact, α-synuclein aggregation preceding LB formation has been proposed to begin in enteric neurons, autonomic and peripheral nervous system, lower brainstem nuclei, and in olfactory bulb (Braak and Del Tredici 2008; Braak et al. 2003). A major route of disease progression may originate in the enteric nervous system and retrogradly reach the dorsal motor nucleus of the vagal nerve in the lower brainstem (Del Tredici and Braak 2016). Interestingly, several studies have shown that α-synuclein can be secreted by neurons and transported to neighbouring target neurons via endocytosis following its association with exosomes (see reviews Longhena et al. 2017; Quek and Hill 2016) which could explain the prion-like spreading of pathological α-synuclein in the brain. This proposed mechanism was supported by the detection of LB-like inclusions in the grafted human embryonic DA neurons in the post-mortem brains of PD patients (Kordower and Brundin 2009; Li et al. 2008, 2010). In addition, α-synuclein expression in the peripheral and autonomic nervous system progresses in the CNS where the progressive degeneration of the dopaminergic nigrostriatal system goes along with a widespread extranigral pathology affecting different anatomical structures such as locus coeruleus, nucleus basalis of Meynert, hypothalamus, amygdala, and cerebral cortex (Jellinger 2015). It has been reported that some non-dopaminergic neurons, such as cholinergic neurons in the pedunculopontine nucleus and substance P-containing neurons in the motor nucleus of the vagus, can degenerate more extensively and more rapidly than dopaminergic neurons (Halliday et al. 1990; Hirsch et al. 1987; Jellinger 1987, 2012). Likewise, strong evidence from PD animal models revealed that LB pathology occurs much earlier in the locus coerulus than in the SN, and consequently, the loss of the norepinephrinergic projections in the SN could accelerate degeneration of the nigral dopaminergic neurons and manifestation and severity of motor deficits (see review (Vermeiren and De Deyn 2017)) Overall, these observations could explain the wide variety of motor and non-motor symptoms in PD patients (Borgonovo et al. 2017; Burke et al. 2008; Cerasa et al. 2016).

The mode of propagation of pathological α-synuclein in the brain has recently been highlighted in an NHP model. Intracerebral injection of synthetic α-synuclein fibrils into adult wild-type marmoset caudate nucleus and/or putamen was shown to result in development of abundant phosphorylated α-synuclein pathologies similar to those observed in PD/Dementia with LB, in various brain regions, as early as 3 months after injection (Shimozawa et al. 2017). In addition, strong LB-like inclusions were formed in TH-positive neurons suggesting retrograde spreading of abnormal α-synuclein from striatum to SN (Shimozawa et al. 2017). This was also associated with a significant decrease in the numbers of TH-positive neurons in the injection side of the brain. Furthermore, these inclusions were positive for fluorescent β-sheet ligands thioflavin-S and 1-fluoro-2,5-bis (3-carboxy-4-hydroxystyryl) benzene (FSB) suggesting amyloid fibril formation. Interestingly, neurons with abnormal α-synuclein

inclusions are reported to be phagocytosed by microglial cells likely to reduce inflammation in the brain (Shimozawa et al. 2017). No apparent symptoms or motor deficits were observed 3 months after α-synuclein injection probably because of the low levels of dopaminergic denervation in these marmosets (20–40% decrease) (Shimozawa et al. 2017). This is the first NHP model that replicates the prion-like propagation of α-synuclein and it will likely be useful to decipher the mechanisms involved in the spreading of α-synuclein and to develop new disease-modifying treatments for α-synucleopathies and PD. Unfortunately, no behavioral assessment was performed in these animals. Therefore, additional studies should be undertaken to indentify and evaluate the non-motor symptoms, if there is, in this marmoset model of PD.

The progression of pathological α-synuclein in peripheral and CNS emphasizes the clinical heterogeneity of PD both in the prodromal phase as well as during the course of the disease. Accordingly, the International Parkinson and Movement Disorder Society (MDS) has included a range of non-motor symptoms to be included in the PD diagnosis (Postuma et al. 2015). In this context, the existence of several subtypes of PD was highlighted in cluster analysis studies that evaluated non-motor and motor symptoms in newly diagnosed untreated patients (Erro et al. 2013; Marras and Chaudhuri 2016; Pont-Sunyer et al. 2015; Reijnders et al. 2009; Todorova et al. 2014; Zis et al. 2015; 2014). Incorporation of non-motor symptoms as an obligatory clinical assessment could help to develop subtype-directed treatment strategies (personalized therapies) to avoid suboptimal care (Sauerbier et al. 2016). In addition, recruitment of non-motor symptoms subtype-based PD patients might help design clinical studies primarily focused on non-motor symptoms outcomes (Klingelhoefer and Reichmann 2017; Sauerbier et al. 2016).

The preclinical and prodromal stages of PD provide a window of opportunity to initiate disease-modifying or neuroprotective therapies. The search for specific clinical, genetic, biochemical, and imaging biomarkers of PD in the prodromal stage becomes a major challenge to identify individuals with high risk of developing the disease (Noyce et al. 2012; Postuma and Berg 2016). Based on results from prospective studies, clinical markers that have been identified as being highly predictive of PD include REM sleep behavior disorder, olfactory loss, constipation, depression, and anxiety (Postuma and Berg 2016).

Given that the majority of non-motor symptoms in the prodromal phase and in early stages of PD are at least partially independent of DA, it is difficult to develop an animal model associated with these symptoms. For instance, systemic administration of MPTP to rhesus monkeys did not mimic a full range of changes in peripheral catecholamine systems that characterize the human disease (Chaumette et al. 2009; Goldstein et al. 2003). However, rhesus monkeys chronically treated with 6-OHDA have been shown to develop cardiac sympathetic neurodegeneration and loss of catecholaminergic enzymes in the adrenal medulla, suggesting that these monkeys can be used to evaluate disease-modifying strategies for peripheral neuroprotection (Joers et al. 2014).

Several studies have shown that non-motor symptoms can be induced in MPTP-intoxicated NHP PD model. In fact, deficits in maintenance of a response set and shifting attentional sets as well as impaired ability to sustain spatial attention or to focus attention deficit in motor readiness and planning and impaired time estimation were observed in MPTP-treated rhesus monkeys (Decamp and Schneider 2004; Pessiglione et al. 2004). As seen in human, L-Dopa treatment does not reverse cognitive impairment and, under certain conditions, can even worsen these deficits (Decamp and Schneider 2009). In addition, rhesus monkeys that received low doses of MPTP during several days changed dramatically the execution of visually guided saccades with small amplitude and corrective saccades even at the presymptomatic stage of the MPTP syndrome (Tereshchenko et al. 2015). In addition, in rhesus monkeys that received chronic low-doses of MPTP to obtain a slow onset of symptoms, a rapid alteration (within 1 week) of rest-activity cycles and cognitive deficits was observed, while parkinsonian motor deficits were apparent 3–5 weeks after initiation of the chronic MPTP treatment (Vezoli et al. 2011). The presence of both cognitive deficits and chronobiological alterations persisted for several months and L-Dopa treatment improved cognitive performance but did not affect rest-activity rhythms (Vezoli et al. 2011).

Dramatic disruption of sleep-wake architecture was observed in MPTP-treated rhesus monkeys characterized by reduced sleep efficacy, increased daytime sleepiness, fragmentation and reduction of sleep efficiency at night time, reduced in REM sleep time, increased muscle tone during REM and non-REM sleep episodes, and increased number of awakenings and movements (Barraud et al. 2009; Belaid et al. 2014). In addition, in mild parkinsonian MPTP-treated marmosets, significant REM sleep-specific changes were observed without alteration of wake motor behaviors (Verhave et al. 2011). L-Dopa treatment of MPTP-treated rhesus monkeys improved sleep disorders induced by the lesion; a combined L-Dopa treatment with a cholinergic pedunculopontine nucleus lesion induced a transient sleep impairment followed by a significant improvement of sleep quality (Belaid et al. 2014). These authors suggest that improvement of sleep quality after cholinergic pedunculopontine nucleus lesion could be a consequence of a reduction in night-time bradykinesia (Belaid et al. 2014).

In MPTP-lesioned marmosets, treatment with L-Dopa can induce psychotic-like behaviors and hyperactivity that may be related to neuropsychiatric symptoms and impulse control disorder often experienced by PD patients after chronic L-Dopa treatment (Fox et al. 2010; Verhave et al. 2011). The neuropsychiatric-like behaviors were reported to appear the first day following L-Dopa treatment and their severity did not correlate with duration of treatment (Fox et al. 2010). A neuropsychiatric-like behavior rating scale was developed by these authors including four categories of neuropsychiatric behaviors: hyperkinesia, repetitive grooming, response to non-apparent stimuli, and stereotypies (Fox et al. 2010). Interestingly, the neuropsychiatric-like behavior rating scale demonstrated high inter-rater reliability between three trained raters of differing professional background (Fox et al. 2010).

## Translational values of primate models

The NHP models of PD reproduce well the response of motor symptoms to effective DA medications in PD (Duty and Jenner 2011). A good antidyskinetic drug in NHP models is more difficult to translate for humans PD. Indeed, antidyskinetic activity of a compound is sought while maintaining antiparkinsonian activity; this has been sought with non-dopaminergic adjunct treatments with L-Dopa. Moreover, this requires from the animal models to reproduce also the non-dopaminergic pathological changes in PD thus adding complexity to the search.

Glutamate is an important neurotransmitter in PD and LID and is, therefore, a primary target for antidyskinetic drug development. Amantadine has antidyskinetic activity in monkey models of PD (Blanchet et al. 1998; Gregoire et al. 2013; Rylander et al. 2010a). These results in animal models translate well in PD patients.

Compounds targeting metabotropic glutamate receptors (mGlu receptors) are the objects of intense research for dyskinesias. Several mGlu5 receptor negative allosteric modulators are shown to reduce the severity of dyskinesias in macaques (Johnston et al. 2010; Morin et al. 2010, 2013a; Rylander et al. 2010a). Clinical studies investigating LID in PD patients with dipraglurant are on going; for mavoglurant, the first clinical studies in PD patients reported a reduction of LID (Berg et al. 2011) but not the later studies.

Serotoninergic activity is another target to treat LID under active investigation. For example, Sarizotan, a serotonergic 5-$HT_{1A}$ agonist at low doses reduced LID in MPTP primates, while at higher doses, it reduced the L-Dopa-induced locomotor response (Gregoire et al. 2009). Similarly, in PD patients, Sarizotan at low doses was shown to reduce the duration and severity of dyskinesias, while at higher doses, Sarizotan's dopaminergic antagonist property appears causing a deterioration of the antiparkinsonian response. Dyskinesias are highly sensitive to placebo effect, and in a large double-bind placebo controlled clinical trial, all effects in the Sarizotan group were statistically explained by the placebo-effect regression model (Goetz et al. 2008).

The adenosine $A_{2A}$ receptor is another target investigated to treat motor complications. Istradefylline (KW-6002), a selective adenosine $A_{2A}$ antagonist, has recently been approved as an adjunct treatment in PD for the management of L-Dopa-induced motor complications (Dungo and Deeks 2013; Pinna 2014). It extends the therapeutic action of L-Dopa while exacerbating the expression of certain dyskinesias (Chen et al. 2013; Kondo 2015). Similarly, a recent study reported in MPTP NHP that Istradefylline treatment alleviates postural deficits, increases L-Dopa on time, but exacerbates dyskinesias (Ko et al. 2016). By contrast, an earlier study in MPTP-lesioned NHP reported that Istradefylline with L-DOPA or with selective D1 or D2 DA agonists increases antiparkinsonian activity but not dyskinesias (Kanda et al. 2000). Moreover, Istradefylline was shown to improve cognition in L-DOPA-treated MPTP-treated macaques (Ko et al. 2016). Parkinsonian NHP and human PD findings for sarizotan and Istradefylline show that care should be taken in translating NHP results to human PD. For example, dose–responses, extent of the lesion to model early or later stage diseases, should be carefully investigated for a better assessment of non-dopaminergic treatments.

The present models in primate were designed to reproduce the nigrostriatal pathology and the main DA loss and may not reproduce all pathological changes of PD. Moreover, MPTP monkeys with severe dyskinesias may alter their pattern of movement to prevent their appearance such as grasping 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.

### *Limits of MPTP primate models for pharmacotherapy testing*

There are also experimental limitations of using MPTP primates for translational studies. There is inter-animal variability of PD symptoms and LID (Potts et al. 2014). Parkinsonian symptoms as well as dystonic/choreic dyskinesias will differ for each animal, independently of the dose of MPTP and L-Dopa received (Boyce et al. 1990a) and some primates will not develop LID even with chronic L-Dopa (Aubert et al. 2005; Guigoni et al. 2005). Nevertheless, this models the clinical situation, since not all

patients will develop LID over time (Ahlskog and Muenter 2001).

Monophasic, or peak dose, dyskinesias are mainly observed in MPTP-lesioned monkeys (Clarke et al. 1987; Crossman et al. 1987). Peak dose dyskinesias are also observed in PD patients treated with chronic L-Dopa but dystonia and biphasic dyskinesias (at onset and end-of-dose) also occur (Vidailhet et al. 1999). The latter are seldom observed in parkinsonian primates (Boyce et al. 1990b). The development of LID in monkeys is faster than in idiopathic PD appearing within days or weeks of exposure to L-Dopa (Boyce et al. 1990a; Gregoire et al. 2008) and stabilizes at a given dose (Pearce et al. 1995). Interestingly, LID also appeared rapidly in humans exposed to MPTP that received L-Dopa treatment (Ballard et al. 1985). By contrast in idiopathic PD patients, LIDs generally develop after many years of L-Dopa administration (Ahlskog and Muenter 2001) and increase in severity and duration (Fox and Brotchie 2010). Hence, the long-term adaptation to DA loss and L-Dopa treatment bringing fluctuating levels to the brain leading to LID may differ in the primate model as compared to idiopathic PD.

While the MPTP-lesioned primate remains an excellent model to assess compounds for their antiparkinsonian activity as mono-therapy or as add-on to L-Dopa as well to inhibit LID some have failed in clinical trials. Fox and Brotchie (2010) proposed that it may be because of a lack of equivalent endpoints employed in primate studies compared to clinical trials (Fox and Brotchie 2010). They suggested to measure "good" on time that is time when there is reversal of PD symptoms with no or non-disabling dyskinesias compared to "bad-on" time when animals have reversal of PD symptoms but with disabling dyskinesias. Compounds may be active in MPTP-lesioned NHPs to reduce parkinsonian signs and LID at higher doses than used for human PD (Di Paolo et al. 2014; Rascol et al. 2014). Off target activities of compounds tested in MPTP-lesioned NHPs may limit their translation for human PD treatment.

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