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Chronic MPTP administration regimen in monkeys: a model of dopaminergic and non-dopaminergic cell loss in Parkinson's disease

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Abstract Parkinson's disease (PD) is a progressive neurodegenerative disorder clinically characterized by cardinal motor deficits including bradykinesia, tremor, rigidity and postural instability. Over the past decades, it has become clear that PD symptoms extend far beyond motor signs to include cognitive, autonomic and psychiatric impairments, most likely resulting from cortical and subcortical lesions of non-dopaminergic systems. In addition to nigrostriatal dopaminergic degeneration, pathological examination of PD brains, indeed, reveals widespread distribution of intracytoplasmic inclusions (Lewy bodies) and death of non-dopaminergic neurons in the brainstem and thalamus. For that past three decades, the MPTP-treated monkey has been recognized as the gold standard PD model because it displays some of the key behavioral and pathophysiological changes seen in PD patients. However, a common criticism raised by some authors about this model, and other neurotoxin-based models of PD, is the lack of neuronal loss beyond the nigrostriatal dopaminergic system. In this review, we argue that this assumption is largely incorrect and solely based on data from monkeys intoxicated with acute administration of MPTP. Work achieved in our laboratory and others strongly suggest that long-term chronic administration of MPTP leads to brain pathology beyond the dopaminergic system that displays close similarities to that seen in PD patients. This review critically examines these data and suggests that the chronically MPTP-treated nonhuman primate model may be suitable to study the pathophysiology and therapeutics of some non-motor features of PD.

Keywords Parkinson's disease · MPTP monkey · Nigrostriatal dopamine · Extra-striatal dopamine · Norepinephrine · Serotonin · Acetylcholine · α-Synuclein

Introduction

Parkinson's disease (PD) is a progressive movement disorder clinically characterized by bradykinesia, tremor, rigidity and postural instability. The pathological hallmarks of PD are the loss of nigrostriatal dopaminergic (DA) neurons and the widespread distribution of cytoplasmic inclusions composed of pre-synaptic α-synuclein protein, termed Lewy bodies. The motor signs appear when ~50–60% of DA cells in the substantia nigra par compacta (SNC) and ~60–80% of striatal DA terminals have been lost (Bernheimer et al. 1973; Hornykiewicz 1975, 1998; Hornykiewicz and Kish 1987). Apart from lesion of the nigrostriatal dopamine system, the PD pathology involves profound loss of brainstem noradrenergic, serotonergic and cholinergic neurons (Braak et al. 2003b; Chan-Palay 1991; Del Tredici et al. 2002; German et al. 1992b; Patt and Gerhard 1993; Zarow et al. 2003b). Loss of these non-dopaminergic neuronal groups likely contributes to some of the cognitive, autonomic and psychiatric impairments that are commonly seen in PD patients (Aarsland et al. 1999, 2004; Grimbergen et al. 2004; Langston 2006; Zesiewicz et al. 2003). However, because of the lack of animal models to study the pathophysiology of these non-

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motor signs, advances in the development of therapeutics have been limited and remain a major challenge in PD research for years to come.

Since the discovery that nigral dopamine loss is the key pathological hallmark of PD, various neurotoxin- and genetic-based models of PD that display profound nigrostriatal dopaminergic degeneration have been developed in rodents. Previous reviews have discussed in detail the strengths and weaknesses of these models and their relevance towards our understanding of the pathophysiology of motor and non-motor signs of PD (Bove and Perier 2012; Cenci et al. 2015; Duty and Jenner 2011; Jackson-Lewis et al. 2012; Jagmag et al. 2015; Lindgren and Dunnett 2012; Morin et al. 2014; Solari et al. 2013; Tolwani et al. 1999; Yue 2012). Although these models have made significant contribution to the field of PD research and therapeutics, their acute nature and the limited pathology to the nigrostriatal dopaminergic system limits their use for studying non-motor signs in PD (Dunnett and Lelos 2010; Fifel et al. 2016; Jenner 2002; Lindgren and Dunnett 2012; Taylor et al. 2010). The recent attempt at developing mice models that display chronic exposure to neurotoxin or genetically induced reduced expression of vesicular monoamine transporters have shown promising results in regards to pathology of non-dopaminergic cell groups and the development of some non-motor deficits commonly seen in PD (Betarbet et al. 2000; Fornai et al. 2005; Hoglinger et al. 2003b; Johnson and Bobrovskaya 2015; McNaught et al. 2004; Taylor et al. 2009).

The discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a contaminant of street drugs in the mid-1980s had a major impact in the field of PD because of its use as potent dopaminergic neurotoxin and its impact on the epidemiology of environmental toxins in the development of PD (Langston et al. 1983). Since then, the MPTP-treated nonhuman primate model is recognized as the "gold standard" model of PD (Bezard and Przedborski 2011; Dauer and Przedborski 2003; Emborg 2007; Fox and Brotchie 2010; Johnston and Fox 2015; Morissette and Di Paolo 2017; Porras et al. 2012). However, like most neurotoxin-based models of PD, a common criticism put forward by some authors in recent years was the lack of pathological neuronal loss beyond the nigrostriatal dopaminergic system in this model (Blandini and Armentero 2012; Dauer and Przedborski 2003; Forno et al. 1993). Although this may be the case for monkeys that undergo acute exposure to the toxin, evidence from the literature suggests that chronic systemic administration of MPTP leads to pathological neuronal loss that extends far beyond the ventral midbrain dopaminergic cell groups (Forno et al. 1993; Fox and Brotchie 2010; Karachi et al. 2010; Masilamoni et al. 2011b, 2016; Villalba et al. 2014). Furthermore, various groups have shown that MPTP-treated

monkeys display early cognitive impairments and other non-motor features of PD that likely result from non-dopaminergic lesions (Pessiglione et al. 2004; Roeltgen and Schneider 1991; Schneider and Kovelowski 1990; Slovin et al. 1999; Taylor et al. 1990; Vezoli et al. 2011).

In this review, we will critically examine the current state of knowledge of the brain pathology and related motor and non-motor deficits reported from nonhuman primate studies using various regimens of MPTP as neurotoxin-based models of PD. We will argue that monkeys treated chronically with low doses of MPTP should be considered as reliable animal models to study the pathophysiology and therapeutics of some non-motor features of PD.

MPTP: discovery and relevance for PD

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine was first identified as a PD-related drug in the 1980s after Californian heroin addicts displayed severe parkinson-like motor syndrome following self-administration of a potent pethidine derivative contaminated with MPTP (Langston et al. 1983; Langston and Ballard 1983). These victims displayed symptoms of bradykinesia and rigidity almost identical to those seen in idiopathic PD patients (Langston et al. 1983; Langston and Ballard 1983). Furthermore, their positive response to Levodopa therapy and the subsequent development of motor and non-motor side effects commonly associated with long-term exposure to such treatment provided compelling evidence that these individuals had been rendered parkinsonian through MPTP exposure. Postmortem pathological studies of brains from some of these individuals confirmed the profound dopaminergic neuronal loss in the ventral midbrain and striatal dopamine denervation (Langston et al. 1999).

Since its discovery, the mechanisms of action of MPTP towards dopaminergic cell loss have been characterized and discussed in detail in previous reviews (Dauer and Przedborski 2003; Forno et al. 1995; Fox and Brotchie 2010; Jenner and Marsden 1986; Johannessen 1991; Langston et al. 1999; Meissner et al. 2003; Porras et al. 2012; Rappold and Tieu 2010). In brief, once it has crossed the blood–brain barrier and got to the brain, MPTP is rapidly converted into the toxic MPP+ metabolite by glial monoamine oxidase-B (MAO-B). Because of its high affinity for MPP+, dopamine transporters (DAT), heavily expressed on nigrostriatal dopamine terminals, become the main gateway for MPP+ to preferentially access and kill nigral dopamine neurons (Dauer and Przedborski 2003; Jenner and Marsden 1986). Albeit a lower affinity for norepinephrine and serotonin transporters (NET, SERT), MPP+ is also picked up by these transporters, providing a

substrate for MPTP-induced noradrenaline and serotonin cell loss in some PD models (Boulet et al. 2008; D'Amato et al. 1986; Fornai et al. 2005; Herkenham et al. 1991; Masilamoni et al. 2011b; Perez-Otano et al. 1991; Pifl et al. 1996; Unguez and Schneider 1988). Because of differential ratios of intracerebral vs. systemic MAO-B expression between rodents and primates, the MPTP dosages used to induce cell death in the monkey brain are many orders of magnitude lower than those used in mice (Duty and Jenner 2011; Giovanni et al. 1994b; Jenner 2002; Johannessen et al. 1985). In rats, MPTP is largely ineffective at permanently killing brain cells (Giovanni et al. 1994a; Jenner 2002).

Non-human primates (NHP) treated with MPTP develop motor abnormalities that closely resemble those seen in PD patients, including bradykinesia, rigidity and postural abnormalities. These animals display a strong positive response to L-DOPA (Burns et al. 1983) which, after chronic exposure, lead to human-like treatment-related motor complications; in particular, the L-DOPA-associated dyskinesias (LID) (Boyce et al. 1990; Pearce et al. 1995; Potts et al. 2014). Recent evidence also suggests MPTP-treated monkeys display early cognitive impairments and other non-motor deficits reminiscent of those described in PD patients. In the following account, the brain pathology and behavioral changes reported in MPTP-treated monkeys will be critically examined and their relevance towards PD will be discussed.

Do MPTP-treated monkeys display a pattern of nigrostriatal dopaminergic denervation similar to PD?

The major sources of DA in the central nervous system are in the ventral midbrain comprising areas A8 (retrorubral field; RRF), A9 (SNc), and A10 (ventral tegmental area; VTA). The SNc neurons are further segregated into a dorsal (SNCd) and ventral (SNCv) tiers based on the expression or not of the calcium binding protein, calbindin D28k (CB) (Masilamoni et al. 2010, 2011b) (Fig. 1a, b). Although all dopaminergic cell groups undergo degeneration in PD, the SNCv is recognized as the most sensitive region, while the VTA is the least affected ventral midbrain area (Damier et al. 1999a, c; German et al. 1992a; Lu et al. 2006) (see Table 1). The presence of CB, low level expression of DAT, VMAT2 and more profuse norepinephrine innervation may contribute to the differential sensitivity of VTA/SNCd vs. SNCv neurons to PD pathology (Dopeso-Reyes et al. 2014; Iacopino et al. 1992a; Kilbourn et al. 1998; Liang et al. 1996b; Masilamoni et al. 2010, 2016; Mejias-Aponte et al. 2009; Miller et al. 1999a; Rommelfanger et al. 2004; Sanghera et al.

1997; Yuan et al. 2013). However, the importance of these features on the overall pattern of MPTP-induced neuronal degeneration can be assessed only if monkeys are treated with slow progressive MPTP regimen (Airaksinen et al. 1997; Porras et al. 2012). Using CB as specific marker of SNCd and VTA neurons, monkeys administered chronically with weekly low doses of MPTP (0.2–0.5 mg/kg MPTP, once a week for 21 weeks) display the same pattern of midbrain DA degeneration as shown in PD patients (Damier et al. 1999b, d; Fearnley and Lees 1991), i.e., a profound loss of CB-negative SNCv neurons over CB-positive SNCd, VTA and RRF neurons (Lavoie and Parent 1991; Masilamoni et al. 2010, 2011b) (Table 1). In contrast, when monkeys are made parkinsonian through a more acute and aggressive regimen of MPTP, the extent of DA degeneration is the same in both SNCv and SNCd (Collier et al. 2007). Thus, although CB may be neuroprotective against the toxic effects of low doses of MPTP in chronically treated animals (Dopeso-Reyes et al. 2014; Iacopino et al. 1992b; Liang et al. 1996a; Yuan et al. 2013), these properties are overcome by high doses of MPTP. Other features that have been put forward to explain the relative sparing of SNCd/VTA neurons vs. SNCv cells in response to MPTP (or other neurotoxins) include the relatively low levels of DAT expression on VTA/SNCd striatal dopamine terminals compared with SNCv neurons (less uptake sites for the dopaminergic neurotoxin MPP+) and /or the neuroprotective effects of a much more profuse norepinephrine innervation of VTA/SNCd neurons than SNCv neurons (Kilbourn et al. 1998; Masilamoni et al. 2016; Mejias-Aponte et al. 2009; Rommelfanger et al. 2004; Sanghera et al. 1997). Thus, the biochemical differences between the various groups of midbrain DA neurons and their respective extent in NE innervation may contribute to the differential sensitivity of SNCd/VTA vs. SNCv neurons to PD pathology and MPTP toxicity.

This pattern of DA neuronal degeneration holds true for susceptibility to MPTP-induced degeneration. This differential degeneration at the cell body level is represented in the striatum by a more severe loss of dopaminergic innervation in the dorsal (targeted mainly by SNCv neurons) than the ventral striatum (targeted by VTA neurons). In the dorsal striatum, the dopamine loss is not homogeneous, but rather displays a progressive caudo-rostral gradient, i.e., it affects preferentially the post-commissural putamen (known as the sensorimotor striatal territory) over the anterior putamen and the caudate nucleus (known as associative striatal regions) (Davis et al. 2003; Kish et al. 1988). Although there is no clear explanation as to why SNc neurons that project to the sensorimotor putamen are more sensitive to PD degeneration than those that innervate the cognitive striatal regions, some hypotheses have been put forward ranging from a different ratio of DAT/VMAT2

Fig. 1 Photomicrographs of adjacent calbindin (CB) and tyrosine hydroxylase (TH)-immunostained coronal sections at the level of ventral midbrain of control (**a**, **c**) and MPTP-treated parkinsonian monkey (**b**, **d**). CB immunostaining was used to delineate TH/CB-positive neurons in the dorsal tier of the SNC (SNCd) and the ventral tegmental area (VTA) from TH-positive/CB-negative neurons in ventral tier of the SNC (SNCv). **e** Percentage loss of TH-positive neurons in SNCv, SNCd and VTA regions of three MPTP-treated monkeys (M1, M2 and M3) based on unbiased stereological estimates of total TH-positive cell counts (see Masilamoni et al. 2011b for additional details)
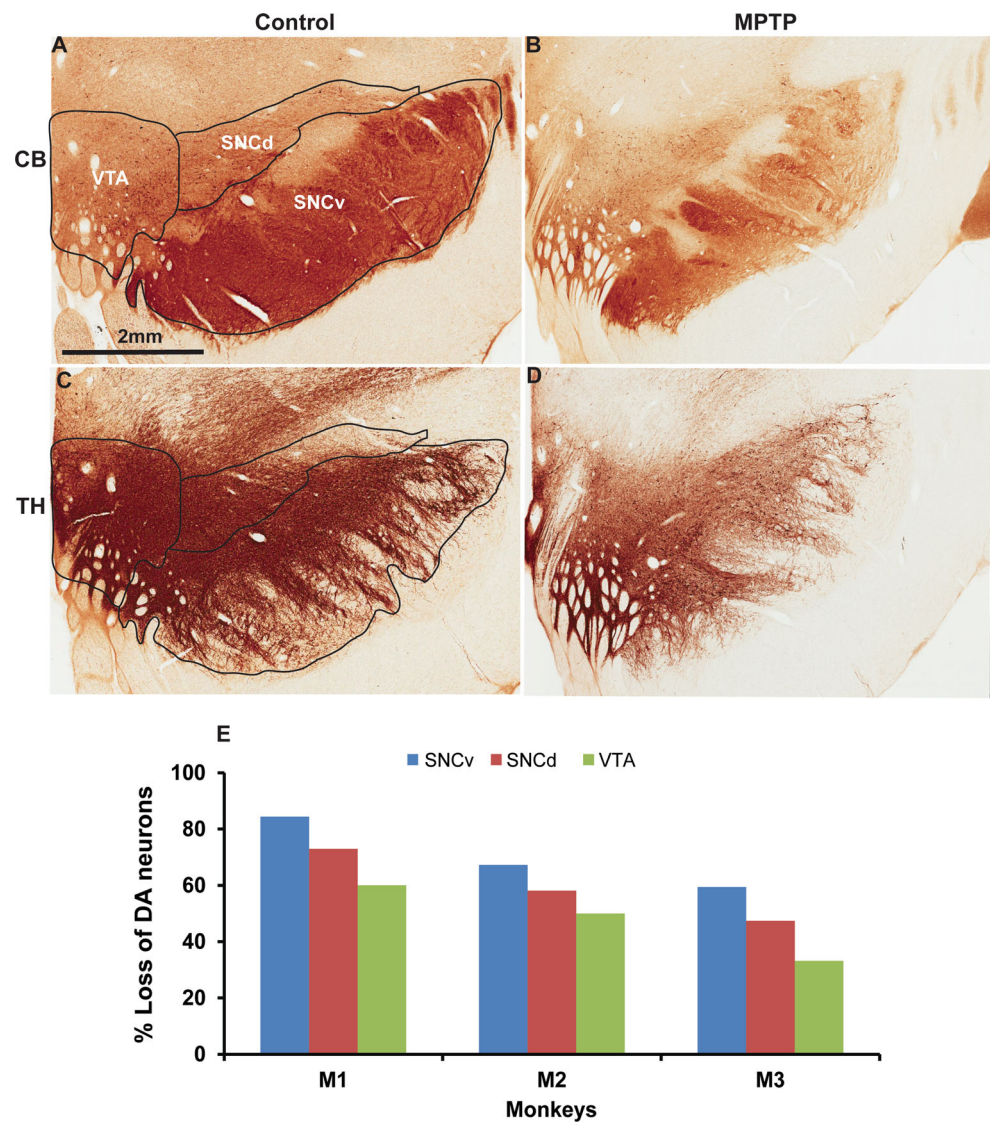
on dopamine terminals in the caudate nucleus vs. putamen (Miller et al. 1999a, b) to a differential synaptic innervation of dopamine neurons that project to the caudal striatum compared with other dopamine-projecting neurons in the mouse SNc (Menegas et al. 2015).

There has been various reports indicating that the preferential dopamine denervation of the post-commissural putamen over other dorsal striatal regions was not found in monkeys treated with acute or a high-dose regimen of MPTP (Alexander et al. 1992; Bezard et al. 2001; Di Monte et al. 2000; Elsworth et al. 1989; Fernagut et al. 2010; Hantraye et al. 1992; McCallum et al. 2006; Pifl et al. 1988a). However, data from our laboratory and others using chronic low-dose MPTP exposure revealed that the progressive loss of striatal dopamine terminals reported in PD patients, i.e., a greater DA depletion in the post-commissural putamen than ventral striatum and caudate (Fig. 2a–f), can also be seen in parkinsonian monkeys

(Hantraye et al. 1993; Iravani et al. 2005; Masilamoni et al. 2010, 2011b; Moratalla et al. 1992; Mounayar et al. 2007). Thus, dopamine terminals in the post-commissural putamen are more sensitive to degeneration than any other nigrostriatal afferents in PD and in monkeys chronically intoxicated with low doses of MPTP.

Early dopaminergic denervation of striosomes over matrix in chronically MPTP-treated monkeys

During brain development and early postnatal period, striatal DA innervation is compartmentally organized, giving rise to the so-called "dopamine islands" which, in adults, corresponds to the striosomal striatal compartment (Graybiel et al. 1981; Prensa et al. 2000). Striosomes and matrix can also be differentiated from each other neurochemically or anatomically based on the heterogeneous

Table 1 Striatal and nigral dopamine loss in PD patients and MPTP-treated monkeys

| Species	Age (years)	Sex	PD patients/MPTP dose	MPTP regimen	Parkinsonian clinical symptom	Pathology observation (nigral dopamine cell/striatal DA levels loss in %)	References
Midbrain dopaminergic neurons							
Human	62–83	M, F	PD	–	Fully Parkinsonian	VM 71 VL 91 PL 61 DM 47 DL 57	Fearnley and Lees (1991)
Human	72 ± 4	–	PD	–	Fully Parkinsonian	SNC v nigrosomes 95 SNC v matrix 80 SNC d 57	Damier et al. (1999b, d)
Callithrix jacchus	–	F	1–4 mg/kg/day for 5 days, i.p	Acute high-dose treatment	Fully Parkinsonian	SNC 82 VTA 59	Waters et al. (1987)
Papio papio			0.2–0.5 mg/kg i.v once a week until a full parkinsonian	Chronic low-dose treatment	Fully Parkinsonian	VM 73.8 VL 90.9 PL 89.5 DM 46 DL 56.6 VTA 53	Varastet et al. (1994)
Cercopithecus-aethiops	4–6	M	0.4–0.6 mg/kg i.m Progressive intoxication: (injections spaced 4–5 days)	Chronic low-/high-dose treatment	Fully Parkinsonian monkeys	SNC 71 RRF 35 VTA 34	Mounayar et al. (2007)
Macaca mulatta	8–9 young 15–17 middle 21–31 old	F	2.3–3.00 mg, unilateral intracarotid administration	Single dose	Hemiparkinsonian monkey	SNC 81.8 SNC 82.8 SNC 81.0	Collier et al. (2007)
Macaca mulatta	3–6	F	0.2–0.5 mg/kg i.m once a week until a full parkinsonian	Chronic low-dose treatment	Moderate Parkinsonian monkeys Fully Parkinsonian monkeys	SNC v 64 SNC d 53 VTA 42 SNC v 85 SNC d 73 VTA 60	Masilamoni et al. (2011b)

Table 1 continued

Species	Age (years)	Sex	PD patients/MPTP dose	MPTP regimen	Parkinsonian clinical symptom	Pathology observation (nigral dopamine cell/striatal DA levels loss in %)	References
Macaca fascicularis	4–5	M	0.5 mg/kg i.v once in 2 weeks	Chronic low-dose treatment	Moderate Parkinsonian monkeys	SNC 74, RRF 40, VTA 34, SNC 84, RRF 45, VTA 33	Blesa et al. (2012)
Nigrostriatal dopamine innervation							
Human	–		–		Fully Parkinsonian	Pre-commissural CA 90, Commissural CA 82, Post-commissural CA 70, Pre-commissural PU 93, Commissural PU 97, Post-commissural PU 98	Kish et al. (1988)
Human	–			–	Fully Parkinsonian	CA 84, PU 98	Pifl et al. (1988b)
Human	–			–	Fully Parkinsonian	CA 80, PU 98	Kish et al. (2008)
Macaca mulatta	10–17		0.15 mg/kg for the first 3 days and consecutively 0.24–0.4 mg/kg per day until severe Parkinson-like symptoms	Acute low-dose treatment	Fully Parkinsonian monkeys	CA 99, PU 99	Pifl et al. (1988b)
Cercopithecus-aethiops sabaeus			0.4 mg/kg for 5 days	Acute low-dose treatment	Fully Parkinsonian monkeys	CA 98, PU 96	Elsworth et al. (1989)
Callithrix jaccus	1–2	M, F	1.25–2.5 mg/kg s.c. was given twice a week up to development of symptom	Chronic high-dose treatment	Fully Parkinsonian monkeys	CA 95, PU 95	Perez-Otano et al. (1991)
Macaca fascicularis			Daily injections (0.25–0.50 mg/kg)	Acute low-dose treatment	Fully Parkinsonian monkeys	PU 97, CA 98	Alexander et al. (1992)
Macaca fascicularis	–		3 consecutive i.v injection at 0.7 mg/day	Acute high-dose treatment	Fully Parkinsonian monkeys	CA 94, PU 93	Hantraye et al. (1992)
Pupio pupio			0.4–0.6 mg/kg i.v once a week until a full parkinsonian	Chronic low dose-treatment	Fully Parkinsonian monkeys	CA 70, PU 90	Hantraye et al. (1993)

Table 1 continued

Species	Age (years)	Sex	PD patients/MPTP dose	MPTP regimen	Parkinsonian clinical symptom	Pathology observation (nigral dopamine cell/striatal DA levels loss in %)	References
Saimiri sciureus	–	M, F	single subcutaneous injection of 2 mg/kg MPTP received multiple subcutaneous injections	Single dose Acute intoxication	No behavioral signs of parkinsonism	CA 63 PU 70 CA 95 PU 99	Di Monte et al. (2000)
Cercopithecus-aethiops sabaeus	–		0.4 mg/kg for 5 days	Acute low-dose treatment	Asymptomatic Mild Moderate Severe	CA 70; PU 58 CA 90; PU 68 CA 94; PU 92 CA 99; PU 99	Elsworth et al. (2000)
Caca fascicularis	3.1 ± 0.3	F	0.2 mg/kg, i.v. daily after 6 injections; D6 After 15 injections; D15 After 15 injections; D25	Acute low-dose treatment	Pre-symptomatic Appearance of symp. Fully Parkinsonian monkeys	Loss of dopamine CA 50; PU 40 PU 85%; CA 90 CA 95; PU 95%	Bezard et al. (2001)
Macaca fascicularis	–	M	Intracarotid injections Single dose of 1.25 mg Single dose of 2.5 mg	Acute low-dose treatment	Hemiparkinsonism	Ipsilateral DA loss CA 99,4; PU, 99.8; AC 74.2 CA 99.3; PU 99.5; AC 90.1	Guttman et al. (1990)
Macaca fascicularis	2–4		5–15 injections of 0.5–1.0 mg/kg spaced one week apart	Chronic high-dose treatment	Fully Parkinsonian	Pre-commissural CA 98 Commissural CA 94 Post-commissural CA 90 Pre-commissural PU 98 Commissural PU 99 Post-commissural PU 99	Perez-Otano et al. (1994a)
Macaca mulatta	3–6	F	0.2–0.5 mg/kg i.m once a week until full parkinsonian	Chronic low-dose treatment	Moderate Parkinsonian monkeys Fully Parkinsonian monkeys	CA 63 PU 80 CA 80 PU 90	Masilamoni et al. (2011b)
Macaca fascicularis	4–5	M	0.5 mg/kg i.v once in 2 weeks	Chronic low-dose treatment	Moderate Parkinsonian monkeys Fully Parkinsonian monkeys	CA 78 PU 79 CA 84 PU 83	Blesa et al. (2012)

VM ventral medial, *VL* ventral lateral, *PL* pars lateralis, *DM* dorsal medial part, *DL* lateral part, *CA* caudate, *PU* putamen, *SNC* substantial nigra, *SNC v* ventral, *SNC d* dorsal, *VTA* ventral tegmental area, *RRF* retrorubral area
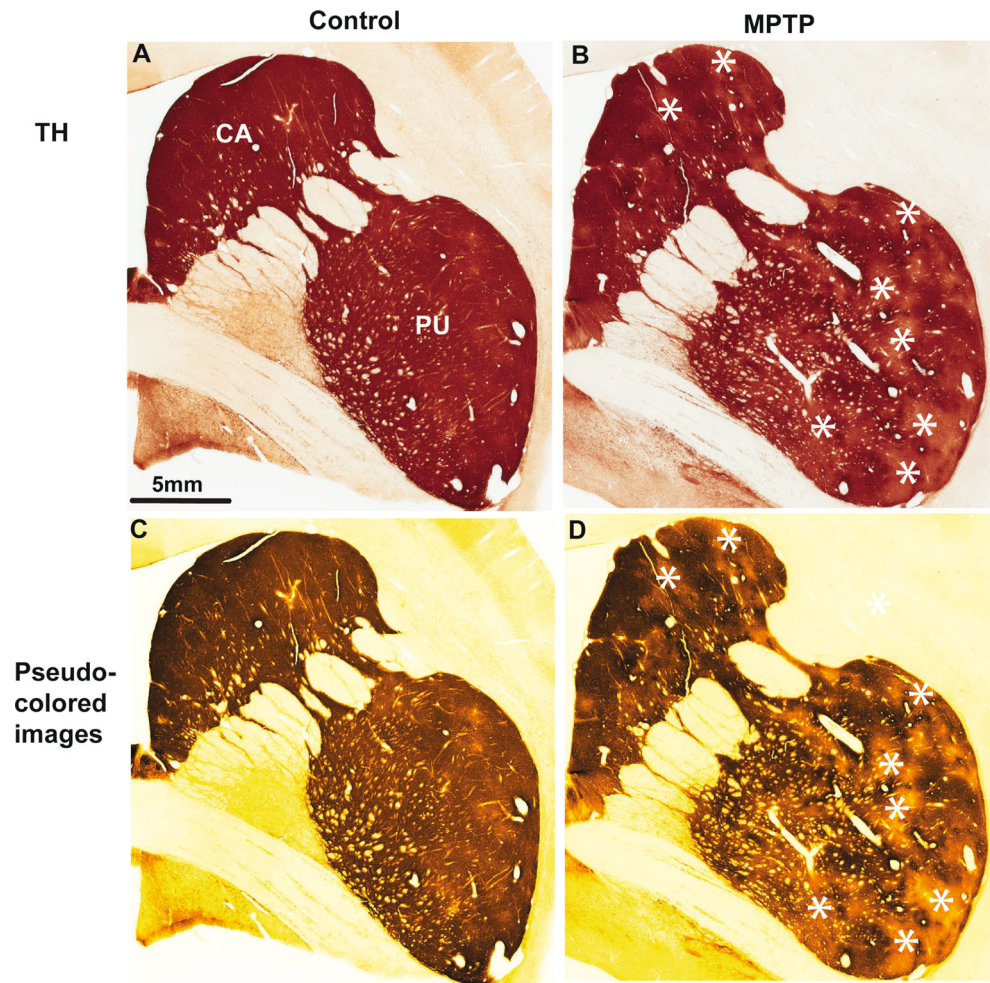
Fig. 2 Photomicrographs of TH-immunostained coronal sections at the level of the pre-commissural (**a**, **b**), commissural (**c**, **d**), post-commissural (**e**, **f**) striatum of a control (*left column*) and a MPTP-treated (*right column*) monkey. *CA* caudate nucleus, *PU* putamen, *GPe* globus pallidus, external segment, *GPi* globus pallidus, internal segment, *Th* thalamus
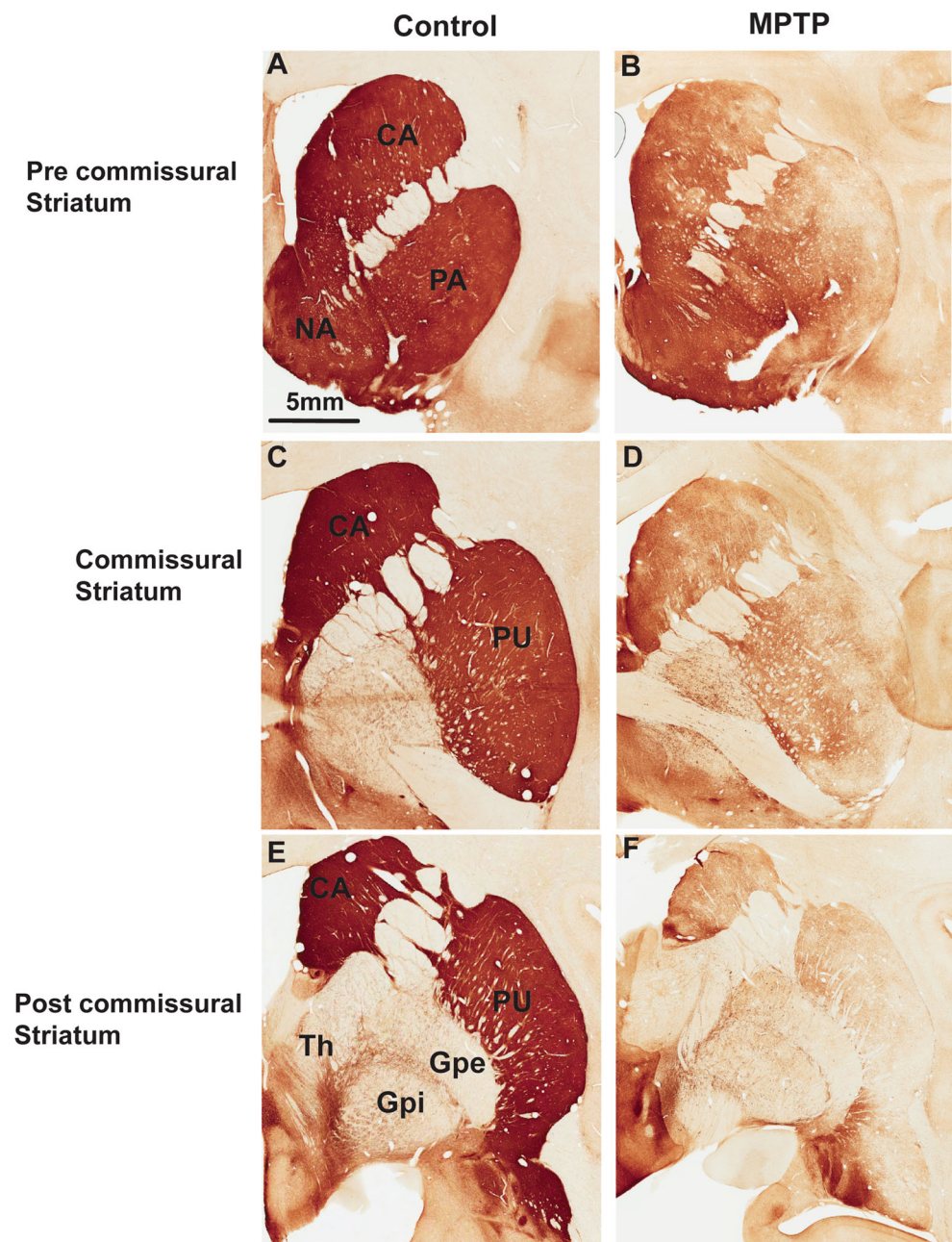
distribution of various neuronal markers and afferents from specific cortical and sub-cortical regions (Gerfen 1984; Gimenez-Amaya and Graybiel 1991; Graybiel and Ragsdale 1978; Herkenham and Pert 1981). Because of its abundance and homogeneous distribution in both compartments, markers of nigrostriatal dopaminergic axons and terminals (TH or DAT immunostaining; Fig. 3a, b) do not display any heterogeneity in the normal adult striatum (Graybiel et al. 1981; Prensa et al. 2000). However, in monkeys chronically treated with low doses of MPTP, dopamine denervation of striosomes in

the caudate nucleus and anterior putamen precedes that of the matrix (Iravani et al. 2005; Lin et al. 2015; Masilamoni et al. 2011b) (see Fig. 3c–f). In this model, early striosomal dopamine loss occurs in parallel with the denervation of the post-commissural putamen (Iravani et al. 2005; Lin et al. 2015; Vingerhoets et al. 1994), suggesting that SNCv nigrostriatal neurons that project to the caudate putamen and the striosomes are most sensitive to MPTP-induced neurodegeneration. Based on recent findings that striatonigral GABAergic projections from striosomes form tight connections with clusters of SNCv

dopaminergic cells (Crittenden et al. 2016), one could speculate that the striosomal striato-nigro-striatal loop is a functional network that displays increased sensitivity to degeneration in PD. Tract-tracing studies showing that anterograde tracer injections into the SNCv produce labeling that predominantly target the striosomes, whereas dorsal injections label preferentially the striatal matrix are consistent with this hypothesis (Fujiyama et al. 2011; Gerfen et al. 1987; Jimenez-Castellanos and Graybiel 1987; Joel and Weiner 2000; Langer and Graybiel 1989). Because striosomes are in a position to modulate and transmit signals to the SNc from limbic-related cortical regions (Crittenden et al. 2016; Eblen and Graybiel 1995; Friedman et al. 2015), early striosomal dopamine loss may affect the control of mood, attention and motivation, non-motor signs that are commonly seen in PD patients. It is noteworthy that imbalanced activity between striosomes and matrix has been proposed as the underlying substrate of a wide variety of motor and non-motor signs in a wide array of basal ganglia disorders (Crittenden and Graybiel 2011).

Extra-striatal DA denervation in PD vs. MPTP-treated monkeys

Although the dorsal striatum is the most severely dopamine-denervated brain region in PD and MPTP-treated monkeys, non-striatal brain nuclei also undergo dopamine depletion (Benazzouz et al. 2014; Lee et al. 2014; Parent and Cossette 2001; Rommelfanger and Wichmann 2010; Smith and Villalba 2008). In contrast to the nigrostriatal dopamine degeneration, which contributes to the pathophysiology of the key parkinsonian motor signs, very little is known about the functional significance of extra-striatal dopamine loss in PD (Smith and Kieval 2000; Rommelfanger and Wichmann 2010). However, because the cortical and subcortical regions affected are involved in broad range motor and non-motor functions, a comparative analysis of the overall pattern of extra-striatal DA degeneration between PD patients and MPTP-treated monkeys is critical for the assessment of the reliability of this animal model towards studies of extra-striatal DA pathology in PD non-motor signs.

Dopamine denervation of the globus pallidus

Immunohistochemical and tract-tracing studies reported that the two pallidal segments (GPe—external and GPi—internal) receive DA innervation from the ventral midbrain dopamine cell groups in both humans and NHPs (Cossette et al. 1999; Hedreen 1999; Nobin and Bjorklund 1973). In normal humans, DA levels in the GPe are nearly six times greater than in the GPi. In PD, the mean loss of DA is severe (82%) in GPe and moderate (51%) in GPi (Rajput et al. 2008). Electrophysiological and pharmacological studies supporting these observations showed that dopamine receptor-related drugs induce significant changes in GPe and GPi neurons through pre- and post-synaptic mechanisms in control and parkinsonian monkeys (Boraud et al. 1998; Filion et al. 1991; Hadipour-Niktarash et al. 2012; Kliem et al. 2010; Rommelfanger and Wichmann 2010; Smith and Kieval 2000). Several studies have shown that DA inputs are differentially distributed in GPe and GPi, with DA fibers arborizing more profusely in the medial "limbic-related" pole of GPi than in other functional sectors of GPe and GPi (Hedreen 1999; Lavoie et al. 1989; Parent and Smith 1987; Parent et al. 1989). In monkeys, the nigropallidal projection originates in part from a subset of dopaminergic neurons different from those that give rise to the nigrostriatal system (Smith and Kieval 2000). The importance of the nigropallidal dopaminergic system in the development of parkinsonian motor symptoms is further supported by pharmacological and electrophysiological data gathered in normal and MPTP-treated monkeys. Thus, infusion of D1 or D2 dopamine receptor antagonists into the GPe of normal rats induces akinesia (Hauber and Lutz 1999). Local intrapallidal delivery of D1 or D2 receptor-related drugs into GPe or GPi of normal and parkinsonian monkeys affect the firing rate and pattern of pallidal neurons (Hadipour-Niktarash et al. 2012; Kliem et al. 2007).

Data from MPTP-treated monkeys support the human studies suggesting that the PD-related pathology of the nigropallidal dopaminergic system is less severe than the nigrostriatal projection, particularly during the asymptomatic or early stages of the disease (Lin et al. 2015; Mounayar et al. 2007; Pifl et al. 1990). In fact, an increase in ^{18}F-dopa uptake was demonstrated in the GPi of early PD patients compared to aged match controls, suggesting a compensatory response of the nigro-GPi system to nigrostriatal dopamine denervation (Moore et al. 2008; Pavese et al. 2011; Rakshi et al. 1999; Whone et al. 2003). Thus, data from both human and MPTP-treated monkeys suggest a relative sparing or up-regulation of the nigro-pallidal dopamine projection in the early stages of PD representing adaptive mechanism to preserve functionality.

Dopamine denervation of the subthalamic nucleus

Anatomical and tracing studies have demonstrated the existence of SNC-STN projections in both monkeys and humans (Augood et al. 2000; Cossette et al. 1999; Francois et al. 2000; Gauthier et al. 1999; Hassani et al. 1997; Hedreen 1999; Lavoie et al. 1989). However, very few vesicle-filled dopamine axonal profiles and terminals were reported in electron microscopic analysis of the monkey STN, raising questions about the source and mechanism of release of dopamine by nigrosubthalamic axons (Smith and Kieval 2000). The situation is different in the rodent STN, which is far more enriched in dopamine terminals than the primate STN (Cragg et al. 2004). Various DA receptor subtypes are expressed pre- and post-synaptically in the primate and rodent STN (Augood et al. 2000; Flores et al. 1999; Galvan et al. 2014; Parry et al. 1994; Rommelfanger and Wichmann 2010; Smith and Villalba 2008). Intra-subthalamic applications of D1 or D2 receptor agonists alter the firing rate and pattern of STN neurons in control and MPTP-treated monkeys (Galvan et al. 2014).

There is a substantial loss of dopamine innervation of the STN in MPTP-treated monkeys (Francois et al. 2000; Pifl et al. 1990, 1991) and in human PD patients (Hornykiewicz 1998; Pavese et al. 2011). In contrast to the nigropallidal projection that is relatively spared in motor asymptomatic MPTP-treated monkeys, the nigrosubthalamic system is severely degenerated in these animals (Pifl et al. 1991), thereby suggesting that the nigropallidal, but not the nigrosubthalamic, system might functionally compensate striatal dopamine denervation in early parkinsonian state. Thus, one would speculate that the DA loss in the STN may concomitantly contribute to the abnormal increased activity of these glutamatergic neurons and eventually lead to the expression of motor signs in PD (Bergman et al. 1994; Fox and Brotchie 2010; Galvan et al. 2014; Rommelfanger and Wichmann 2010; Wichmann and DeLong 2003).

Dopamine denervation of the cerebral cortex

Dopamine innervation of prefrontal cortices is well established and heavily studied because of its possible role in psychiatric disorders (Akil et al. 1999; Arnsten et al. 1995, 2015; Devoto et al. 2012; Dreher and Burnod 2002; Drouot et al. 2004; Erickson et al. 2000; Fallon et al. 2015; Goldman-Rakic 1998; Ko et al. 2013; Naneix et al. 2009; Narayanan et al. 2013; Sutoo et al. 2001; Thompson et al. 2014; Venator et al. 1999; Winterer and Weinberger 2004). Imaging and tract-tracing studies have shown that the mesocortical dopamine system is far more extensive in primates than in rodents (Akil and Lewis 1994; Berger et al. 1991; Lewis et al. 1987, 1994, 2001; Preuss 1995;

Sesack et al. 1995; Williams and Goldman-Rakic 1998a). Layer I is a widespread target of dense dopaminergic innervation in all areas of the macaque and human neocortex, while it is mainly confined to prefrontal cortical regions in rats (Berger et al. 1988, 1992; Gaspar et al. 1989; Petrides and Pandya 1999; Zilles et al. 1996; Preuss 1995). Significant interspecies differences have also been demonstrated in the origin of the mesocortical system between rodents and primates, such that it arises almost exclusively from the VTA in rats (Berger et al. 1991; Deutch et al. 1988; Hosp et al. 2011; Luft and Schwarz 2009), while neurons in the SNc and the retrorubral area (RRA) significantly contribute to that system in monkeys (Gaspar et al. 1992; Williams and Goldman-Rakic 1998b).

Using ^{18}F-dopa PET imaging (Brooks and Piccini 2006) showed a significant loss of DA terminals in M1 and PFC of PD patients compared with age-matched control subjects. Postmortem data have revealed a significant degeneration of the dopaminergic inputs throughout M1 in humans, most strongly affecting dopaminergic fibers in layer I in PD patients (Gaspar et al. 1991, 1992). These observations are consistent with previous anatomical data (Jan et al. 2003), and with biochemical findings showing a 30–40% decrease of dopamine levels in M1 of MPTP-treated parkinsonian monkeys (Jan et al. 2003; Pifl et al. 1991; Scatton et al. 1983). Abnormal cortical metabolic activity was also noticed in both PD patients and MPTP-treated monkeys (Carbon et al. 2003; Dogali et al. 1994; Eckert et al. 2008; Eidelberg et al. 1994; Huang et al. 2007) with an earlier occurrence and greater magnitude in the M1 than in the PFC (Huang et al. 2007). Knowing that premotor and prefrontal cortical areas are under the influence of the dopamine system directly through the meso-cortical network, one would expect that changes in these networks may contribute to these cortical metabolic dysfunctions. It has, indeed, been demonstrated that even very subtle cortical dopamine depletion may lead to a severe loss of action selection ability (Leblois et al. 2006), highlighting the important role of cortical dopamine in mediating these regulatory effects.

Thus, because of the evolutionary increase in cortical dopamine innervation between rodents and primates, and the comparable extent of degeneration of this system in motor and non-motor cortices in PD patients and MPTP-treated monkeys, nonhuman primates are the species of choice to study the role of cortical dopamine degeneration in the development of motor and non-motor parkinsonian symptoms.

Dopamine denervation of the thalamus

Anatomical studies have shown that various thalamic nuclei receive a significant dopaminergic innervation in humans and NHP (Brown et al. 1979; Garcia-Cabezas et al. 2007, 2009; Goldman-Rakic and Brown 1981; Oke and Adams 1987; Pifl et al. 1990, 1991; Sanchez-Gonzalez et al. 2005). The innervation of midline limbic nuclei, the mediodorsal and lateral posterior association nuclei, and the ventral lateral/ventral anterior motor nuclei (Brown et al. 1979; Garcia-Cabezas et al. 2007, 2009; Goldman-Rakic and Brown 1981; Oke and Adams 1987; Pifl et al. 1990, 1991; Sanchez-Gonzalez et al. 2005) is particularly dense. This distribution suggests thalamic dopamine may play important roles in regulating emotion, attention, cognition, complex somatosensory and visual processing, and motor control. In contrast to primates, the dopamine innervation of the rodent thalamus is very scant (Papadopoulos and Parnavelas 1990; Voorn et al. 1988). The functional significance of this important species difference is unknown, but combined with the more widespread dopamine innervation of the cerebral cortex (see above), it suggests that dopamine modulatory functions of thalamo-cortical and corticothalamic relationships may be more complex in primates than non-primates (Berger et al. 1991; Papadopoulos and Parnavelas 1990).

Dopaminergic cell groups in the VTA, retrorubral field, periaqueductal gray and hypothalamus are the main sources of the primate thalamus innervation (Sanchez-Gonzalez et al. 2005), although another study suggested that collaterals of the nigrostriatal dopamine projection innervate the primate thalamus (Freeman et al. 2001).

In PD patients and MPTP-treated parkinsonian monkeys, DAT binding is significantly decreased throughout the thalamus (Brownell et al. 2003; Freeman et al. 2001; Pavese et al. 2010; Pifl et al. 1990, 1991). Postmortem studies showed that the dopaminergic innervation of the MD and CnMd nuclei is most affected in PD patients and MPTP-treated parkinsonian monkeys (Freeman et al. 2001; Pavese et al. 2010; Pifl et al. 1990, 1991) Although the role of dopamine in the primate thalamus remains to be established, it is reasonable to suggest that thalamic dopamine denervation may contribute to the pathophysiology of abnormal activity and transmission of motor and non-motor innervation through the basal ganglia-thalamocortical loops.

MPTP-induced dopamine denervation in nonhuman primates: concluding remarks

In PD, postmortem studies have demonstrated that dopaminergic lesion affects cortical and sub-cortical regions beyond the nigrostriatal system. Similarly, chronic MPTP administration in adult monkeys results in a broad degeneration of dopaminergic projections to non-striatal regions. Extra-striatal basal ganglia nuclei such as the globus pallidus and subthalamic nucleus are both affected,

but in opposite directions. Most importantly, widespread cortical dopamine pathology is also induced in this animal model. Because the mesocortical dopamine innervation of sensorimotor cortices is far more extensive in primates than rodents, the MPTP-treated monkey model is essential to assess the importance of cortical dopamine denervation on sensorimotor dysfunctions associated with parkinsonism. Another dopaminergic system that underwent a significant expansion in primates, and was found to be affected in MPTP-treated monkeys and PD patients is the meso-thalamic dopaminergic network. Although the function of this system remains unknown, its widespread termination in thalamic nuclei involved in the processing of motor, sensory, limbic and cognitive information suggests degeneration of the meso-thalamic system may have broad consequences on the pathophysiology of the thalamocortical and corticothalamic relationships that underlie some of the motor and non-motor symptoms of PD.

Thus, the dopaminergic brain pathology induced in the chronic MPTP-treated monkey model is closely similar to that reported in PD patients, indicating that chronic MPTP-treated monkeys can be used to assess the importance of dopamine denervation beyond the nigrostriatal dopaminergic system that potentially contribute to a wide variety of non-motor symptoms in PD.

Chronic MPTP administration in non-human primates induces severe loss of non-dopaminergic neurons relevant to Parkinson's disease

In this section, we will review reports about the loss (or not) of non-DAergic cell groups in MPTP-treated monkeys, and discuss their relevance towards the pathophysiology and the development of non-motor signs in Parkinson's disease.

Fig. 4 Photomicrographs of TH-immunostained coronal sections at the level of noradrenergic cell groups (a, b), 5HT-immunostained serotonergic cell groups (c, d) and ChAT-immunostained pedunculopontine nucleus (e, f) of a control (a, c, e) and a MPTP-treated (b, e, f) monkey. A5,A7 noradrenergic cell groups A5 and A7, PPN pedunculopontine nucleus (see Masilamoni et al. 2011b for more details)
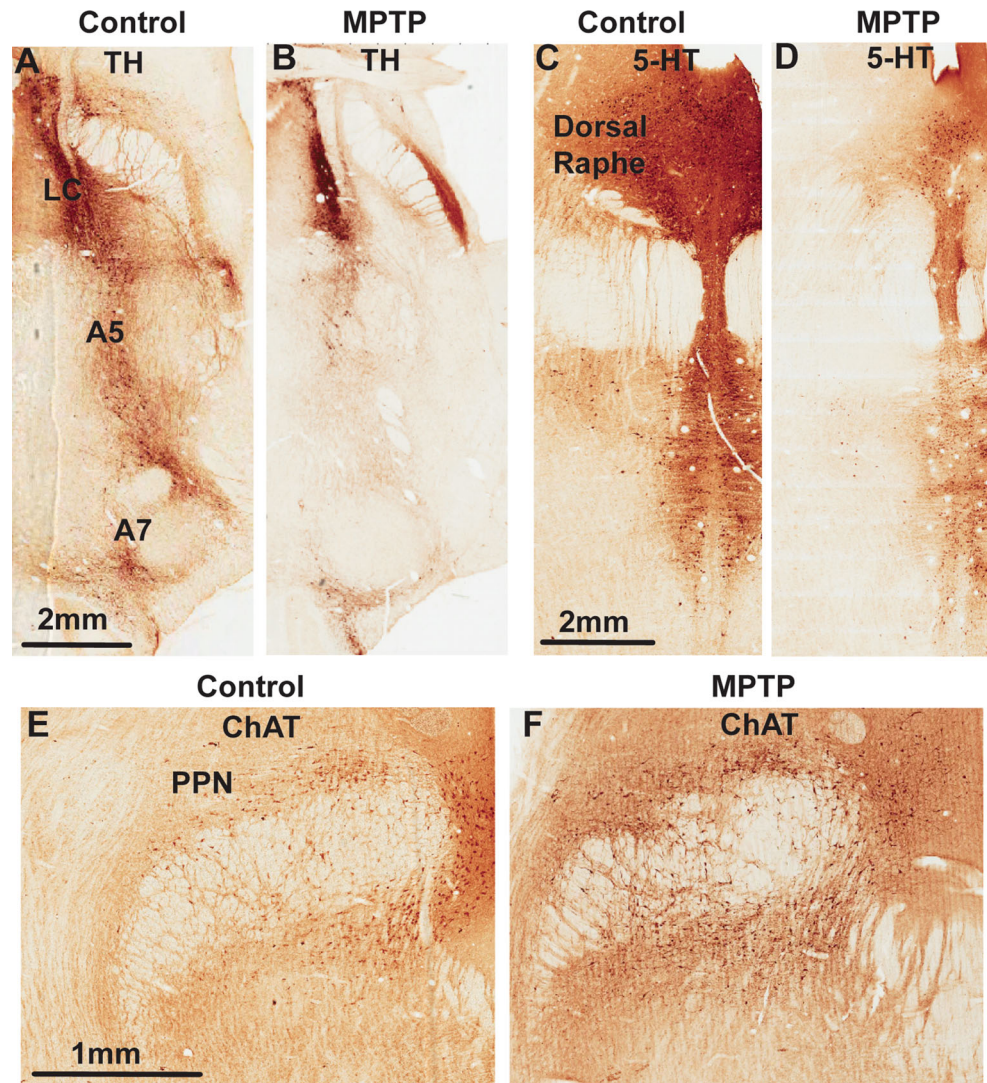
Norepinephrine pathology-locus coeruleus and related brainstem noradrenergic cell groups

There is strong agreement across postmortem pathological studies that the loss of locus coeruleus (LC) noradrenergic neurons in PD patients is as prominent as that of the nigral dopaminergic neurons (Braak et al. 2003b; Chan-Palay 1991; Del Tredici and Braak 2013; German et al. 1992b; Patt and Gerhard 1993; Zarow et al. 2003a). However, reports about noradrenergic cell loss in LC of MPTP-treated monkeys have been inconsistent (Forno et al. 1986; Gibb et al. 1989; Herrero et al. 1993a), most likely because of differences in MPTP treatment regimens. Acute MPTP administration induces parkinsonian motor symptoms with massive nigrostriatal DA loss, but without significant LC neuronal death (Forno et al. 1993; Gibb et al. 1989). On the other hand, monkeys that undergo chronic systemic MPTP administration display prominent LC neurodegeneration (Herrero et al. 1993b; Masilamoni et al. 2011b) (Fig. 4a, b). In light of these findings, it appears that the regimen of MPTP administration may account for the differences in norepinephrine cell loss reported in these studies, such that chronic administration regimen is essential to induce significant LC neuronal death.

Another noticeable feature of the noradrenergic system degeneration in MPTP-treated monkeys is that NE terminal loss in the midbrain and cerebral cortex is more pronounced than the magnitude of LC neuronal loss (Buddhala et al. 2015; Masilamoni et al. 2016; Nayyar et al. 2009), suggesting that NE nerve terminals are the primary target of the degenerative process after MPTP administration and in PD patients.

Thus, chronic MPTP injections recreate a pathological state of the noradrenergic system that mimics human PD more accurately than acute MPTP bolus injections. These observations suggest that severe and prolonged stress may trigger the onset of sporadic PD, thereby contributing to its progression (Herkenham et al. 1991). It is noteworthy that similar observations were reported for rotenone, i.e., only continuous administration of this neurotoxin induces LC neuronal loss (Hoglinger et al. 2003a, b). Even when administered at high doses, acute administration of rotenone damages only the nigrostriatal DA system (Ferrante et al. 1997; Heikkila et al. 1985).

Because LC plays a central role in cognitive performance (Coull et al. 1999; Sterpenich et al. 2006), sleep–waking cycle (Jouvet 1972) mood regulation and various autonomic functions, the degeneration of the LC and its projections likely contribute to a wide variety of non-motor symptoms in PD patients. Thus, the chronic MPTP-treated monkey model provides a unique tool needed to better understand the pathophysiology and refine therapy for these parkinsonian non-motor signs (Abbott et al. 2005; Barraud et al. 2009; Lees and Smith 1983; Schneider et al. 1999).

Serotonergic pathology

Serotonergic cell loss in raphe neurons has been well-documented in advanced PD patients (D'Amato et al. 1987; Halliday et al. 1990; Ohama and Ikuta 1976). Consistent with these postmortem pathological observations, PET imaging studies have reported profound and widespread neocortical and striatal decrease of 5-HT transporter ligand binding in advanced PD patients (Albin et al. 2008; Guttman et al. 2007; Politis et al. 2010). However, in early PD state the serotonergic system is involved in compensatory phenomenon with an up-regulation or no change in the expression of 5-HT receptors in the striatum (Kaasinen et al. 2001; Kumakura et al. 2010; Moore et al. 2008; Rakshi et al. 1999; Whone et al. 2003). This compensatory mechanism fades away as the disease progresses so that advanced PD patients show reduced 5HT tracer uptake in cortical and striatal regions (Moore et al. 2008; Rakshi et al. 1999). Because dysfunction of the serotonergic system is involved in the pathophysiology of depression (Cummings 1992; Kostic et al. 1987; McCance-Katz et al. 1992), cognitive impairments (Brown and Marsden 1988; Pillon et al. 1989) and other psychiatric disorders (Cooney and Stacy 2016; Lenka et al. 2016; Reichmann et al. 2016), dysregulation of this system may contribute to some of the commonly encountered non-motor psychiatric and sleep disorders in PD (Abbott et al. 2005; Barraud et al. 2009; Lees and Smith 1983; Schneider et al. 1999). Mood changes in PD are, indeed, responsive to antidepressants including serotonin and norepinephrine (NE)-selective reuptake inhibitors (Blier 2006; Brooks and Doder 2001; Lemke 2008; Miyasaki et al. 2006; Zesiewicz and Hauser 2002).

Reports about serotonergic pathology in MPTP-treated monkeys have been variable (Ballanger et al. 2016; Beaudoin-Gobert et al. 2015; Boulet et al. 2008; Gaspar et al. 1993; Mihatsch et al. 1991; Mounayar et al. 2007; Perez-Otano et al. 1994a, b; Pifl et al. 1991; Zeng et al. 2010). Increased serotonergic fibers (Boulet et al. 2008; Gaspar et al. 1993; Mounayar et al. 2007; Zeng et al. 2010) and serotonin levels (Boulet et al. 2008) have been reported in both MPTP-treated monkeys that recovered from transient motor symptoms and symptomatic animals. These reports suggested that this serotonin up-regulation may compensate for the loss of dopamine and delay the appearance of motor symptoms. There is evidence from animal models of PD that the relative sparing of striatal serotonin innervation over the nigrostriatal dopamine system may contribute to the development of L-DOPA-induced dyskinesia via storage and non-physiological release

of dopamine following L-DOPA administration (Carta et al. 2007). On the other hand, we and others have recently shown significant neuronal loss in the raphe nuclei (Fig. 4c, d) (Masilamoni et al. 2011a; Unguez and Schneider 1988) and a corresponding decrease in serotonin innervation of the prefrontal cortex and striatum (Masilamoni et al. 2011a; Pifl et al. 1991; Russ et al. 1991) in chronically MPTP-treated monkeys. The variations of MPTP dosage schedules and survival times after intoxication probably account, at least in part, for the differences in the pattern of serotonin loss between these studies.

Cholinergic pathology

Three major sources of acetylcholine display significant pathology in PD. Loss of basal forebrain cholinergic neurons in the nucleus basalis of Meynert (nbM), which provide inputs to the entire cortical mantle, is well-documented in PD brains (Candy et al. 1983; Nakano and Hirano 1984; Rogers et al. 1985; Tagliavini et al. 1984; Whitehouse et al. 1983). A significant correlation between the extent of cortical cholinergic denervation and the severity of cognitive dysfunction has been reported in some PD patients (Bohnen and Albin 2011; Korczyn 2001; Perry et al. 1985). However, very limited data has been collected about the state of the nbM cholinergic neurons in MPTP-treated monkeys. To our knowledge, the only significant report comes from Garvey et al. (1986), who observed no significant cholinergic cell loss in nbM of acutely MPTP-treated marmosets. However, low-dose chronic MPTP administration to macaque monkeys significantly reduced cortical cholinergic innervation, and induced changes in nicotinic AChR expression in the frontal cortex, similar to those observed in human PD patients (Aubert et al. 1992; Court and Clementi 1995; Court et al. 2000; Forgacs and Bodis-Wollner 2004; Lange et al. 1993; Mundinano et al. 2013). Furthermore, stable early cognitive deficits that can be improved with the β4*-selective nAChR agonist SIB-1553A treatment were reported in macaque monkeys chronically treated with low doses of MPTP (Schneider and Kovelowski 1990; Schneider et al. 1999). Additional pathological studies are needed to further assess the state of the basal forebrain cholinergic cell group and its cortical innervation in chronically MPTP-treated monkeys.

The pedunculopontine nucleus–laterodorsal tegmental complex (PPN) is another cholinergic cell group of potential importance in PD pathology. Cholinergic neurons in this region provide widespread ascending and descending inputs to the all basal ganglia nuclei, the basal forebrain, thalamus, cerebellum, several brainstem nuclei, and the spinal cord (Heckers et al. 1992). Importance of these systems in regulating sleep–wake cycle, vigilance, attention, gait and other motor functions has been suggested (Datta et al. 2002; Delwaide 2001; Gilman et al. 2003; Gut

and Winn 2016; Munro-Davies et al. 1999; Nandi et al. 2002; Steriade 2005; Takakusaki et al. 2004; Thevathasan et al. 2010). Various neuropathological studies reported that around 50% of the cholinergic neurons are degenerated in the lateral part of the PPN, pars compacta in PD (Gai et al. 1991; Hirsch et al. 1987; Jellinger 1988; Zweig et al. 1989). Recently, (Karachi et al. 2010) reported that aged, but not young, MPTP-treated monkeys display significant PPN cholinergic cell loss. Preliminary studies from our laboratory confirmed the lack of significant cholinergic pathology in the PPN/LDT of chronically MPTP-treated young adult rhesus monkeys (Masilamoni et al., unpublished observations; Fig. 4e, f). Thus, chronic MPTP intoxication can recapitulate some aspect of the brainstem cholinergic pathology in aged, but not young adult monkeys. Further studies are needed to determine the extent of non-cholinergic cell loss in the PPN/LDT region of both PD patients and MPTP-treated monkeys.

Another major group of cholinergic neurons known to play an important role in basal ganglia function in normal and diseased states are the striatal cholinergic interneurons (Tanimura et al. 2017). Although there is evidence for dysregulation of the intrastriatal cholinergic function in PD, very few studies have assessed changes in the morphology or number of striatal cholinergic interneurons in PD patients (Gonzales and Smith 2015; Kharkwal et al. 2016). Two recent studies addressed this issue in MPTP-treated monkeys and came up to different conclusions. On the one hand, some authors reported that the total number of striatal cholinergic neurons is not changed in the striatum of parkinsonian monkeys, but that a significantly larger number of cholinergic neurons co-express calretinin immunoreactivity in parkinsonian animals than in controls (Petryszyn et al. 2016). On the other hand, recent findings from our laboratory showed a 30–40% increase in the total number of ChAT-IR neurons in the head of the caudate nucleus of chronically MPTP-treated monkeys, with no significant change in other striatal regions (caudate body, pre- and post-commissural putamen) (Villalba and Smith 2017). Although, there is no clear explanation for the discrepancy between these studies, the different MPTP regimen, monkeys were exposed to may be a contributing factor.

Quantitative studies of the number and density of striatal cholinergic interneurons in the striatum of PD patients are needed to validate the significance of these data from MPTP-treated monkeys towards our understanding of striatal cholinergic pathology in PD.

Olfactory pathology

Deficits in odor detection, discrimination and identification are commonly seen during the prodromal stage of PD

(Berendse and Ponsen 2009; Mesholam et al. 1998). This olfactory dysfunction does not respond to L-DOPA therapy (Doty et al. 1992; Hawkes et al. 1997). Various groups have reported an increased number of DA cells in the olfactory bulb (OB) of PD patients with olfactory deficits (Berendse et al. 2001; Hawkes et al. 1997; Huisman et al. 2004). This increased DA activity in the OB of PD patients may lead to a suppression of olfactory information due to the inhibitory effect of DA on the transmission between olfactory receptor cells and mitral cells within the olfactory glomeruli (Doty and Risser 1989; Duchamp-Viret et al. 1997; Hsia et al. 1999; Koster et al. 1999; Mundinano et al. 2011; Wilson and Sullivan 1995). Recent findings revealed that DA levels are also increased in the OB of chronically MPTP-treated monkeys irrespective of their state of parkinsonism, such that motor asymptomatic and moderate or severe parkinsonian animals display comparable increases in OB DA levels (Pifl et al. 2017). These findings are consistent with the previous report of an increased number of intrinsic DA neurons in the OB of chronically MPTP-treated monkeys (Belzunegui et al. 2007). However, because olfactory tests were not performed in these monkeys, the significance of these anatomical observations remains unclear and warrants further studies.

Thalamus CM/PF pathology

A profound degeneration ($\sim$40–50% cell loss) of the caudal intralaminar thalamic nuclei, namely the centromedian (CM) and parafascicular nuclei (Pf) has been reported in idiopathic PD patients (Henderson et al. 2000a, b). The extent of CM/Pf cells loss is not related to the severity of parkinsonian motor signs. Even patients in early stages of the disease harbor major thalamic pathology (Henderson et al. 2000a, b), suggesting that CM/Pf degeneration is an early event that likely starts during the prodromal period of PD, even before the degeneration of midbrain dopaminergic neurons (see Smith et al. 2014 for discussion). Because CM/Pf neurons are the main sources of the thalamostriatal glutamatergic system (Galvan and Smith 2011; Smith et al. 2004, 2009, 2011, 2014), early degeneration of these neurons may significantly disrupt the glutamatergic drive of striatal projection neurons and cholinergic interneurons. In light of recent studies showing that CM/Pf neurons are sensitive to salient sensory stimuli and may play an important role in cognitive processes related to attention and reinforcement, it has been suggested that the loss of CM/Pf neurons may contribute to early cognitive impairments in attentional set-shifting or behavioral switching commonly found in PD patients (Smith et al. 2014).

We have recently shown that CM/Pf degeneration can be induced in chronically MPTP-treated rhesus monkeys (Villalba et al. 2014). Although the mechanisms by which MPTP kills these glutamatergic thalamic cells remain to be established, there is evidence that CM/Pf loss occurs early during the course of MPTP intoxication, an reach its maximum extent even before the development of parkinsonian motor signs. As expected, this thalamic cell loss results in decreased thalamic innervation of striatal neurons (Villalba and Smith 2011). Behavioral studies are currently in progress to assess the potential role of CM/Pf pathology on cognitive and motor functions in these monkeys. Thus, the chronic MPTP-treated monkey model of PD is a suitable tool to assess the potential contribution of the thalamostriatal degeneration to early attentional cognitive deficits in PD (Decamp and Schneider 2004, 2006; Ko et al. 2016; Roeltgen and Schneider 1994; Schneider 2006).

Lewy body pathology in monkeys

In addition to the profound degeneration of various dopaminergic and non-dopaminergic cell groups, another key element of PD pathology is the development of cytoplasmic inclusions called Lewy bodies. These inclusions are made up of protein aggregates that are found throughout the whole brain of PD patients, but are particularly abundant in lower and upper brainstem regions and the ventral midbrain dopaminergic cell groups (Baba et al. 1998; Devine et al. 2011; Irizarry et al. 1998; Spillantini et al. 1997). One of the key component protein of Lewy bodies is α-synuclein, a ubiquitous pre-synaptic protein that likely plays an important role in the pre-synaptic regulation of neurotransmission throughout the brain. Because of its abundance in Lewy bodies (Niu et al. 2015), alpha-synuclein has become a major target of PD pathobiology. Its abnormal aggregation throughout the parkinsonian brain may lead to disruption of axonal transport and contribute to a wide array of motor and non-motor symptoms of PD. Recent evidence suggest that these aggregates may be transported throughout the brain in a prion-like fashion has generated significant interest in the field (Braak and Braak 2000; Braak et al. 2003a; Chu and Kordower 2015; Dunning et al. 2012, 2013; Rey et al. 2016). However, significant controversy exists in understanding the mechanisms by which these aggregates are transported from one structure to another in the mammalian CNS (Surmeier et al. 2017).

Because of the increased significance of alpha-synuclein pathology in the etiology, degeneration process and possible development of PD motor and non-motor symptoms, efforts at developing a nonhuman primate model of PD that displays alpha-synuclein aggregates and Lewy body-like pathology could be of utmost importance for future therapeutic and neuroprotective studies in PD. As discussed in

another review of this Special Issue (Marmion and Kordower 2017), attempts at developing such model are currently in progress in various laboratories (Collier et al. 2016; Low and Aebischer 2012; Niu et al. 2015; Recasens et al. 2014; Yang et al. 2015). Although transgenic models offer insights into the causes of PD pathogenesis or LB-like formation, the absence of consistent neuronal loss in the SNc remains a major limitation for these models. On the other hand, viral transduction of wild type or mutant α-synuclein protein has been shown to induce loss of DA neurons, and cause motor impairment in both mice and rats (Oliveras-Salva et al. 2013) but it is limited to the region targeted (Eslamboli et al. 2007; Koprich et al. 2016; Yang et al. 2015). Recently, Shimozawa et al. (2017) reported that intracerebral injection of synthetic α-synuclein fibrils into wild-type marmoset brains (caudate nucleus and/or putamen) results in the formation of abundant α-synuclein-positive inclusions in midbrain TH-positive neurons, suggesting the retrograde spreading of abnormal α-synuclein from the striatum to the SNC. Moreover, the authors reported a significant decrease in the number of nigral DA neurons ipsilateral to the striatal injection sites of α-synuclein fibrils. However, despite such pathology, these monkeys did not exhibit any apparent motor deficits up to 3 months after inoculation. Further studies are needed to establish the relationship between pathologies and symptoms in wild-type marmosets.

A common criticism raised about the MPTP-treated NHP model of PD is that it fails to produce cytoplasmic inclusion bodies in DA neurons and other brain regions. Although protein aggregates structurally similar to Lewy bodies are, indeed, not found in the brain of MPTP-treated monkeys, there is strong evidence that chronic MPTP treatment induces the formation of alpha-synuclein-positive inclusion bodies or aggregates. Early reports have described eosine-positive inclusion bodies in the SNC, LC, nucleus basalis of Meynert, dorsal motor nucleus of the vagus, and raphe nucleus of MPTP-treated aged squirrel monkeys (Forno et al. 1986, 1993). More recently, we and others have demonstrated α-synuclein aggregation in midbrain DA neurons and dystrophic nigrostriatal axons in chronically MPTP-treated young adult squirrel and rhesus monkeys (Masilamoni and Smith 2011; McCormack et al. 2008) (Fig. 5a–d). Although this issue remains to be addressed in a more systematic fashion, these observations suggest that MPTP treatment induces alpha-synuclein inclusions only when mild and prolonged inhibition of the mitochondrial respiratory chain causes a chronic decrease of the ubiquitin-proteasome activity.
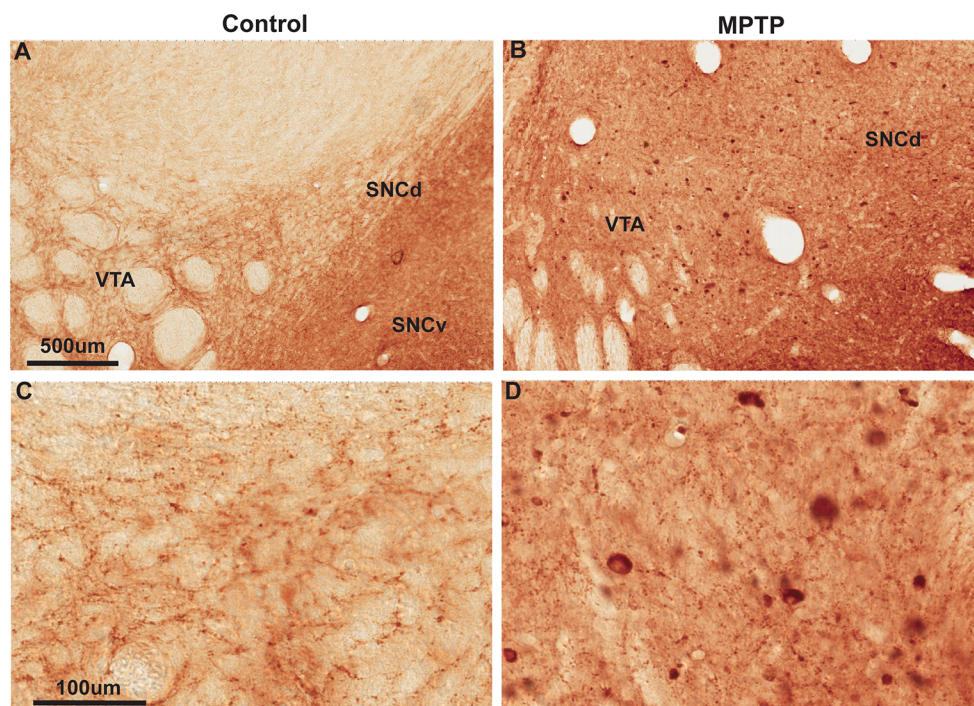

Fig. 5 Photomicrographs of α-synuclein-immunostained coronal sections at the level of the ventral midbrain (**a–d**) of a control (*left column*) and a MPTP-treated (*right column*) monkey. Alpha-synuclein-positive aggregates in SNCd and VTA of chronically MPTP-treated monkeys are shown in **b** and **d**

Concluding remarks

In conclusion, the MPTP-treated monkey model has been recognized as the gold standard model of PD because the degeneration of the dopaminergic nigrostriatal system leads to parkinsonian motor signs that closely mimic those seen in PD patients. This model has been instrumental to our understanding of the pathophysiology of the basal ganglia-thalamocortical loops in PD and to the rejuvenation and refinement of surgical therapies for the disease.

However, as is the case for most neurotoxin-based models of PD, it is recognized by many investigators as a mere model of nigrostriatal dopaminergic lesion that does not involve other monoaminergic brain systems affected in PD. In this review, we discussed series of data published by various groups over the years that negate this misconception. It is clear from the literature that monkeys treated chronically with low doses of MPTP display brain pathological changes that extend far beyond the nigral dopaminergic neurons. Among the various systems that are known to be partly degenerated in PD, chronically MPTP-treated monkeys exhibit loss of noradrenergic neurons in the locus coeruleus and related brainstem regions, serotonergic neurons in the dorsal raphe, glutamatergic neurons in the thalamic CM/Pf nuclear complex and loss of cholinergic neurons in the pedunculopontine region (only in aged animals). Because these systems are involved in a wide range of cognitive and limbic functions and that their disruption leads to various neuropsychiatric and sleep disorders, their sensitivity to chronic MPTP intoxication adds some significant value to the MPTP-treated monkey model as a tool to study the pathophysiology and develop new therapies for non-motor features of PD.

Compliance with ethical standards

Conflict of interest No conflicts of interest, financial or otherwise, are declared by the authors.

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