A. Bjorklund and M. A. Cenci (Eds.)
Progress in Brain Research, Vol. 184
ISSN: 0079-6123

CHAPTER 7

The MPTP-lesioned non-human primate models of Parkinson's disease. Past, present, and future

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Abstract: Non-human primate (NHP) models of Parkinson's disease (PD) have been essential in understanding the pathophysiology and neural mechanisms underlying PD. The most common toxin employed, MPTP, produces a parkinsonian phenotype in NHPs that is very similar to human PD with excellent response to dopaminergic drugs and development of long-term motor complications. Over the past 25 years, MPTP-lesioned NHP models, using several species and a variety of MPTP administration regimens, have been used to understand disease pathophysiology, investigate several stages of the disease progression, from pre-symptomatic to advanced with motor complications, and apply knowledge gained to develop potential therapeutics. Many treatments in common use in PD patients were developed on the basis of studies in the MPTP model, in particular dopamine agonists, amantadine, and targeting the subthalamic nucleus for surgical treatment of PD. Continued development of novel therapies for PD will require improving methods of evaluating symptoms in NHPs to ease translation from NHP to patients with homogenized scales and endpoints. In addition, recent studies into non-motor symptoms of PD, especially in response to chronic treatment, is expanding the usefulness and impact of MPTP-lesioned NHP models. Despite these obvious successes, limitations still exist in the model, particularly when considering underlying mechanisms of disease progression; thus, it appears difficult to reliably use acute toxin administration to replicate a chronic progressive disorder and provide consistent evidence of Lewy-like bodies.

Keywords: Non human primate; MPTP; Parkinson's disease; non-motor

Discovery of MPTP—a new dawn fades

Prior to the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), non-human primate (NHP) models for investigating PD were limited by lack of specificity for the dopaminergic system

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DOI: 10.1016/S0079-6123(10)84007-5

and consequent phenotype. The earliest models were generated using acute administration of cholinergic agonists, carbachol and harmaline, that resulted in a tremor that lasted for the duration of the drug action (Everett et al., 1956; Poirier et al., 1974). Longer-lasting models were attempted by electrolytic lesions of the midbrain, resulting in hypokinesia and tremor (Pechadre et al., 1976; Poirier, 1960). However, these lesions also encroached onto the red nucleus and thus symptoms were not entirely due to lesioning of the substantia nigra pars compacta (SNC). The successful use of the synthetic neurotoxin 6-hydroxydopamine (6-OHDA) in rodents to generate a unilateral lesion of the SNC (Ungerstedt, 1976) was applied to NHPs. A unilateral model was attempted with stereotactic infusion into the medial forebrain bundle of baboons (Apicella et al., 1990) and marmosets (Annett et al., 1995) which resulted in unilateral hypokinesia. Multiple stereotaxic injections of 6-OHDA into the primate striatum are required to reduce spontaneous recovery that may occur after a few weeks (Eslamboli, 2005; Eslamboli et al., 2003). The advantage of the unilateral deficit is that the contralateral brain can be used as a control and animals are less severely compromised in the early stages and can thus feed themselves. A bilateral model was also tried that resulted in profound hypokinesia that required intensive care of the animals (Mitchell et al., 1995). Use of the 6-OHDA-lesioned NHP has not been widespread due to the practical difficulties of surgical infusions.

The discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was able to induce human parkinsonism (Langston and Ballard, 1983) was therefore a critical development in modeling parkinsonism in animals. MPTP is a protoxin that crosses the blood–brain barrier and is converted to 1-methyl-4-phenylpyridium ion (MPP^+), predominantly in serotonergic neurons and glia, via the action of monoamine oxidase B (MAO-B) (Chiba et al., 1984; Westlund et al., 1985). The mechanism whereby MPP^+ is released from glia remains unclear (Inazu et al., 2003), but once in the extracellular space, MPP^+ is selectively transported by the dopamine transporter (DAT) into dopaminergic neurons (Javitch et al., 1985). The relative selectivity of some dopaminergic neurons to MPP^+-induced cell death, i.e., the SNC rather than the ventral tegmental area (VTA), may relate to the higher concentration of DAT in the midbrain (Kitayama et al., 1993).

Cell death occurs following MPP^+ uptake into mitochondria and inhibition of complex 1 function (Ramsay et al., 1986). Other factors involved include superoxide radicals and nitric oxide that are produced secondary to MPP^+ intoxication, and combine to produce perooxynitrite that nitrates tyrosine residue in intracellular proteins, including tyrosine hydroxylase with resultant loss of dopamine cells (Przedborski et al., 2000). Microglial activation in the SNC occurs following MPTP administration, and glial cells also produce free radicals and nitric oxide synthase (Vazquez-Claverie et al., 2009). Removal of MPP^+ from the cytoplasm into synaptic vesicles occurs via the vesicular monoamine transporter (VMAT2), which prevents further toxic action (Miller et al., 1999). Loss of striatal VMAT2 may be a factor in MPTP toxicity; thus, a recent position emission tomography (PET) study using a chronic dosing schedule of MPTP reported VMAT loss in the striatum of asymptomatic primates, 2 months before changes in dopamine receptors and DAT (Chen et al., 2008).

The ability of MPTP to produce nigral and striatal dopamine cell loss similar to that of human PD has led to multiple investigations into potential disease processes. (*For an update on neurodegenerative processes—see Section I (Genetic and molecular mechanisms of neurodegeneration in PD) of Volume 183)*. To date, the understanding of MPTP toxicity has led to the assessment of MAO-B inhibitors, such as selegiline and rasagiline, as potential neuroprotective agents (PSG, 1989; Olanow et al., 2009). However, the real power of the MPTP NHP model probably lies in the link between the pathology and the clinical phenomenology of the disease. In this respect, the model remains unique in neurological disease research and continues to be the gold standard in drug development for PD.

Update on practicalities of the MPTP model

A variety of NHP species have been used to induce a parkinsonian model, with macaques being the most common (including rhesus (sp mulatta) and cymologous (sp fascicularis) (Burns et al., 1983)), followed by common marmosets (Jenner et al., 1984), squirrel monkeys (Langston et al., 1984), African green monkeys (Taylor et al., 1997), and baboons (Todd et al., 1996). The most common implementations of the model produce bilateral parkinsonism that mimics the phenotype of human PD and is created using repeated systemic administration of MPTP (e.g., 1–2 mg/kg) over several days to months (Burns et al., 1983; Fox et al., 2002; Visanji et al., 2009b). In such models, parkinsonian features develop over 2–3 months until stable. Recovery may occur after a few months, requiring further MPTP to maintain the model. Individualized dosing is often required due to inter-animal variability in vulnerability to MPTP. One such factor in MPTP sensitivity is age of the animals, with older animals being more sensitive to MPTP (Ovadia et al., 1995). Older animals (> 5-year old) may be better in terms of modeling the human disease as PD becomes more common with aging, and like humans, older normal NHPs have age-related loss of striatal dopamine and reduced markers of tyrosine hydroxylase positivity (Collier et al., 2007).

More chronic delivery of MPTP with lower daily doses (0.2 mg/kg) over 2–3 weeks has been proposed as a means of modeling a progressive loss of dopamine that does not recover (Bezard et al., 1997; Meissner et al., 2003). Indeed, in such models symptoms develop over time and there is a period, up until 8–12 administrations have been made, when there are no motor symptoms, though there is demonstrable loss of dopaminergic functions. This "preclinical" stage may be a useful model to investigate potential pre-symptomatic compensatory mechanism and thus neuroprotective strategies (Bezard et al., 2001a,b). Even longer treatment schedules over weeks to months have been used to extend the use of the model. Thus intermittent chronic dosing of low-dose MPTP, 1–2 times per week every 1 or 2 weeks for several weeks or months has been proposed as a model of a more progressive onset of parkinsonism with recovery between injections to investigate compensatory mechanisms (Hantraye et al., 1993; Mounayar et al., 2007). However, some studies have failed to demonstrate a delayed neurodegenerative process in dopaminergic neurons after concluding MPTP injections, suggesting this dosing schedule does not initiate a truly progressive degenerative process (Garrido-Gil et al., 2009). Shorter treatments using MPTP (1 mg/kg for 3 days) have also been used to generate partial lesions, e.g., 60% tyrosine hydroxylase cell loss compared to the usual 90%, in an attempt to model a milder stage of the disease (Iravani et al., 2005). These animals have less motoric problems and do not respond to levodopa, in contrast to models described above.

Hemiparkinsonism can also be modeled by intracarotid infusion of a single low dose of MPTP to induce a unilateral parkinsonian syndrome (Bankiewicz et al., 1986). The advantage of hemiparkinsonian animals is that they are less severely affected, thus can be maintained more easily without a need to initiate symptomatic therapy, as well as providing a contralateral side of the brain that can be used as a control. However, recent reports of necrotic basal ganglia lesions and the possibility of effects of the lesion being apparent on the injected side of the brain, may limit the use of these models (Emborg et al., 2006).

Detailed information on the practical use of MPTP and safety issues have been reviewed elsewhere (Emborg, 2007; Przedborski et al., 2001).

Pathology of MPTP-parkinsonism in the NHP

Dopamine and other monoamine cell loss

Dopamine cell loss in the SNC is the key pathological feature of MPTP-induced parkinsonism. The pattern of destruction of dopaminergic cells in the SNC is similar to human PD with a ventro-lateral

predominance (Burns et al., 1983; Gibb et al., 1987). Depending on dosing and age of the animal, other dopaminergic systems may be affected. Thus cortical and limbic dopamine (Perez-Otano et al., 1991) and VTA cell loss may occur (Mitchell et al., 1985; Rose et al., 1989), although to a much lesser extent than in the SNC. In contrast to human PD, the pattern of dopamine loss in the striatum is usually more uniform, rather than the preferential loss in the putamen (Perez-Otano et al., 1994; Pertwee and Wickens, 1991). A secondary effect of loss of striatal dopamine is a reduction in spine density, with up to 50% reduction in spines in both the caudate nucleus and putamen, with the sensorimotor post-commissural putamen being the most severely affected region for both dopamine depletion and spine loss (Villalba et al., 2009). Such loss of spines may be a compensatory effect of excessive cortico- or thamalo-striatal glutamatergic activity (Garcia et al.).

Other monoamines can be affected by MPTP, although to a lesser degree than dopamine. Thus 5-HT levels are reduced by 75–90% in the cingulate and frontal cortex, with less reduction in the striatum (Perez-Otano et al., 1991; Russ et al., 1991). One study has reported no changes in brainstem serotonergic neurons (Gaspar et al., 1993). Cell loss within the locus coeruleus has been reported in the MPTP macaque (Forno et al., 1986; Mitchell et al., 1985) with reduction in noradrenaline in the frontal cortex (Alexander et al., 1992; Pifl et al., 1991). To date, the role of these monoamines has been investigated as potential therapeutic targets for motor symptoms of PD and in particular levodopa-induced motor fluctuations (see below). However, recent pathophysiology studies in human PD are highlighting the potential role of such neurotransmitters in many non-motor symptoms experienced by PD patients, e.g., mood disorders, psychosis, and autonomic problems (Lim et al., 2009). Thus future studies into these monoamine systems in the MPTP-primate should focus on investigating non-motor aspect of PD that may involve these non-dopaminergic systems.

Other non-dopaminergic neurotransmitters

The MPTP-primate has been used to investigate the neuropharmacology of parkinsonism and levodopa-induced dyskinesia, in particular the role of non-dopaminergic systems. These have been reviewed in several recent publications (Brotchie, 2005; Fox et al., 2006a). Table 1 summarizes changes in non-dopaminergic neurotransmitters and pharmacological studies performed to date in the MPTP-primate.

Alpha synuclein

Alpha synuclein pathology occurs in MPTP-primates, but not to the extent seen in human PD. Thus, there is increased intraneuronal alpha synuclein immunoreactivity within the SNC; however, this is not in the usual structural form of a Lewy body (Kowall et al., 2000). Following a single injection of MPTP, there is an increase in phosphorylated alpha synuclein after 1 week that is associated with 10% dopamine nigral cell loss, while after 1 month dopamine cell loss progresses to 40% with alpha synuclein within cell bodies, suggesting a direct link between cell death and alpha synuclein deposition (McCormack et al., 2008; Purisai et al., 2005). The absence of Lewy bodies in MPTP-primates has been suggested to relate to the relatively short time post MPTP that pathological studies are performed; however, a recent study in two animals confirmed no Lewy bodies even 10 years post MPTP (Halliday et al., 2009).

The lack of Lewy bodies in MPTP-primates is important in understanding the pathogenesis of PD in humans. Thus, the recent pathological studies reporting Lewy body pathology in fetal tissue transplanted in PD patients has been suggested to be due to factors such as inflammation and excitotoxicity (Kordower et al., 2008). However, both inflammation and excitotoxicity occur in the MPTP-primate suggesting other causes for the development of Lewy bodies occurring in human brain. One suggestion may be age. In the human post-mortem studies, only tissue transplanted after

Table 1. Non-dopaminergic neurotransmitters in MPTP-lesioned primates

Receptor class	Receptor subtype	Changes in receptors	Drug	Motor symptoms			Non-motor symptoms
				Parkinsonian signs	Wearing-off	Dyskinesia	
Acetyl-choline Muscarinic (mAChR) antagonists	M_1, M_4, possibly M_3	[^{3}H]-QNB (M1) binding increased in GPi in dyskinesia (Griffiths et al., 1990)	Trihexy-phenydyl	+ Enhance effect of levodopa (Domino and Ni, 1998)		+; May reduce levodopa-induced dystonia but worsens chorea (Pearce et al., 1999)	
			Biperidin	+ Enhance effect of levodopa (Domino and Ni, 2008)			
Acetyl-choline Nicotinic (nAChR) agonists	Non-selective agonists	Decreased in striatum in PD (Kulak et al., 2002)	Nicotine			+ (Quik et al. 2007)	
	beta2*–beta4* α4β2 nAChRs	Decreased in striatum and cortical regions, e.g., cingulate gyrus in PD (Bordia et al., 2007); (Kulak et al., 2007)	SIB-1508Y	+ Enhanced effect of levodopa (Schneider et al., 1998)			
Adenosine antagonists	A_{2A}	Increased in striatum dyskinesia (Morissette et al., 2006)	Istradefylline	+ (Grondin et al., 1999a, Kanda et al. 1998), (Bibbiani et al. 2003)	+ (Kanda et al. 2000)		
			ST1535	+ (Rose et al. 2006)	+ (Rose et al. 2006)		
	A_{2A} and A_{1A}		ASP5854	+ (Mihara et al. 2008)			

(*Continued*)

Table 1 (*Continued*)

Receptor class	Receptor subtype	Changes in receptors	Drug	Motor symptoms			Non-motor symptoms
				Parkinsonian signs	Wearing-off	Dyskinesia	
Glutamate NMDA antagonists	Non-selective		Amantadine MK801, LY235959	− Can worsen at high doses (Gomez-Mancilla and Bedard, 1993); (Rupniak et al., 1992)		+ Can reduce chorea but also worsen dystonia (Blanchet et al., 1998); (Papa and Chase, 1996); (Visanji et al., 2006)	Increases psychosis-like behavior (Visanji et al., 2006)
	NR2A-NMDA antagonist	No changes (Ouattara et al., 2009) Increased NR2A subunit in dyskinesia (Hallett et al., 2005)	MDL 100,453			− Worsened dyskinesia (Blanchet et al., 1999)	
	NR2B-NMDA antagonist	Decreased in PD; increased in striatum and cortical regions in dyskinesia (Hurley et al., 2005); (Ouattara et al., 2009)	Ifenprodil; CP-101,606	+ (Nash and Brotchie 2000)			
				+ Potentiated action of levodopa (Nash et al., 2004); (Steece-Collier et al., 2000).		Exacerbates dyskinesia (Nash et al., 2004; Steece-Collier et al., 2000)	
			Ro 25-6981				
		Synaptosomal cycling of NR2B (Hallett et al., 2005)	Co 101244	+ Potentiated action of levodopa (Loschmann et al., 2004)			
						+ (Blanchet et al. 1999)	
			CI 1041			Prevent dyskinesia (Hadj Tahar et al., 2004)	

AMPA antagonists	AMPA	No change (Silverdale et al., 2002) Increased in striatum in dyskinesia (Calon et al., 2002)	LY300164 GYKI-47261	+ Potentiated effects of levodopa (Konitsiotis et al., 2000)		+ (Konitsiotis et al. 2000) + (Combined with amantadine) (Bibbiani et al., 2005)	
Metabotropic glutamate receptor (mGLuR)	mGluR2/3	Decreased in striatum and GP dyskinesia (Samadi et al., 2008)					
	$mGluR_4$ agonist			+			
	$mGluR_5$ antagonist	Increased in putamen and GP in dyskinesia (Samadi et al., 2008); (Sanchez-Pernaute et al., 2008) Possibly increased in striatum (Ouattara et al., 2010)	MPEP/MTEP			+ (Morin et al. 2010) + But possible reduced parkinsonism (Johnston et al., 2010)	
Alpha adreno-receptors	$Alpha_2$ agonist					+	
	$Alpha_{2A/2c}$ antagonist		Yohimbine			+ (Gomez-Mancilla and Bedard 1993)	
			Idazoxan	+ (Bezard et al. 1999)	+ (Henry et al. 1999), (Domino et al. 2003, Fox et al. 2001)	+ (Bezard et al. 1999), (Fox et al. 2001)	
			Fipamezole		+ (Savola et al. 2003)	+ (Savola et al. 2003)	
	$Alpha_1$ adreno-receptor antagonist		Prazosin				Reduced L-dopa-induced hyperactivity (Visanji et al., 2009b)

(*Continued*)

Table 1 (*Continued*)

Receptor class	Receptor subtype	Changes in receptors	Drug	Motor symptoms			Non-motor symptoms
				Parkinsonian signs	Wearing-off	Dyskinesia	
Serotonin	5-HT_{1A} agonists	Increased in striatum and motor cortex (Huot et al., in submission-b)	R)-(+)-8-OHDPAT			+ But worsened PD (Iravani et al., 2006)	
			Sarizotan			+ (Bibbiani et al. 2001, Gregoire et al. 2009)	
	5-HT_{1B} agonists		SKF-99101			+ But worsened PD (Jackson et al., 2004)	
			MDMA			+ (Iravani et al., 2006; Johnston et al. 2009)	No change in psychosis-like behaviours
	5-HT_{2A} antagonists	Increased in striatum and motor cortex (Huot et al., 2010)	Methy-sergide			+ But worsens PD (Gomez-Mancilla and Bedard, 1993)	
			ACP 103			+ (Vanover et al. 2008)	
	5-HT_{2C} receptor antagonists (mixed)		Clozapine			+ (Visanji et al., 2006), can worsen PD at higher doses (Grondin et al., 1999b)	Reduces psychosis-like behaviors (Visanji et al., 2006)
			Quetiapine			+ (Oh et al. 2002, Visanji et al. 2006)	
Exogenous cannabinoids	CB_1 agonist		Nabilone			+ (Fox et al. 2002)	
	CB_1 agonist	Increased CB1 binding in striatum in untreated parkinsonism that reverses with	Rimonabant	+ (van der Stelt et al. 2005)/− (Meschler et al. 2001)			

		chronic levodopa (Lastres-Becker et al., 2001) Enhanced endo-cannabinoids in the GPe in untreated parkinsonism (Di Marzo et al., 2000)			
			Carboxylic acid amide benzenesulfonate (CE)	+ Enhanced action of levodopa (Cao et al., 2007)	
Opioid	δ-opioid agonist	PPEA mRNA; enkephalin protein increased in striatum in PD; further increased in dyskinesia; PPE-B mRNA and dynorphin decreased in PD and increased in dyskinesia (Bezard et al., 2001b); (Herrero et al., 1995); (Morissette et al., 1997; Quik et al., 2002)		+ (Hille et al. 2001)	+
	κ-Opioid agonist		Enadoline	+/− (Maneuf et al. 1995), (Hill and Brotchie 1995)	
			U50,488		+ Worsens PD (Cox et al., 2007)

(*Continued*)

Table 1 (*Continued*)

Receptor class	Receptor subtype	Changes in receptors	Drug	Motor symptoms			Non-motor symptoms
				Parkinsonian signs	Wearing-off	Dyskinesia	
	Opioid-like receptor (ORL-1) antagonist		J113397	+/− Mild effect (Viaro et al., 2008) + enhanced effect of L-dopa but worsened dyskinesia (Visanji et al., 2008)			
	Non-selective antagonist		Naloxone/ naltrexone			+/− (Gomez-Mancilla and Bedard 1993), (Henry et al. 2001, Klintenberg et al. 2002, Samadi et al. 2003)	
	μ-Opioid antagonist	Increased μ-opioid receptors in dyskinesia (Chen et al., 2005; Hallett and Brotchie, 2007)	Cyprodime ADL5510			+ (Henry et al. 2001); (Fox et al. 2010b)	
	δ-Opioid antagonist	Increased δ-opioid receptors (Hallett and Brotchie, 2007)	Nor-BNI			+ (Henry et al. 2001)	
Histamine	Histamine H_3 agonist					+ Reduces chorea not dystonia (Gomez-Ramirez et al., 2006)	
	H_2 antagonist					+ Reduces chorea, increases dystonia (Johnston et al, 2010)	

Key:
+ = improves
− = worsens

at least 11 years contained Lewy bodies. The NHP study only investigated animal to 10 years (Halliday et al., 2009). There is an effect of age on the level of alpha synuclein in NHPs; thus, older animals are more likely to have higher levels, similar to human PD (Chu and Kordower, 2007). The effect of age is thought to be due to increased stabilization of the alpha synuclein protein allowing accumulation, rather than increased mRNA expression (Li et al., 2004). However, this process also occurs in MPTP-primates thus suggesting other processes are required to initiate Lewy body formation in PD patients. One suggestion has been termed "permissive templating" and may occur with prions, amyloid, and tau whereby a concentration-dependent formation of a pathogenic protein oligomer occurs, followed by a non-concentration-dependent process of further aggregation onto the oligomeric template (Hardy, 2005). The MPTP-primate thus continues to be useful in understanding the pathology of human PD.

Pathological changes beyond the basal ganglia

The pathology of idiopathic PD extends beyond the dopaminergic cells of the SNC (Lim et al., 2009). Indeed, the proposed progression of PD according to Braak (Braak et al., 2003) starts in the dorsal motor nucleus of the vagus and olfactory tract and extends through brainstem structures into cortical regions. Premotor symptoms in PD are known to include anosmia, sleep disorders, constipation, and mood problems all suggesting extranigral pathology that may involve such brainstem structures. In addition, the non-motor symptoms of advanced PD, including psychiatric, sleep, and autonomic also implicate many non-dopaminergic systems. To investigate these features of PD, appropriate models are needed. The MPTP-primate may fulfill the need for some of these systems (see later); however, to date there have been few pathological or imaging studies. Table 2 summarizes pathological studies performed to date. Investigation of non-motor symptoms is discussed below.

Updates on phenomenology of the model; motor and non-motor features

MPTP-parkinsonism—motor phenotype

MPTP-lesioned NHPs exhibit the typical motor signs of PD seen in patients, including bradykinesia, rigidity, tremor, and postural instability (Hughes et al., 1992). The cardinal feature is bradykinesia or akinesia when animals become

Table 2. Extranigral pathology and behavioral consequences in the MPTP-primate

Region	Pathological changes induced by MPTP	Behavioural observations
Olfactory system	TH positive cells in glomerular layer of olfactory bulb increased by 100% compared to controls (Belzunegui et al., 2007)	Olfactory impairment reported in MPTP-lesioned marmoset (Miwa et al., 2004)
Pedunculopontine nucleus (PPN) region	Loss of dopamine transporter-positive fibers in the PPN compared with control animals (Rolland et al., 2009)	Microinjections of GABA antagonist bicuculline into the PPN reverses akinesia (Nandi et al., 2008)
Gastrointestinal tract	Increase in nitric oxide synthase immunoreactive (IR) neurons in myenteric plexus vs. controls; decrease in tyrosine hydroxylase-IR neurons by 70% compared to controls, no change in cholinergic or vasoactive peptide (Chaumette et al., 2009)	None reported
Cardiovascular	MPTP does not mimic changes seen in PD (Goldstein et al., 2003)	None reported

slower in all movements, particularly walking. In addition, some animals will have episodes of "freezing" with an inability to move for a few seconds, as if stuck in one place. Bradykinesia is also evident in an overall reduced range of movement with less spontaneous movement, less exploratory behavior, and less head movement. A reduced blinking rate may occur, in a similar manner to PD patients with the classical masked facies. Postural abnormalities are seen with a forward head tilt that can often reach to the floor. However, unlike PD patients, animals rarely fall. The classical 4–6 Hz resting tremor of PD is not usually observed in the MPTP-primate but may occur in the African green monkeys (Bergman et al., 1998). More commonly, a postural tremor may be seen when an animal is walking and reaching for objects.

Several rating scales have been published for measuring parkinsonian disability in the MPTP-lesioned NHP (Gomez-Ramirez et al., 2006; Imbert et al., 2000; Visanji et al., 2009b). The strength of the MPTP-primate models is that these scales are similar to rating scales used to assess PD patients such as the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2008). The NHP scales consist of subjective clinical assessment of severity, and possibly disability, of range of movement, bradykinesia, posture, alertness, and tremor. Rigidity is harder to assess, particularly in smaller primates. A recent objective method using EMG, force, and elbow angle measures has been proposed (Mera et al., 2009).

Due to the time-consuming nature of this analysis and possibility of subjectivity, other more objective measures of total or global motor activity have been proposed. Video analysis systems where images of freely moving animals are captured at half-second intervals and movement is quantified as the number of pixel changes between consecutive images have been shown to correlate with portable accelerometers and infrared activity counting (Togasaki et al., 2005). Hemiparkinsonian primates have also been evaluated using such video systems (Liu et al., 2009). Although potentially useful for objective measures for overall level of motor activity, such systems generally fail to distinguish movement due to reversal of parkinsonism and increased movement due to dyskinesia.

Other non-validated quantitative methods proposed include video recordings of animals in a "behavioral observation hallway" and measurement of a range of activities including displacement time across the hallway, reaching time towards rewards, number of rewards obtained, and level of the highest shelf reached for rewards before and after levodopa, called the Hallway task (Campos-Romo et al., 2009). Further behavioral tests in marmosets have been reported including a measure of akinesia using the marmoset's natural jumping behavior, called the "Tower", and a measure of axial rigidity using the marmoset's natural righting reflex, the "Hourglass"; both are impaired with MPTP (Verhave et al., 2009). However, the effects following treatment with dopaminergic drugs is not clear and further validation of these tests are required. To date, clinical observation is still the gold standard to fully evaluate motor features of parkinsonism, in particular the presence of bradykinesia.

Levodopa-induced motor complications

Long-term treatment of MPTP-lesioned NHPs with levodopa results in the development of both choreiform and dystonic dyskinesias which are essentially identical to dyskinesia in humans (Clarke et al., 1987; Jenner, 2003b). There are species differences in the expression of dyskinesia. Thus, Old World species have less overall motor activity and exhibit dyskinesia easily distinguishable as either chorea or dystonia (Boyce et al., 1990a, b). However, practically, such large primates provide logistical challenges and thus the marmoset model of levodopa-induced dyskinesia has been developed to facilitate the conduct of studies with robust statistical outcomes (Henry

et al., 1999; Pearce et al., 1995). The marmoset tends to be overall more active and often chorea and dystonia may be difficult to distinguish unequivocally.

In all species used, in a similar manner to patients with PD, the severity of dyskinesia relates to the severity of parkinsonism (Schneider et al., 2003), although not consistently (Guigoni et al., 2005), and the dose and duration of levodopa therapy (Smith et al., 2003). The dyskinesia is stable and consistent on separate days of dosing (Pearce et al., 1995; Visanji et al., 2006, 2009a). Likewise, chronic levodopa alters the dose–response curve to levodopa, or so-called short-duration response (Nutt et al., 2002) in a similar way to PD patients. Thus in *de-novo* animals, there is a dose response in reversal of PD motor disability and production of dyskinesia, whereas following chronic treatment with levodopa, this changes to a shorter latency to reversal of PD ("switch-on") and an all-or-none response with no increase in dyskinesia severity with increased doses (Mestre et al., 2010). Dyskinesia experienced by MPTP-lesioned primate animals is commonly present when the levels of levodopa are maximal, i.e., "peak-dose" dyskinesia (Fox et al., 2001). PD patients with dyskinesia can also experience dyskinesia at the onset and end of a dose of levodopa termed "diphasic dyskinesia" and often experience dystonia in the off-state (Obeso et al., 2000); these are rarely described in NHPs, though it is clear that they do occur (Boyce et al., 1990b).

Other motor fluctuations appear in the long-term levodopa-treated MPTP-lesioned primate. Thus, reduction in duration of action of levodopa on successive treatment days, "wearing off" occurs (Fox et al., 2010a; Jenner, 2003a). Animals can also exhibit what is termed "beginning and end-of-dose worsening", in a similar way to PD subjects (Quinn, 1998). Thus, following an acute dose of levodopa, there is a transient worsening of motor function before improvement, and then as the beneficial response to levodopa is declining there is a rebound worsening of parkinsonism to below-baseline values (Kuoppamaki et al., 2002). The advantage of recognizing such additional levodopa-induced motor fluctuations in the MPTP-primate improves the ability to evaluate efficacy of novel drugs for treating fluctuations in PD and enhances the ability to design phase II and phase III clinical studies to better improve positive outcomes.

Non-motor phenotypes

Appreciation of non-motor problems in PD has now been reflected in developing NHP models to investigate pathophysiology and novel treatments for these issues.

Psychosis-like behaviors as a model of neuropsychiatric symptoms

PD patients experience a range of neuropsychiatric symptoms both due to disease-related pathology and as side-effects of medications. These symptoms include psychosis, ranging from illusions, well-formed visual hallucinations to delusions and hypomania. Side-effects of dopaminergic agents include impulsive and compulsive disorders, psychomotor agitation, and complex motor stereotypies (Voon and Fox, 2007).

MPTP-lesioned primates treated with levodopa and dopamine agonists also exhibit abnormal repetitive, exaggerated, and driven gross motor behaviors which are distinct from dyskinesia and parkinsonism and may represent behavioral correlates of neural processes of these neuropsychiatric symptoms in PD. Prior studies in both MPTP-lesioned marmosets and macaques have commented on some of these behaviors, including agitation (Pearce et al., 1995), climbing behavior (Boyce et al., 1990b), "hallucinatory-like behavior" (Blanchet et al., 1998), and hyperactivity (Akai et al., 1995) but with limited quantification. Recent study of abnormal psychotomimetic behaviors seen in the levodopa-treated MPTP-lesioned marmoset has demonstrated that four behavioral

categories exist: hyperkinesia (fast movements), response to non-apparent stimuli (possible hallucinatory-like behaviors), repetitive grooming (representing compulsive activity), and stereotypies (including pacing, repetitive side-to-side jumping, and running in circles). These can be rated using a neuropsychiatric-like behavior rating scale (Fox et al., 2006b, 2010; Visanji et al., 2006). The particular strength of this model is that it has predictive validity in terms of response to treatments that both exacerbate or attenuate psychosis-like behaviors in PD patients. Thus in the model, the atypical antipsychotics, clozapine and quetiapine, reduce psychosis without worsening PD, in contrast to the effects of haloperidol that worsen PD, while amantadine increased psychosis (Visanji et al., 2006). The subjective nature of psychotic behaviors can clearly not be assessed in the MPTP-lesioned marmoset; rather, these psychosis-like behaviors might be a physical manifestation of similar processes in the NHP brain.

The advantage of using the MPTP model in assessing the risk of developing psychiatric problems is that impulse control disorders were only appreciated after many years of use of dopamine agonist (Voon et al., 2006). Recent clinical studies investigating potential agents for PD now routinely include assessment of impulse control disorders as part of the evaluation of side-effects and the updated UPDSR rating scales for PD patients include questions on behavioral issues (Goetz et al., 2008).

Sleep disorders

Sleep disorders are a common feature of PD. Patients can experience nocturnal issues due to disease pathology including disturbance of the sleep–wake cycle with insomnia and excessive daytime sleepiness, as well as specific sleep-related issues such as REM sleep behavior disorders (RBD). Such problems can arise before the motor features of PD appear; in particular, excessive daytime sleepiness and RBD and are thought to be due to early brainstem dysfunction (Postuma et al., 2009). Sleep problems can also be side-effects of antiparkinsonian medications in PD. To date there have been limited investigation of these issues in MPTP monkeys. One study measured hormone levels and reported no circadian changes in cortisol, but possible changes in melatonin and prolactin in MPTP-lesioned animals compared to controls, although no correlation with sleep states was performed (Barcia et al., 2003).

More recent studies of sleep architecture in MPTP-lesioned primates using long-term continuous electroencephalographic monitoring via implanted miniaturized telemetry device has shown that decreased dopamine turnover following a single MPTP intoxication completely suppressed REM sleep, while chronic MPTP with development of parkinsonism resulted in progressive sleep deterioration, fragmentation, and reduced sleep efficacy with a corresponding increased sleepiness during the day by about 50%. However, there was no evidence of RBD, i.e., REM sleep without atonia (Barraud et al., 2009). Thus, the MPTP-primate model does experience some of the sleep disorders encountered in PD and can be used to further study these problems as well as identify side-effects of new medications.

Cognitive impairment

A range of cognitive problems are encountered in PD subjects from mild cognitive impairment to dementia (Hely et al., 2008; Mamikonyan et al., 2009). Modeling such symptoms in the MPTP-primate has been attempted using behavioral paradigms and has shown evidence of fronto-striatal cognitive deficits that are consistent with PD patients (Kulisevsky and Pagonabarraga, 2009). Thus many studies have shown chronic deficits in executive and attentional tasks including delayed response, delayed matching-to-sample, visual discrimination, and object retrieval/detour tasks that are impaired even in MPTP-treated primates that have minimal motor deficits (Pessiglione et al.,

2004; Schneider and Kovelowski, 1990; Taylor et al., 1990). In addition, measuring self-initiated and visually-triggered saccades in MPTP-lesioned primates have shown that errors such as number of GO mode (no-response, location, and early release) increased after MPTP treatment and perseverative errors, e.g., switching from the GO to the NO-GO mode, are also consistent with frontal deficits (Slovin et al., 1999). In a similar fashion to PD patients, treatment with levodopa does not reverse these findings and can often worsen cognitive problems (Decamp and Schneider, 2009). The MPTP-primate has thus shown promise as a model of cognitive deficits in PD; however, none of the currently used agents for cognitive problems in PD, such as acetylcholinesterase inhibitors, have been evaluated in this model.

Emerging concepts on the use of MPTP-lesioned NHP in translational medicine

The key role of the MPTP-primate model for more than 25 years has been to increase understanding of the basic neural mechanisms underlying PD and levodopa-induced dyskinesia. Thus, the seminal studies, especially using MPTP-lesioned macaques, performed by the groups of Delong (DeLong et al., 1985) and Crossman (Crossman et al., 1985) were instrumental in delineating the role of the direct and indirect striatopallidal pathways and subthalamic nucleus (STN) in control of the output regions of the basal ganglia in motor symptoms of PD and dyskinesia. From an understanding of these basal ganglia pathways, many novel targets/concepts for treating PD and dyskinesia have been evaluated in the MPTP-primate, including non-dopaminergic neurotransmitters (Brotchie, 2005; Gomez-Mancilla and Bedard, 1993) and STN lesioning (Aziz et al., 1991; Bergman et al., 1990) (Table 1). Many have progressed into routine clinical use, e.g., the glutamate antagonist amantadine for dyskinesia and STN DBS for advanced PD (Pahwa et al., 2006).

Improving measurements in the MPTP-NHP to mimic clinical endpoints in trials

The MPTP-primate remains an excellent model to assess agents with potential to improve parkinsonian disability, either as monotherapy or as an add-on to levodopa. In addition, agents that can reduce levodopa-induced dyskinesia or extend the duration of action of levodopa, i.e., treat wearing-off, are commonly assessed (Jenner, 2003a). The strength of the model is the phenomenology of motor features (see above) that enables rating scales for parkinsonism and dyskinesia to be broadly equivalent to human rating scales in PD (Brotchie and Fox, 1999). Many agents can thus be tested using similar rating scales in primates and then at the phase II level (Fox et al., 2006a).

However, several drugs have failed in the translation process from phase II to phase III clinical studies (e.g. Goetz et al., 2007; Manson et al., 2000). One reason may be lack of equivalent endpoints employed in primate studies that are then used in Phase III studies. Recent attempts to improve this include the concept of using a clinical measure of quality of a treatment's benefit in NHP studies rather than just a measure of severity. One suggestion has been to incorporate measures of "good" on time, when there is reversal of PD with either no or non-disabling dyskinesia in contrast to "bad-on time" when the animal has a reversal of parkinsonism but with disabling dyskinesia (Johnston et al., 2009). Such measures are then equivalent to typical endpoints used in phase III studies which provide some measure of proportion of time for which dyskinesia is present (UPDRS part IV, item 32, or MDS-UPDRS item 4.1) (Goetz et al., 2008) and diary measures of "on-time" which incorporate the impact of troublesome dyskinesia such as proportion of "on-time" without troublesome dyskinesia (Hauser et al., 2000). New endpoint measurements of neuropsychiatric and cognitive problems, as discussed above, will potentially allow the MPTP-primate to more fully evaluate potential drugs for PD and include measures of potential adverse effects.

Use of the MPTP-NHP model in developing drugs for neuroprotection

The use of the MPTP-primate to evaluate potential neuroprotective agents has been less successful to date (Bezard, 2006), for example, the failure to replicate the positive effects of infusion of GDNF into the MPTP-lesioned NHP in PD patients (Kordower et al., 2000; Lang et al., 2006). The use of the low-dose chronic MPTP protocols has been one means of attempting to replicate the progression of disease (as discussed above). However, logistical issues of large numbers of animals required to perform such studies have resulted in use of lower-order animals in these settings, e.g., MPTP-lesioned mice. With respect to modeling this aspect of the disease other approaches need to be considered and are currently being evaluated. The most promising of these is the use of alpha synuclein-expressing vectors. Kirik and colleagues have introduced recombinant adeno-associated viral vector (AAV) coding wild-type alpha synuclein or A53T mutated alpha synuclein into the SNC (unilateral) of marmosets (Eslamboli et al., 2007; Kirik and Bjorklund, 2003). The resultant phenotype was spontaneous rotations in animals overexpressing wild-type alpha synuclein while animals expressing A53T mutation had gradual impairment of hand motor tasks and coordination tasks for up to 52 weeks. Pathological studies revealed degeneration of dopaminergic fibers in the striatum and dopamine loss in the ventral midbrain, more prominent in the A53T group than in the wild-type group; alpha synuclein aggregates were also positive for ubiquitin. Further studies are needed to evaluate the potential uses of such models.

On the other hand, it is clear the MPTP model still has much to offer in the search for disease-modifying therapies, for instance, in the understanding of how imaging might provide biomarkers of disease progression that could be used in clinical development. Thus, imaging can determine serial changes in markers of nigrostriatal dopamine function in MPTP-primates. Several centers are developing these techniques to measure markers of striatal dopamine, dopamine transporters (DAT), vesicular monoamine transporter-type 2 (VMAT2), and D2-dopamine receptors (Collantes et al., 2008; Doudet et al., 2006; Nagai et al., 2007; Tabbal et al., 2006). Such techniques will enable use of the MPTP-lesioned NHP in assessing potential neuroprotective drugs by combining a biomarker with clinical assessment of the parkinsonian phenotype.

Conclusion

The MPTP-lesioned NHP remains the gold-standard in modeling motor symptoms and complications of long-term levodopa therapy in PD. Improving outcome measures for translating preclinical findings into potentially useful drugs for PD will continue to maximize the potential of this model. Future uses include understanding non-motor symptoms of PD, such as neuropsychiatric and sleep issues that occur in this model to increase understanding and develop novel treatments for PD.

Abbreviations

NHP	Non-human primate
PD	Parkinson's disease
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
STN DBS	Subthalamic nucleus deep brain stimulations
MPP+	1-methyl-4-phenylpyridium ion
MAO-B	Monoamine oxidase B
DAT	Dopamine transporter
SNC	Substantia nigra pars compacta
VTA	Ventral tegmental area
VMAT2	Vesicular monoamine transporter
5-HT	5-Hydroxytryptamine (serotonin)
RBD	Rapid eye movement sleep behavior disorder

REM	Rapid eye movement
STN	Subthalamic nucleus
UPDRS	Unified Parkinson's disease rating scale
MDS-UPDRS	Movement disorder society Unified Parkinson's disease rating scale
6-OHDA	6-Hydroxydopamine
AAV	Adeno-associated viral vector
GABA A	Gamma aminobutyric acid A
mAChR	Muscarinic acetylcholine receptor
nAChR	Nicotinic acetylcholine receptor
NMDA	*N*-methyl D-aspartate
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
mGLuR	Metabotropic glutamate receptor
PPEA	Preproenkephalin-A
PPEB	Preproenkephalin B
PPN	Pedunculopontine nucleus
IR	Immunoreactivity

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