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Review

Modeling Parkinson's disease in monkeys for translational studies, a critical analysis

Lisa F. Potts [a], Hao Wu [b], Arun Singh [a], Irene Marcilla [c], Maria R. Luquin [c], Stella M. Papa [a,d,*]

[a] Yerkes National Primate Research Center, Emory University School of Medicine, Neuroscience Building, Atlanta, GA 30329, USA
[b] Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA 30322, USA
[c] Laboratory of Regenerative Therapy, Department of Neurology and Neuroscience Division, Centre for Applied Medical Research (CIMA), University of Navarra, Pamplona, Spain
[d] Department of Neurology, Emory University School of Medicine, 6000 WMRC, 101 Woodruff Circle, Atlanta, GA 30322, USA

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ABSTRACT

The non-human primate MPTP model of Parkinson's disease is an essential tool for translational studies. However, the currently used methodologies to produce parkinsonian monkeys do not follow unified criteria, and the applied models may often fall short of reproducing the characteristics of patients in clinical trials. Pooling of data from the parkinsonian monkeys produced in our Centers provided the opportunity to evaluate thoroughly the behavioral outcomes that may be considered for appropriate modeling in preclinical studies. We reviewed records from 108 macaques including rhesus and cynomolgus species used to model moderate to advanced parkinsonism with systemic MPTP treatment. The attained motor disability and the development of levodopa-induced dyskinesias, as primary outcomes, and the occurrence of clinical complications and instability of symptoms were all analyzed for correlations with the parameters of MPTP administration and for estimation of sample sizes. Results showed that frequently the MPTP-treated macaque can recapitulate the phenotype of patients entering clinical trials, but to produce this model consistently it is important to adapt the MPTP exposure tightly according to individual animal responses. For studies of reduced animal numbers it is also important to produce stable models, and stability of parkinsonism in macaques critically depends on reaching "marked" motor disability. The analyzed data also led to put forward recommendations for successfully producing the primate MPTP model of Parkinson's disease for translational studies.

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* Corresponding author at: Yerkes National Primate Research Center, Department of Neurology, Emory University School of Medicine, 954 Gatewood Rd, Atlanta, GA 30329, USA. Fax: +1 404 727 9294.
E-mail address: spapa@emory.edu (S.M. Papa).

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Introduction

New therapies for Parkinson's disease (PD) are assessed for efficacy and safety in preclinical studies using various animal models including primates. Currently, the primate model produced with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is considered the gold standard animal model because of its close resemblance to PD with the exception of only two characteristics: damage to other monoaminerigc systems and classic Lewy body formation in the brain (Dauer and Przedborski, 2003). MPTP has high affinity for dopaminergic neurons, but lesions of adrenergic, serotoninergic, and other systems have been reported inconsistently (Forno et al., 1986; Jenner, 2008). Regarding the pathologic hallmark of PD, definite Lewy bodies have not been confirmed following MPTP toxicity in human or monkey (Forno et al., 1993). Nevertheless, this model, particularly with systemic MPTP treatment in large monkeys (macaques), characteristically replicates marked cellular loss in the substantia nigra pars compacta, the cardinal motor symptoms of PD including abnormalities in axial and appendicular movements and postures, and the full extent of motor complications associated with chronic dopaminergic treatment (Jenner, 2000, 2003). Furthermore the primate MPTP model can reproduce non-motor symptoms of PD including cognitive, sleep and gastrointestinal dysfunction (Barraud et al., 2009; Chaumette et al., 2009; Schneider et al., 2010). These exceptional characteristics of the primate MPTP model generated high expectations for its application since its original descriptions (Bankiewicz et al., 1986; Bloem et al., 1990; Burns et al., 1983). For three decades, parkinsonian monkeys have been used extensively and successfully in a variety of translational studies (Bibbiani et al., 2005; Eden et al., 1991; Liang et al., 2008; Luquin et al., 1999; Stockwell et al., 2009), and the model is recognized to have "fantastic translational potential" (Bezard and Przedborski, 2011).

The large experience in the use of MPTP-treated primates led to the publication of several reviews where the model pros and cons and its comparisons with other animal models of PD were discussed (Collier et al., 2003; Fox and Brotchie, 2010; Marin et al., 2006; Morin et al., 2013; Olanow and Kordower, 2009). However, commonly applied methodologies for MPTP treatment and the characteristic features of the produced parkinsonian monkeys have never been formally surveyed. The information obtained from these studies is key for adequately modeling PD in monkeys, and can be used to establish guidelines for application of the model. This is particularly important for translational studies, which rely on reproducibility and consistency of parkinsonian behaviors in the monkeys. The MPTP lesion is largely dependent on individual features of the monkeys (species, gender, age, health conditions, etc.) and the toxin bioavailability determined by dosages, schedules, etc. As a result, the phenotypes in the primate MPTP model may bear considerable variability, and despite the lack of systematic comparisons, it can be predicted that the groups of parkinsonian monkeys currently in use are quite heterogeneous. For instance, a large number of interventional treatments target the middle/advanced stages of PD that develop after years of disease progression and antiparkinsonian drug therapy. Presumably, this long-standing parkinsonism has not always been reproduced in the primate model within the context of modern, rapid-pace research and a lack of common inclusion criteria. Taking advantage of a large data sample from 108 monkeys (macaques) produced in two Institutions (Emory University, Center 1 and University of Navarra, Center 2), we retrospectively reviewed the clinical monkey records to analyze differences in commonly used primate models using consistent assessment of motor behavior and thorough statistical processing. These analyses of behavioral outcomes in relation to the MPTP treatments led to discuss the key methodological points and provide guidelines that may help avoid shortcomings so that the application of MPTP-treated monkeys can be optimally reliable and useful.

Production of the primate MPTP model

Animals

Data (n = 108) included two species of macaques, rhesus and cynomolgus (RM and CM; *Macaca mulatta* and *fascicularis*) with bilateral parkinsonism following intravenous (i.v.) MPTP injections for use in a variety of studies for clinical translation; therefore, models were prepared similarly in Centers 1 and 2 (see Table 1 for demographic details). Because of similar animal characteristics and procedures between the two Centers, monkeys could be grouped by species. All studies were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals or the European Union guidelines, and approved by the Institutional Animal Care and Use Committees of respective Universities. The animals were maintained in similar living conditions in both Centers. While the EU and US regulations differ regarding housing size, they are similar in all other aspects (nutrition, environmental conditions, social housing, enrichment, etc.). The housing differences between the two Centers were minimized because of the guidelines for cage size adjustment according to animal size/weight at the US Center 1 (Yerkes National Primate Research Center).

Methodological considerations in the production of the model for the analyzed dataset are primarily concerned with differences in the included macaques and the applied systemic MPTP treatments. The macaques used in Centers 1 and 2 studies originated from non-selective breeding and had similar characteristics (Table 1). Males and females of each macaque species were included, but in the CM group gender was skewed by a higher number of males (78 males and 7 females) to

Table 1
Characteristics of parkinsonian monkeys.

Species (*Macaca*)		Rhesus	Cynomolgus	Comparison
MPTP administration		i.v.	i.v.	
Number of animals		N = 23	N = 85	
Center[a]	Emory	23	10	
	Navarra	0	75	
Gender	Female	12	7	$p < 0.0001$[b]
	Male	11	78	
Age (years)		4.6 ± 0.5 (2–10)	4.3 ± 0.2 (1.7–7.0)	$p = 0.6$[c]
Weight (kg)		5.8 ± 0.4 (2.9–9.9)	3.7 ± 0.1 (2–7.3)	$p < 0.0001$[c]

[a] Each Center, Emory University (Atlanta, GA, USA) and University of Navarra (Pamplona, Spain) with the corresponding number of monkeys. The distribution of gender, age and weight is shown in each species (RM and CM). Most CM monkeys were males selected for pharmacological studies to avoid cyclic hormonal effects of females. Weight difference between species is expected as RM are typically larger than CM. Data are mean ± SEM and the ranges are given in parenthesis.
[b] Fisher's exact test.
[c] Two sample t-test.