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Overview

1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Lesioned Model of Parkinson's Disease, with Emphasis on Mice and Nonhuman Primates

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Animal models play a critical role in our understanding of the cause of human diseases and provide an opportunity to evaluate new therapeutic treatments. The usefulness of an animal model is dependent, in part, on how closely it resembles neurochemical, neuropathologic, and behavioral features of the human condition. Other considerations that may enhance the value of a model include expense, availability, reproducibility, animal morbidity and mortality, and investigator experience. Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by slow movements, tremor, and walking impairment due to loss of midbrain nigrostriatal neurons and depletion of striatal dopamine. In the PD research field, a number of neurotoxic, pharmacologic, and transgenic animal models are available for research studies. We will focus on the advantages and disadvantages of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned mouse and nonhuman primate models of PD. Our goal is to guide researchers in the appropriateness of the MPTP models in their studies by balancing understanding of the models, objectives of the study, and health and safety of the animals. In addition, the technical use and safe handling of MPTP are discussed.

Parkinson's disease (PD) is a progressive neurodegenerative disorder with clinical features that include bradykinesia (slowness), postural instability (balance), rigidity, and resting tremor as well as autonomic dysfunction and psychiatric manifestations (64, 194). The principal neuropathologic feature of PD is selective degeneration of midbrain dopamine-producing neurons of the substantia nigra pars compacta (SNpc) that make up the nigrostriatal pathway, which results in depletion of dopamine in the caudate nucleus and putamen (collectively termed the striatum). A pathologic hallmark of PD is the presence of eosinophilic inclusions called Lewy bodies localized to neurons of the substantia nigra in addition to other brain regions including the locus coeruleus and cortex (68, 104). The cause of PD is unknown, but may result from the complex interaction of environmental and genetic factors (145, 156, 160, 215, 239). Currently, age is the only known risk factor for PD. The recent identification of specific mutations in kindreds with familial PD has resulted in the isolation of several genes, including a-synuclein (PARK1), parkin (PARK2), ubiquitin carboxy-terminal hydrolase L1 (UCH-1), DJ-1 (also called PARK7), and others that may play a role in the cause of basal ganglia disorders including idiopathic PD (235). Given that a number of genes may be involved in the pathogenesis of PD, it is believed that PD may represent a common final pathway of a number of disorders that share the common end point of nigrostriatal neuronal degeneration (168). Currently, treatment of PD is empiric and consists principally of dopamine replacement through the oral administration of 3,4-dihydroxy-L-phenylalanine (L-DOPA), the biosynthetic precursor of dopamine. Unfortunately, over time, the effectiveness of L-DOPA decreases and erratic responses develop.

The goal in developing animal models of human disease is to replicate as closely as possible many of the pathologic, biochemical, and clinical features of the human condition. These models can serve to evaluate new therapeutic strategies and to test hypotheses of the cause of the disease. Such objectives must be balanced with the ability to generate models in timely manner, with high reproducibility and high animal survivability. For PD, a major objective in the development of animal models has been to replicate many of the characteristic features, including nigrostriatal cell loss, dopamine depletion, and parkinsonian features. With this in mind, a number of models of PD have been developed by use of surgical, neurotoxicant, and genetic/developmental approaches (170, 171, 235). Comprehensive reviews of many of the available research models have been published (17, 27, 43, 52, 108, 170, 171, 175, 190, 213). The review presented here will focus on the neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and the MPTP-lesioned nonhuman primate and mouse models. Advantages and disadvantages of these models will be presented, and their usefulness will be highlighted. In addition, the technical and safety issues associated with the administration and handling of MPTP will be discussed. An important goal in neurodegenerative disease research is to develop a thorough understanding of the various animal models and their limitations, to determine the most appropriate application of the

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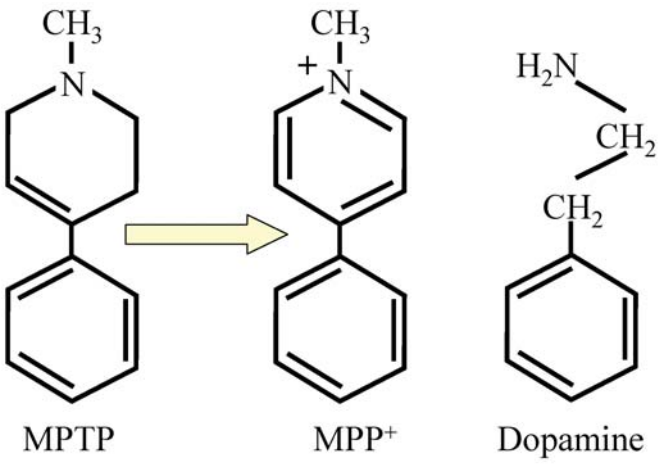

Figure 1. Structure of 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine (MPTP) resembles dopamine. Enzymatic conversion of MPTP to 1-methyl-4-pyridinium (MPP^+) by monoamine oxidase B produces a toxin that structurally resembles the neurotransmitter dopamine.

model, and to consider parameters that will minimize pain, distress, and discomfort in animals used for PD research.

Brief History of MPTP

Inadvertent self-administration of MPTP by heroin addicts in the late 1970s and early 1980s induced an acute form of parkinsonism, the clinical features of which were indistinguishable from those of idiopathic PD (53, 127). The initial cohort of seven MPTP-lesioned patients, from a population of over 300 to 400 exposed heroin addicts, suffered from severe bradykinesia, tremor, and impaired balance in addition to other PD-related features including dementia. Similar to patients with idiopathic PD, this MPTP-lesioned cohort had an excellent response to L-DOPA and dopamine agonist treatment. Positron emission tomography (PET) using [^{18}F]-DOPA revealed severely reduced uptake similar to that of late-stage PD that was progressive (31, 217, 233). Also, similar to idiopathic PD cases, the MPTP-induced parkinsonian cohort developed L-DOPA-related motor complications (including involuntary flowing movements termed dyskinesia in limbs, trunk, and neck). Interestingly, motor complications developed within a short period (weeks) of starting dopamine replacement therapy compared with years for idiopathic PD. The rapid onset with which these motor complications appeared presumably reflected the severity of substantia nigra neuronal degeneration induced by MPTP exposure. The neuropathologic findings in three MPTP-lesioned addicts indicated cell loss restricted to the SNpc and absence of Lewy bodies (130). The lack of Lewy bodies may be age-dependent in these young-onset MPTP-induced parkinsonian patients since age may be an important factor for development of Lewy bodies. This is supported by the fact that inclusion bodies have been observed in aged MPTP-lesioned monkeys, but not younger monkeys (69). Also, young-onset PD, such as the autosomal recessive juvenile parkinsonism form due to a mutation in the parkin gene, is not associated with formation of Lewy bodies, but is clinically similar to idiopathic PD. In light of the paucity of Lewy bodies in young-onset PD patients, it may not be necessary to document this pathologic feature in all animal models of PD. Immediately after its identification, MPTP was administered to rodents and nonhuman primates, and some of the most valuable animal models of PD were developed (36, 37, 129, 143).

Mechanism of MPTP-Induced Toxicosis

After systemic administration, MPTP crosses the blood-brain barrier. It is converted to 1-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$) by monoamine oxidase B (MAO-B, principally in astrocytes), then spontaneously oxidizes to 1-methyl-4-pyridinium (MPP^+), its toxic form (Fig. 1). The MPP^+ acts as a substrate of the dopamine transporter (DAT) and is taken up by SNpc neurons, leading to inhibition of mitochondrial complex I, depletion of ATP, generation of reactive oxygen species, and death of dopaminergic neurons (Fig. 2). Administration of MPTP to mice and nonhuman primates destroys dopaminergic neurons of the SNpc, the same neurons affected in patients with PD (100). Similar to PD, other catecholaminergic neurons, such as those in the ventral tegmental area (VTA) and locus coeruleus, are affected, but to a lesser degree (68, 70-73, 151). In addition, dopamine is depleted in the putamen and caudate nucleus, targets of the SNpc neurons. The preferential lesioning of either the putamen or caudate nucleus may depend on animal species and regimen of MPTP administration (20, 114, 183). Unlike PD, Lewy bodies have not been reported in MPTP-lesioned animals; however, eosinophilic inclusions (reminiscent of Lewy bodies) have been described in aged nonhuman primates (73). The time course of MPTP-induced neurodegeneration is rapid and, therefore, represents a major divergence from the chronic progressive disease course typical of idiopathic PD. Interestingly, data from humans exposed to MPTP indicate that the toxic effects of MPTP may be more protracted than was initially believed (130, 233).

Numerous factors, including species, strain, and age of the animal, contribute to the sensitivity to and toxic effects of MPTP. For example, the nonhuman primate is very sensitive to the toxic effects of MPTP. In particular, Old World monkeys are more sensitive than are New World monkeys. The mouse, cat, dog, and guinea pig are less sensitive, and the rat is the least sensitive. There are strain differences within species. For example, the C57 BL/6 mouse is the most sensitive of all mouse strains tested, whereas strains such as CD-1 and BALBc appear almost resistant (90, 157). Even within the same strain designation, differences in MPTP sensitivity have been documented among different supply houses. For example, differences in MPTP sensitivity in the outbred strain of Swiss Webster mice from various vendors have been reported (92). Therefore, investigators should stay consistent with the strain and vendor used in lesioning studies and keep in mind that sensitivity is strain dependent. This is especially important for transgenic mouse lines where backcrossing a transgenic mouse line to the C57 BL/6 background for at least ten generations to establish an inbred strain can reduce genetic contribution to MPTP toxicity/resistance from non-transgenic genes. The mechanisms involved in MPTP sensitivity can be evident at many stages, including those highlighted in Fig. 2. They include: bioavailability of MPTP and MPP^+ through interactions with peripheral organs, especially detoxification enzymes found in the liver; ability of MPTP to cross the blood-brain barrier (especially conversion to MPP^+ [which cannot cross] in the periph-

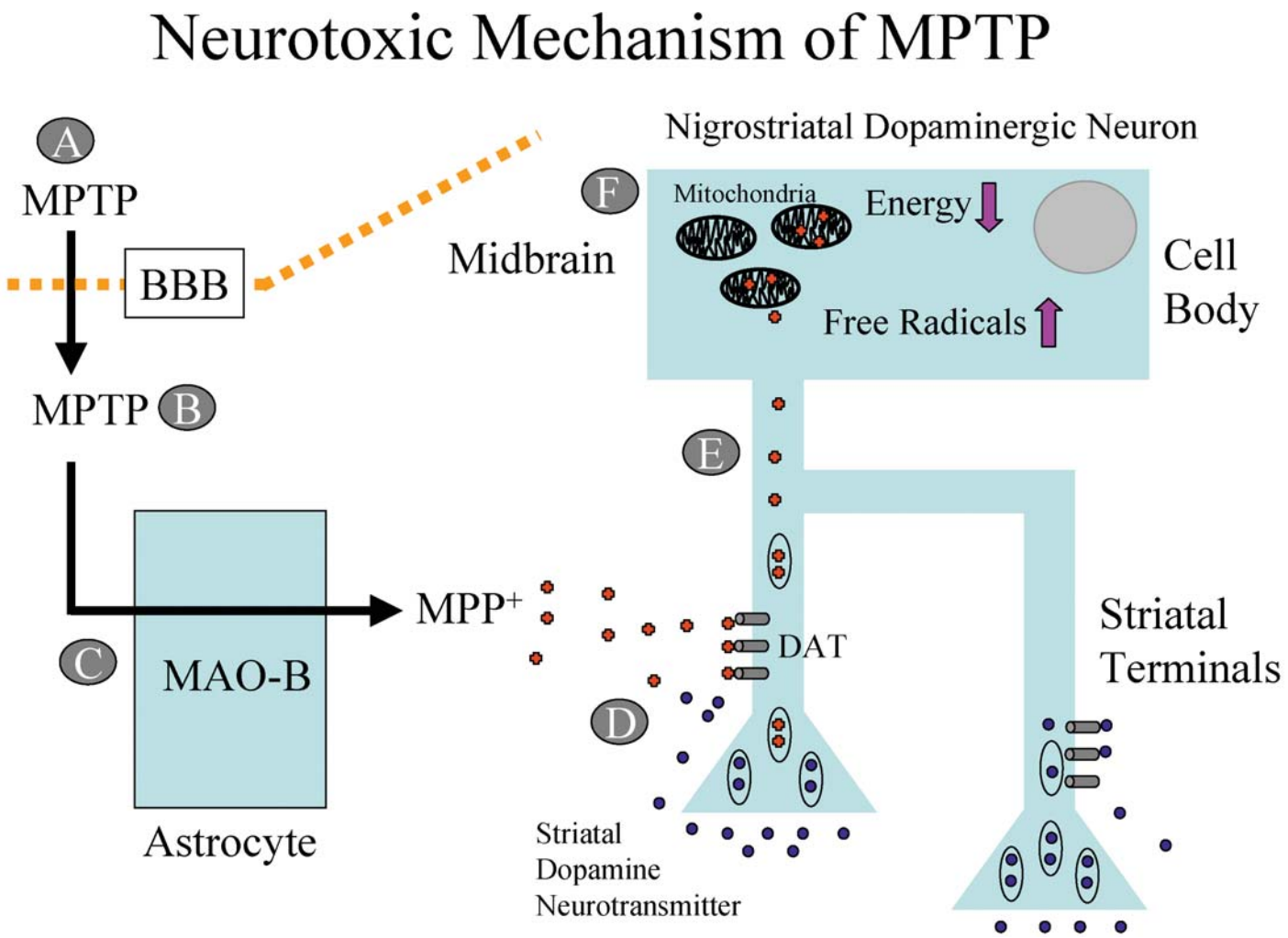

Figure 2. Initial biochemical steps leading to depletion of nigrostriatal dopaminergic neurons by the neurotoxin MPTP are illustrated. They include: (A) peripheral injection of MPTP into the blood; (B) MPTP crossing the blood brain barrier (BBB) and entering the brain; (C) conversion of the pretoxin MPTP to the toxic form MPP^+ principally by astrocytic monoamine oxidase B; (D) MPP^+ competing with intrinsic dopamine for uptake into the striatal terminals of nigrostriatal dopaminergic neurons via the dopamine transporter (DAT); (E) transporting of MPP^+ from striatal terminals to the neuronal cell body; and (F) targeting of MPP^+ to complex I of mitochondria, resulting in energy depletion and formation of reactive oxygen species (ROS), and resulting in nigrostriatal terminal loss, leading to striatal dopamine depletion and neuronal cell death.

ery); uptake of MPP^+ via the dopamine transporter; storage and sequestering of MPP^+ in vesicles; and interaction of MPP^+ with mitochondrial enzymes. Age is another factor that influences the sensitivity of animals to the neurotoxicant effects of MPTP; older mice (and nonhuman primates), for example, are more sensitive to MPTP-lesioning (4, 103, 162). Age-dependent differences may be due, in part, to differences in MPTP metabolism, since cells of older mice contain higher MAO-B activity than do those of younger mice (196). In an attempt to understand the genetic basis of MPTP sensitivity, use of quantitative trait loci analysis has identified a number of genetic loci that may contribute to MPTP-lesioning susceptibility or resistance (90, 208-210). Some of those genes may be intrinsic to neurons, whereas others point to a glial contribution of strain-dependent susceptibility (214).

Human Exposure to and Precautions for MPTP during Administration

The acute effects of MPTP in humans and animals have raised caution for its use in the laboratory setting. To date, there has been only one report of cutaneous exposure to MPTP causing acute parkinsonism. A pharmaceutical chemist was working, unprotected, and was exposed to a large amount of MPTP (up to 3 kg over an 8-year period [128]). To the authors' knowledge, the sensitivity of humans to MPTP and, in particular, the amount needed to induce a parkinsonian state in humans, is not known. The original cohort of seven heroin addicts who had developed MPTP-induced parkinsonism (out of approximately 300 to 400 exposed heroin addicts) is estimated to have self-injected tens to hundreds of milligrams of MPTP (131). Of those that had injected MPTP but did not manifest immediate clinical symptoms, some had reduced dopamine uptake on the basis of results of PET imaging, but like many others exposed to MPTP, their potential for progression of clinical motor symptoms is unknown (31, 233). Despite the uncertainty of the degree of sensitivity of humans to MPTP, established laboratory safety precautions are always taken. These precautions deal with limiting the exposure of MPTP to personnel

during preparation of MPTP stock and injection concentrations, animal handling and injection period, and postinjection animal care and husbandry. The MPTP (free base) and MPP^+ are now supplied in pre-weighed amounts in secure septum-sealed vials, allowing re-suspension at the desired concentration and minimizing the amount of exposure that potentially could occur during weighing of the powder. The stock concentration of MPTP can be removed to make the necessary concentration for injection by simply passing a syringe needle through the rubber septum. Highly trained and experienced technicians should carry out the administration of MPTP to animals. Administration of MPTP and post-MPTP-lesioning animal husbandry should take place in an isolated and secure procedure room. During injection, personnel should be fully protected by use of protective gowns, double gloves, face shield (or goggles), and filtered mask. To avoid a self-inflicted needle stick, it is important to restrain the animal either securely by hand or by using an appropriate restraining device. Eldepryl (seligiline) is a compound that blocks MAO-B and, therefore, prevents the conversion of MPTP to its toxicant form MPP^+ (42, 57, 93). In an emergency situation after a needle stick or splash of MPTP, Eldepryl should be made readily available, and may be orally administered at a dose of up to 10 mg (two 5-mg tablets) at one time. A neurologist familiar with the diagnosis and management of Parkinson's disease should be accessible to assist in the emergency care of an MPTP-exposed researcher. Procedures should be carried out to limit post-MPTP lesioning exposure. The principal route of bodily elimination of MPTP is through the urine (133). The half-life of MPTP ranges from 3 to 12 h, depending on the animal species (96, 113). Therefore, animals should be isolated for approximately 72 h before being returned to their home colony. Contaminants (absorbing bedding) should be incinerated and cages thoroughly decontaminated using a solution of 1% bleach (sodium hypochlorite). Additional details regarding safety precautions were published recently (175).

The MPTP-Lesioned Mouse Model of Parkinson's Disease

Administration of MPTP to mice results in degeneration of SNpc neurons and depletion of striatal dopamine. The severity of MPTP lesioning depends on the regimen of administration. A wide range of administration regimens has been reported that varies with respect to the total amount of MPTP administered, the route (intraperitoneally [i.p.] versus subcutaneously [s.c.]), and time between injections. Table 1 lists some of the various MPTP-lesioning regimens reported in literature, with a few advantages and disadvantages. These result in differences in the degree of dopamine depletion, SNpc cell death, behavioral motor deficits, and time course of recovery (18, 19, 100, 124). For example, using an acute regimen consisting of four i.p. injections of 20 mg/kg of body weight (free base), 2 h apart, for a total of 80 mg/kg in C57 BL/6 mice, leads to 90% depletion of striatal dopamine and 60 to 70% loss of nigrostriatal dopaminergic neurons (100, 102). The severity of the injury can be titrated using lower concentrations or fewer injections of MPTP (100). Besides inducing a rapid degree of cell death and dopamine depletion, the acute regimen of MPTP lesioning may lead to morphologic features of dying neurons that differ from those described using a chronic regimen. A chronic regimen often consists of a series of single daily injections of MPTP (20 to 30 mg of free base/kg) over 5 to 10 days. This chronic regimen leads to morphologic features resembling apoptotic cell death rather than necrotic features of SNpc neurons observed during the acute regimen. Additional differences between these two regimens may also involve alterations in biochemical and molecular pathways, including those involved in basal ganglia recovery (100, 126, 223).

Behavioral effects of MPTP in mice have been characterized and resemble some of the features of human parkinsonism. For example, bradykinesia, akinesia, altered balance and other motor features can be observed through various behavioral analyses, including open-field activity monitoring, swim test, pole test, grip coordination, treadmill running velocity and duration, and rotarod balance (67, 210, 230). Whole-body tremor and postural abnormalities also have been reported, but principally in the first day after lesioning (210). In general, these behavioral alterations tend to be highly variable, with some mice developing severe deficits whereas others exhibit little or no behavioral change (210). This behavioral variability may be due to a number of factors, including degree of SNpc lesioning, mouse strain, test sensitivity, and period after lesioning when recovery may occur. It should be noted that early behavioral changes within 24 h after MPTP administration may be due to the systemic effects of MPTP in the liver, heart, and kidneys due to the conversion of MPTP to MPP^+ by peripheral MAO-B (35, 79-82, 243, 247). These systemic effects may include alterations in blood pressure, core body temperature, and liver function (9, 77, 85, 94, 243). They may be sufficiently severe to result in poor animal health during the early phase of MPTP-lesioning, resulting in reduced behavioral measures. Therefore, behavioral assessment should be carried out when cell death is complete and when MPTP/MPP^+ concentrations are depleted, which is typically 3 or 4 days after the last injection of MPTP. Also, one must keep in mind that the MPTP-lesioned mouse model is a dynamic model where dopamine concentrations, striatal terminals, and other molecular parameters change in the weeks to months after MPTP administration (102, 183). This time course in recovery (and hence, lesion stability) can be age dependent (182).

Investigators should be aware of the potential change in animal survivability after systemic administration of MPTP. Loss of mice tends to occur within the first 24 h after MPTP administration due to the effects of MPTP/MPP^+ on peripheral targets such as the liver, kidney, and heart. Acute lesioning paradigms with multiple injections of MPTP tend to result in greater loss compared with that associated with chronic low-dose injection regimens. We also found that core facility temperature kept warm to avoid severe hypothermia, careful injection of small volumes of MPTP (typically 100 µl/injection, i.p.), and screening of different vendor sources will lead to animal survival exceeding 90 to 95%. One must also keep in mind that any changes in the lesioning paradigm (such as strain, vendor, volume, or concentration) require validation of the effects of MPTP on dopamine depletion and cell loss. Also, post-lesioning behavioral changes should be monitored, especially aggressive behavior in MPTP-lesioned C57 BL/6 mice that may require individual housing of animals.

Administration of MPP^+

The active toxin of MPTP, MPP^+, is commercially available

Table 1. Comparison of common lesioning regimens used for the administration of MPTP to mice and nonhuman primates

MPTP Model	Notes on typical lesioning regimen	Advantages	Disadvantages
Mouse		• Inexpensive, small, and easy to handle • Genetically identical strains • Experimental design can use large numbers of animals • Animals of different ages and sensitivity available	• Neuroanatomic differences compared with primates • Motor behavioral features different from primates • Cognitive studies difficult • Variability in stain susceptibility • Variability in age susceptibility
Mild acute lesion	Single injection at 10, 20, or 30 mg/kg, s.c. or i.p.	• High degree of animal survival • Mild cell loss • Mild dopamine depletion	• Variability in degree of lesioning • Lesion may be too mild for some studies • Robust recovery
Severe acute lesion	Series of 4 injections at high concentration of 20 mg/kg, s.c.	• Fast; cell death complete in 1 to 3 days • Significant dopamine depletion and cell loss • Surviving neurons act as template for intervention • Potential for animal death	• Necrotic cell death distinct from apoptotic pathway • Fast; not progressive kinetics of cell death • Recovery in weeks to months
Chronic lesion	Series of daily injections for 5, 10, or 20 days at 4, 20, or 30 mg/kg i.p., s.c.	• High survival • Progressive cell death with apoptotic morphology	• Requires consistent lesioning administration for reproducibility • Long lesioning period
Chronic + acute	Additional bolus 30 mg of MPTP/kg 30 days after chronic regimen	• Higher degree of stability, with less recovery • Effect second hit in lesioned background	• Long lesioning period
Chronic + probenecid	2 weekly injections of MPTP with probenecid for 5 weeks	• Inclusions resembling Lewy bodies • Longer stability compared with MPTP alone • Progressive cell death	• Long lesioning period
Nonhuman primate		• Neuroanatomy resembles human • Motor behavioral features similar to human	• Expensive • Experiments have small "n" • Out-bred, with variability in motor behavior deficits
New World monkeys including squirrel monkey and marmoset	Series of s.c., i.v., i.p., or i.m. systemic injections	• Small, easy to handle • Inexpensive compared with Old World monkeys • Neuroanatomy resembles human • High survival • Animals able to care for themselves • Remaining dopamine cells serve as template for intervention • L-DOPA-induced dyskinesia	• Cognitive studies difficult • Peripheral effects of MPTP • Lesioning period may take several months
Old World monkeys including macaques		• Neuroanatomy resembles human • Cognitive studies possible	• Large, require restraint • Expensive • Extreme MPTP sensitivity may require extensive husbandry
Systemic	Systemic s.c. , i.v., i.p., or i.m. injections	• Bilateral motor features • Bilateral dopamine depletion • Degree of lesioning can be titrated	• High sensitivity to MPTP-lesioning • High potential for animal mortality • Require extensive husbandry • Recovery of motor features
Hemi-lesion	Intracarotid injection to one side only	• Extensive depletion predominates on one hemisphere • Near complete lesion side serves as template for transplant • Nonlesioned side can serves as a control	• Requires surgical intervention for MPTP delivery • Animal rotation may develop • Difficult to rate motor deficits on affected side
Bilateral Intracarotid	Bilateral intracarotid injections weeks to months apart at various concentrations	• Extensive bilateral dopamine depletion and cell death • Different degree of lesion on each side • Avoids potential severity of systemic model	• Requires surgical intervention for MPTP delivery • Requires extensive husbandry • Poor L-DOPA responsiveness
Over-lesion	Intracarotid injection to one hemisphere followed by mild systemic injection	• Animals able to care for themselves • One side with extensive dopamine depletion, the other side with partial depletion	• Requires surgical intervention for MPTP delivery • Both sides affected (one mild, other severe)
Chronic	Small doses daily or weekly	• Simple MPTP delivery • High animal survival with small amounts of MPTP • Cognitive impairment may be desirable	• Requires long period • Mild parkinsonian features • Cognitive deficits predominant and may complicate studies

(Sigma Chemical Co., St. Louis, Mo.). Although most often used in cell culture, MPP^+ is occasionally used in animals (such as rats or certain transgenic mice) because of either the inability to convert MPTP to MPP^+ (due to a lack of brain MAO-B, for example), or altered blood-brain barrier permeability to MPTP (86, 87, 180, 181, 219, 255).

Enhancing MPTP-Induced Toxicosis in Mice

Several compounds have been documented to potentiate the neurotoxic effects of MPTP and include diethyldithiocarbamate (DDC), probenecid, acetalaldehyde, and ethanol (46, 169, 253, 254). Diethyldithiocarbamate is a copper-chelating agent that increases the bioavailability of MPP^+ and enhances the toxicity of MPTP so that when it is co-administered with MPTP, the

lesioning effect is enhanced (45, 98, 148, 150, 238). Probenecid delays MPTP metabolism and reduces urinary and neuronal clearance of MPTP and its metabolites (134, 169). Mice treated for 3 weeks with MPTP and probenecid developed small, granular, non-fibrillary inclusions in the substantia nigra that ultrastructurally resembled the dense core of Lewy bodies, an intracytoplasmic inclusion considered a pathologic hallmark of human PD (149). Acetaldehydes and ethanol, as well as several other related compounds, may enhance MPTP susceptibility through a variety of mechanisms, including alteration of dopamine and glutamate receptor expression and dopamine transporter and mitochondrial function. Therefore, these compounds can indirectly lower the threshold for MPTP-mediated toxicosis as well as promote entry of MPP^+ into its molecular targets. In addition to pharmacologic enhancement of MPTP susceptibility, increased toxicity of the drug may be seen in transgenic mouse strains. For example, some transgenic constructs lacking or carrying additional copies of the a-synuclein gene had reduced or enhanced susceptibility, respectively, to MPTP, suggesting possible environmental/genetic interactions that may influence basal ganglia dysfunction (51, 184). One should be cautious in interpreting differences in susceptibility under such circumstances since transgenic mice may have altered dopamine function underlying their response to neurotoxin injury (1).

The bioconversion of MPTP to MPP^+ and uptake of MPP^+ may be influenced by pharmacologic agents. Therefore, studies designed to examine the neuroprotective or neurorestorative properties of a compound on nigrostriatal neurons should also take into consideration any direct effect on the bioavailability of MPTP, which include bioavailability of MPP^+ in the brain due to peripheral clearance by the kidney or liver, ability of MPTP to cross the blood brain barrier, conversion of MPTP to MPP^+ in the brain, and uptake and storage of MPTP in dopaminergic neurons.

The MPTP-Lesioned Nonhuman Primate

Although much of our understanding of the actions of MPTP has been derived from studies in rodents, the nonhuman primate provides a valuable link to the human condition since it shares behavioral and neuroanatomic similarities. For example, anatomic features include the delineation of the striatum into separate caudate nucleus and putamen, as well as similarity of intrinsic and extrinsic neuronal connectivity between human and nonhuman primates. The initial discovery and characterization of MPTP-induced parkinsonism in humans led to administration and study of MPTP in the nonhuman primate (53, 127). The MPTP has been administered to a wide variety of nonhuman primates, including the squirrel monkey (*Saimiri sciureus*) (129), long-tailed macaque or cynomologus (*Macaca fascicularis*) (151), rhesus macaque (*M. mulatta*) (30, 37), Japanese macaque (*M. fuscata*) (48, 111), Bonnet monkey (*M. radiata*) (76), baboon (*Papio papio*) (91, 153), African green monkey or vervet (*Chorocebus aethios*, formerly *Ceropithecus aethiops*) (224), and common marmoset (*Callithrix jacchus*) (111). Administration of MPTP to the nonhuman primate results in signs of parkinsonism, including bradykinesia, postural instability, freezing, stooped posture, and rigidity. Although postural and action tremor have been observed in many species after MPTP treatment, a resting tremor, characteristic of PD, was less commonly documented (91, 177, 229).

Also less commonly documented is the occurrence of Lewy bodies in the MPTP-lesioned nonhuman primate. This may be a reflection of the fact that young adult animals are often used for MPTP-lesioning, and inclusion body formation may be age dependent. This is supported by reports of eosinophilic inclusion-like structures representing Lewy bodies in aged MPTP-lesioned squirrel monkeys and development of parkinsonian pathologic changes in an aged cynomologus monkey (69, 115). In humans, autosomal recessive juvenile parkinsonism (AR-JP) due to mutations in the parkin gene is not associated with formation of Lewy bodies (212), whereas Lewy bodies are common (and a pathologic hallmark) of idiopathic PD in the aged brain (105).

Finally, the mode of MPTP administration may also influence the potential appearance of pathologic change, since inclusion-like structures similar to Lewy bodies have been reported in chronic MPTP lesioning along with use of probenecid (149), and one must be cautious of delineating toxin-induced pathologic with intrinsic age-dependent pathologic changes (29, 206, 237, 244, 246). Further studies in aged nonhuman primates are needed to address these issues.

Similar to patients with PD, the MPTP-lesioned nonhuman primate responds to anti-parkinsonian therapies such as L-DOPA and dopamine receptor agonists. The degree of clinical response to L-DOPA is dependent on the severity of the lesion and parkinsonian state. In general, the degree of motor deficits induced by MPTP lesioning may vary at the inter- and intra-species levels. Variability may be due to age and species phylogeny. For example, aged animals and Old World monkeys (such as rhesus macaques or African Green monkeys) tend to be more sensitive than do young and New World monkeys (such as the squirrel monkey or marmoset) (83, 162, 185). Within a species, behavioral variability also is observed. For example, in our studies, using a regimen of six subcutaneous injections of MPTP (2 mg/kg, free base) 2 weeks apart (total of 12 mg/kg), we documented a range of signs from mild to severe. The molecular and morphologic mechanisms of this variability are complex, and may be attributable to a combination of dopaminergic cell death and postinjury molecular adaptation.

Prior to induction of a parkinsonian state and immediately after administration of MPTP, the nonhuman primate progresses through acute (hours), sub-acute (days), and chronic behavioral phases of toxicosis that are due to the peripheral and central effects of MPTP. The acute phase develops within minutes after MPTP administration, and is characterized by sedation and a hyperadrenergic state. This state may also include hypersalivation, emesis, exaggerated startle, seizure-like activity, and dystonic posturing of trunk and limbs (84, 97, 109, 111, 172). The sub-acute phase generally develops within hours and persists for several days, and may be due to the peripheral actions of MPTP on the autonomic nervous system and peripheral organs such as the liver, kidney, and heart (172). Weight loss, altered blood pressure, and hypothermia may develop, requiring tube feeding and placement in an incubator to stabilize body temperature. In addition, high liver transaminase and creatinine kinase activities may be apparent, reflecting impaired liver function and muscle breakdown. Behaviorally, these animals may appear prostrate and cognitively impaired.

Occasionally, animals may exhibit self-injurious behavior such as finger biting and hyperflexion of the neck and trunk with head banging.

Assessment of parkinsonian features may be confounded by alterations in the general health of the animal. The chronic phase develops within days to weeks after MPTP administration. It is characterized by stabilization of body weight and temperature as well as normalization of certain blood biochemical analytes such as hepatic enzymes. Parkinsonian features clearly emerge and remain stable for weeks to months or longer. The degree of behavioral stability may be predicted, in part, by the initial degree of behavioral impairment, as observed between the subacute to chronic phases. Animals with greater behavioral impairments recover over a longer period. Behavioral recovery after MPTP administration has been reported in most species of nonhuman primates.

Administration of MPTP by use of a number of different dosing regimens has led to development of several distinct models of parkinsonism in the nonhuman primate. Each model is characterized by unique behavioral and neurochemical parameters. Reviews of these various models have been published (24, 43, 107, 108, 144, 159). Each of these models is different with respect to the modality and degree of lesioning as well as behavioral features. Accordingly, a variety of models has been used to test various therapeutic interventions, including cell transplantation, gene delivery, and neuroprotective and neurorestorative therapies. For example, in some models, there is profound striatal dopamine depletion and denervation, with little or no dopaminergic axons or terminals remaining. These models provide an optimal setting to test fetal tissue or progenitor cell grafting since the presence of any tyrosine hydroxylase (the biosynthetic enzyme for dopamine production)-positive axons or sprouting cells would be due to transplanted tissue survival.

Other models have less extensive dopamine depletion and only partial denervation, with a modest-to-moderate degree of dopaminergic axons and terminals remaining. This partially denervated model best resembles mild to moderately affected PD patients. Therefore, sufficient dopaminergic neurons and axons as well as compensatory mechanisms are likely to be present. The effects of growth factors (inducing sprouting) or neuroprotective factors (promoting cell survival) are best evaluated in this situation.

In the systemic lesioned model, administration of MPTP via the intramuscular, intravenous, intraperitoneal, or subcutaneous route leads to bilateral depletion of striatal dopamine and nigrostriatal cell death (59, 61, 228, 240). In this model, the degree of lesioning can be titrated, resulting in a range (mild to severe) of parkinsonian signs. The presence of clinical asymmetry is common, with one side more severely affected. Administration of L-DOPA and dopamine leads to reversal of all behavioral signs of parkinsonism in dose-dependent manner. After several days to weeks of L-DOPA administration, animals develop reproducible motor complications: "wearing-off" and dyskinesia. Animal behavior in this model and others may be assessed using cage-side or video-based observation, automated activity measurements in the cage through infrared-based motion detectors or accelerometers, and examination of hand-reaching movement tasks. The principal advantage of this model is that the behavioral features closely resemble those of idiopathic PD. The systemic model has partial bilateral dopaminergic denervation and probably best represents the degree of loss seen in all stages of PD including end-stage disease where some dopaminergic neurons are still present. This model is well suited for therapeutics, including growth factors, neuroprotective agents, and dopamine modulation, that interact with remaining dopaminergic neurons. Dyskinesia is reproducible and permits extensive investigation regarding mechanism and treatment (108, 132). A disadvantage of this model is spontaneous recovery in mildly affected animals. Another is that bilateral severely affected animals may require extensive veterinary care and dopamine supplementation.

Administration of MPTP via unilateral intracarotid infusion has been used to induce a hemiparkinsonian state in the primate, called the hemi-lesioned model (10). The rapid metabolism of MPTP to MPP^+ in the brain may account for localized toxicosis in the hemisphere ipsilateral to the infusion. Motor impairments appear principally on the contralateral side. Hemi-neglect, manifested by delayed motor reaction time, also develops on the contralateral side. In addition, spontaneous ipsilateral rotation may develop. Administration of L-DOPA reverses the parkinsonian signs and induces contralateral rotation. Substantia nigra neurodegeneration and striatal dopamine depletion (> 99% on the ipsilateral side to the injection) are more extensive than those seen in the systemic model. The degree of unilateral lesioning in this model is dose dependent. Major advantages of the hemi-lesioned model include ability of animals to feed and maintain themselves without supportive care, availability of the unaffected limb on the ipsilateral side to serve as a control, and usefulness of the dopamine-induced rotation for pharmacologic testing. In addition, due to the absence of dopaminergic innervation in the striatum, the hemi-lesioned model is well suited for examining neuronal sprouting of transplanted tissue. A disadvantage of this model is that only a subset of parkinsonian features is evident and is restricted to one side of the body, a situation never seen in patients with idiopathic PD.

The bilateral intracarotid model involves use of an intracarotid injection of MPTP followed several months later by another intracarotid injection on the contralateral side (216). This model combines the less-debilitating features of the carotid model as well as creating bilateral clinical features, a situation more closely resembling idiopathic PD. The advantage of this model is its prolonged stability and limited inter-animal variability. Similar to the hemi-lesioned model, where there is extensive striatal dopamine depletion and denervation, the bilateral intracarotid model is well suited for evaluation of transplanted tissue. However, L-DOPA administration may result in only partial improvement of parkinsonian motor features and food retrieval tasks. This can be a disadvantage since high doses of test drug may be needed to document efficacy, increasing the risk for medication-related adverse effects.

A novel approach to MPTP lesioning is the administration of MPTP via intracarotid infusion followed by a systemic injection (159). This over-lesioned model is characterized by severe dopamine depletion ipsilateral to the MPTP carotid infusion and partial depletion on the contralateral side due to the systemic MPTP injection. Consequently, animals are self sufficient and typically do not require extensive veterinary intervention due to a relatively intact side. The behavioral deficits consist of asymmetric parkinsonian features. The more severely affected

side is contralateral to the intracarotid injection side (58).

Use of L-DOPA results in a dose-dependent improvement in behavioral features; however, the complications of L-DOPA therapy, such as dyskinesia, are not consistently observed. This model combines some of the advantages of the systemic and intra-carotid MPTP models, including stability of the parkinsonian state. This model is suitable for transplant studies, using the more depleted side, and neuroregenerative studies with growth factors, using the partially depleted side where dopaminergic neurons still remain (11-13).

Finally, the chronic low-dose model consists of a series of intravenous injections of a low dose of MPTP administered over a 5- to 13-month period (22). This model is characterized by cognitive deficits consistent with frontal lobe dysfunction reminiscent of PD or normal aged monkeys. These animals have impaired attention and short-term memory processes and perform poorly in tasks of delayed response or delayed alteration. Since gross parkinsonian motor signs are essentially absent at least in early stages, this model is well adapted for studying cognitive deficits analogous to those that accompany idiopathic PD.

The MPTP-Lesioned Cat Model

Administration of MPTP to cats (*Felis catus*) leads to parkinsonian features (bradykinesia), striatal dopamine depletion, and dopaminergic cell death in the SNpc (199, 202, 205). Histologic features are similar to those documented in mice and nonhuman primates. However, the MPTP-lesioned cat is worth noting since it was one of the first species in which behavioral recovery after MPTP-lesioning was studied (78, 187-189, 203). Investigations into the recovery of the MPTP-lesioned cat have proven important in elucidating the mechanisms involved in intrinsic neuroplasticity of the injured basal ganglia. Later studies in the 6-hydroxydopamine-lesioned rat and MPTP-lesioned mouse and nonhuman primate have complemented those early analyses (50, 59, 62, 101, 102, 195, 250-252).

The MPTP-Lesioned Models in Other Species

The MPTP has been administered to a variety of species other than mice and nonhuman primates. These include the leech (*Hirudo medicinalis*) (5), planarian flatworm (*Dugesia japonica*) (118, 119), goldfish (*Carassius auratus*) (173, 174, 248), rainbow trout (*Oncorhynchus mykiss*) (193), frog (*Rana pipiens* and *R. clamitan* [(14, 16]), salamander (*Taricha torosa*) (15), snake (*Elaphe obsolete* and *Nerodia fasciata*) (226), lizard (*Anolis carolinensis*) (139), chicken (*Gallus gallus*) (211), rat (*Rattus rattus* and *R. norvegicus*) (38, 180, 242), guinea pig (*Cavia porcellus*) (33), rabbit (*Oryctolagus cuniculus*) (135), dog (*Canis familiaris*) (165), and pig (*Sus scrofa domestica*) (245). To the authors' knowledge, there are no reports of MPTP administration to the nematode (*Caenorhabditis elegans*) or fruit fly (*Drosophila melanogaster*). Although each of these species has its own merits and drawbacks with respect to behavioral features, dopamine metabolism, MPTP toxicosis, and recovery, their wide range of application and use have not been fully explored. The fruit fly and nematode have recently regained use in PD research, since transgene manipulations and large-scale genetic screens are possible, complementing studies in mice, and avoiding some of the limitations present with nonhuman primates.

Insights from the MPTP-Lesioned Mouse and Nonhuman Primate Models

The principal usefulness of the MPTP-lesioned mouse and nonhuman primate models are to carry out studies in mechanisms of cell death; neuroprotection; dopamine replacement therapy; novel restorative therapy; mechanism of motor complications, including L-DOPA-induced dyskinesia; surgical treatment; and intrinsic recovery. Although each of these topics merits its own extensive review, some examples of each are briefly mentioned.

Understanding the mechanisms of nigrostriatal dopaminergic neuron death in the context of MPTP-lesioning is an approach that is based on the fact that environmental toxins in conjunction with genetic predisposition may underlie the development of PD. For example, early studies of the mechanisms of MPTP-induced cell death pointed toward the mitochondrion, specifically complex I, as a principal biochemical target leading to cell death (52, 106, 161). This disruption has a two-pronged effect, leading to energy depletion by reduced ATP production as well as formation of highly deleterious reactive oxygen species (ROS) and reactive nitrogen species (NOS) (110). Which of the two processes is more relevant to cell death is still a focus of investigation. The loss of ATP production and formation of ROS/NOS can set off a cascade of events, including uncontrolled calcium influx (termed excitotoxicity), direct (due to altered target specificity) or indirect (through reduced protective repair mechanisms) DNA and protein damage, protein aggregation, loss of synaptic function, or reduced axonal transport. The morphologic features of neuronal cell death also have been delineated in the MPTP-lesioned models where either necrotic or apoptotic (programmed) cell death have been documented (100, 223). Those studies have led to the fact that developmental processes may play a role in dopamine neuron cell death and the identification of biochemical targets such as blockage of enzymatic pathways that may lead to cell death.

Development of specific neuroprotective strategies depends on which hypothesis of cell death is proposed. For example, generation of ROS as a mediator of cell death has lead to development and clinical testing of free radical scavengers with the hope of slowing disease progression (89, 116, 198). Other important pharmacologic strategies that have emerged include modulation of glutamate neurotransmission to block excitotoxicity, blocking of apoptotic cell death pathways by targeting regulatory proteins such as the caspase family, and introduction of neurotrophic factors to support the survival of remaining dopaminergic neurons. It is hoped that surviving dopaminergic neurons may compensate for those lost and, therefore, reduce disease progression. An advantage of the MPTP-lesioned model is that the degree of cell loss can be controlled by titrating the administration of MPTP. Surviving dopaminergic neurons can then serve as a template for testing novel pharmacologic modalities. In addition, since the time course of cell death is precise, neuroprotective agents can be tested either before or during the active phase of cell death.

Dopamine replacement therapy is one means to overcome the neurochemical deficit precipitated by the loss of nigrostriatal dopaminergic neurons. Administration of the dopamine-depleting agent reserpine to rabbits in the late 1950s

helped to establish the central hypothesis that loss of dopamine neurotransmission underlies PD (25, 32). Administration of L-DOPA (the precursor for dopamine) still remains the "gold standard" for treatment of PD. Unfortunately, dopamine replacement therapy fails to stop disease progression and the emergence of motor complication. Despite the use of L-DOPA since the mid-1960s, the long-term consequences of dopamine replacement therapy on basal ganglia function are not fully understood and are only now being explored using animal models of PD. Those studies, and others, support a possible role of dopamine replacement therapy on modulation of the basal ganglia beyond the immediate symptomatic benefit including effects on other non-dopaminergic neurotransmitter systems such as glutamate, adenosine, and serotonin.

Novel restorative therapies have recently been developed to investigate a means to either protect or replace nigrostriatal dopaminergic neurons. These strategies include gene delivery using engineered viral vectors, transplantation of engineered cell lines, or introduction or stimulation of stem cells or progenitor cells. The MPTP- and the 6-hydroxydopamine-lesioned models have served as excellent ways to investigate transplantation to restore basal ganglia function. A wide variety of cell sources for dopaminergic production, including fetal mesencephalic tissue, carotid bodies, adrenal medulla tissue, retinal cells, and cultured cell lines, have been used (2, 6-8, 28, 54, 60, 63, 65, 66, 122, 140, 197, 220, 241). The recent characterization of embryonic, fetal, and adult stem cells has provided an additional source of material for transplantation (26, 99, 178). Transplantation of human stem cells into the MPTP-lesioned mouse has revealed limited survival, migration, and phenotypic differentiation to tyrosine hydroxylase neurons (136). Studies in animal models are critical for determining important parameters for successful transplantation, including age, developmental stage, cell number and volume, anatomic targets (caudate nucleus, putamen, or SNpc), pre- and posttransplantation treatment of cells with neurotrophins or antioxidants, and host treatment by use of immunosuppression therapy (56, 179, 218, 221, 227). The inconclusive results of fetal mesencephalic tissue transplant in patients with PD underlies the importance of further research studies in animal models to fully understand this potential treatment strategy (74, 75, 138).

As an alternative to cell transplantation, strategies have been developed to deliver specific gene products, including neurotrophic factors (including glial-derived neurotrophic factor) and enzymes for dopamine production (including tyrosine hydroxylase). Early studies involved use of encapsulated cells or microspheres to target neurotrophic factors in the injured basal ganglia (2, 88, 122). Recently, a variety of different vectors, which are based on engineered infective viruses, has been constructed, including those from herpes simplex virus (HSV), adeno-associated virus (AAV), and lentiviruses (e.g., equine infectious anemia virus). Vectors (AAV and lentiviruses) carrying glial cell line-derived neurotrophic factor (GDNF) have been documented to be neuroprotective and neurorestorative in rodent and nonhuman primate models (23, 120, 121, 147). Stereotactic delivery of vectors carrying glutamic acid decarboxylase to the subthalamic nucleus has provided an inhibitory phenotype to suppress a pathway hyperactive in PD and its models (142). These vectors have a number of advantages as a delivery strategy, including accurate stereotactic targeting to the region of injury, delivery to and integration into non-dividing neurons, avoidance of host immune response, and potential control of gene expression in vivo. In addition to providing potential benefit through vector delivery systems, the same technology is used to deliver genes and proteins (such as α-synuclein) responsible for degenerative diseases in animal models of PD to document their role in the cause of cell death and dysfunction (116, 117).

Parkinson's disease is a progressive and dynamic disorder. Five to seven years after L-DOPA treatment, patients exhibit motor complications including a "wearing-off" effect (loss of sustained dopamine benefit), and chorea in upper and lower limbs and trunk that is termed dyskinesia (44, 123). The MPTP-lesioned nonhuman primate model provides an excellent means to study the mechanism of motor complications, including L-DOPA-induced dyskinesia. The most dramatic display of L-DOPA-induced dyskinesia occurs in the MPTP-lesioned nonhuman primate. It has been best characterized in the systemic model of MPTP-lesioning in the squirrel monkey and marmoset and in some macaques (39, 40, 47, 108, 132, 172). The 6-hydroxydopamine-lesioned rat also exhibits movements in response to L-DOPA administration that are considered analogous to dyskinesia, but are limited to such anatomic distribution as the jaw (34, 141, 234). In the squirrel monkey, L-DOPA-induced dyskinesia can be elicited after only a few doses, even within the window of therapeutic benefit, and the onset is dependent on the degree of SNpc cell loss (200). Therefore, the MPTP-lesioned nonhuman primate provides a valuable tool to investigate the mechanism of L-DOPA-induced dyskinesia and in predicting which compounds are likely to elicit dyskinesia in humans. Studies thus far indicate that the capacity (storage and release) of the nigrostriatal neurons to handle L-DOPA may play an important role in dictating neuronal loss, or through high-dose L-DOPA administration, which overwhelms the cells' buffering system. It is interesting that there have been reports of dyskinesia in non-lesioned monkeys receiving large amounts of L-DOPA (166, 167, 232). The high plasma concentration of L-DOPA in this dosing regimen may serve to exhaust the buffering capacity within the caudate nucleus and putamen of the normal animal and, therefore, lead to pulsatile delivery of L-DOPA and priming of postsynaptic dopaminergic sites for dyskinesia.

There has been a recent re-emergence of surgical treatment for PD and its motor complications (55, 137, 222). Study of the MPTP-lesioned rodent and nonhuman primate have helped identify specific anatomic sites for surgical targeting in patients with idiopathic PD. These targets include the subthalamic nucleus, thalamus, and globus pallidus. Ongoing studies in these models are providing better understanding of neuronal circuitry and electrophysiologic properties of motor pathways within the basal ganglia, as well as extrinsic inputs from the cerebral cortex, thalamus, and pedunculopontine nucleus (112, 146, 163, 164, 176).

An important property of the MPTP-lesioned mouse and nonhuman primate is the potential for intrinsic recovery. Behavioral recovery after MPTP-induced parkinsonism has been reported in New and Old World nonhuman primates (49, 59, 125, 159, 172, 201, 204, 207). The degree and time course of behavioral recovery is dependent on age, species, and regimen of MPTP administration (3, 162, 172, 225). The extent of the ini-

tial MPTP-induced dopamine depletion may be the most important factor in determining the probability of spontaneous recovery (225). Understanding the molecular mechanisms underlying behavioral recovery in the MPTP-lesioned mouse and nonhuman primate may provide insights into neuroplasticity of the brain after injury and may identify new therapeutic targets for the treatment of PD (21, 101, 102, 249, 250). Results of studies investigating the mechanisms of recovery in these models have indicated: alterations in dopamine biosynthesis and metabolism; altered regulation of dopamine transporter expression and function; sprouting and branching of tyrosine hydroxylase fiber; alterations of other neurotransmitter systems, including glutamate and serotonin; and alterations of signal transduction pathways in the direct (dopamine receptor D1) and indirect (dopamine receptor D2) pathways (21, 38, 50, 59, 78, 95, 102, 152, 154, 155, 158, 186, 189, 191, 192, 236). Another goal of ongoing studies is to find means to enhance intrinsic behavioral recovery. Studies from our laboratory and those of others have indicated that treadmill exercise and forced-use paradigms can enhance recovery in models of basal ganglia injury accompanied by changes in dopamine function (41, 67, 231). These exercise studies have now been extended to patients with PD.

Conclusions

The MPTP-lesioned mouse and nonhuman primate models of basal ganglia injury are valuable in understanding the pathophysiology of PD and play an important role in developing and testing new therapeutic modalities. The lesioning regimen and species used result in different degrees of cell loss, dopamine depletion, and motor behavior deficits. Each model has its own advantages and disadvantages, depending on the scientific questions under investigation. Since humans lesioned with MPTP manifest clinical symptoms identical to those associated with idiopathic PD and progress on the basis of neuropathologic changes and PET-imaging studies, this supports the fact that MPTP provides an excellent tool to generate a model that replicates PD. Much of our understanding of PD in humans comes from the analysis of late-stage disease (when brains become available). Since we are able to investigate MPTP-lesioned animals early, during, and in a time-course manner after lesioning in a variety of species and lesioning severities, it forces us to reconsider our understanding of the human disease. New findings in the MPTP-lesioned animal models continuously guide researchers to address hypotheses for the human condition. The MPTP is a valuable research tool, and although it is a potent neurotoxin, it can be used safely taking into consideration procedures to protect research investigators. In addition, other animal models, including those generated by use of various neurotoxic compounds, such as 6-hydroxydopamine, rotenone, or methamphetamine, and newly developed transgenic and spontaneous mutant models, add to our arsenal of scientific tools. It is important that new therapeutic strategies for PD, such as pharmacologic agents, engineered vectors, stem cells, or noninvasive interventions, be fully evaluated in animal models prior to their introduction to the clinical setting. These scientific goals must be balanced with measures to reduce the number of animals used and to minimize potential animal pain, distress, and discomfort.

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