Sympathetic Innervation in the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Primate Model of Parkinson's Disease

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ABSTRACT

Cardiac sympathetic denervation occurs commonly in Parkinson's disease. This study explored whether analogous denervation occurs in primates with Parkinsonism from systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). 6-[^{18}F]Fluorodopamine positron emission tomographic scanning and plasma levels of catecholamines and their deaminated metabolites were used to assess sympathetic and adrenomedullary function in rhesus monkeys, in the untreated state ($n = 3$), 2 weeks after a series of four MPTP injections, before establishment of Parkinsonism (acute phase, $n = 1$); a month later, after four more MPTP doses, associated with severe Parkinsonism (subacute phase, $n = 1$); or more than 2 years from the last dose (remote phase, $n = 3$), with persistent severe Parkinsonism. A positive control received i.v. 6-hydroxydopamine 1 week before 6-[^{18}F]fluorodopamine scanning. Acute MPTP treatment increased cardiac 6-[^{18}F]fluorodopamine-derived radioactivity, whereas 6-hydroxydopamine markedly decreased cardiac radioactivity, despite similarly low plasma levels of catecholamines and metabolites after either treatment. Subacutely, plasma catecholamines remained decreased, but now with myocardial 6-[^{18}F]fluorodopamine-derived radioactivity also decreased. Remotely, MPTP-treated monkeys had lower plasma catecholamines and higher myocardial 6-[^{18}F]fluorodopamine-derived radioactivity than did untreated animals. The results indicate that in nonhuman primates, systemic MPTP administration produces multiphasic effects on peripheral catecholamine systems, with nearly complete recovery by 2 years. MPTP- and 6-hydroxydopamine-induced changes differ markedly, probably from ganglionic or preganglionic neurotoxicity with the former and more severe cardiac sympathetic neurotoxicity with the latter. Because of multiphasic sympathetic and adrenomedullary effects, without cardioselective sympathetic denervation at any time, the primate MPTP model does not mimic the changes in peripheral catecholamine systems that characterize the human disease.

Parkinson's disease features cardiac sympathetic denervation, as evidenced by decreased myocardial concentrations of radioactivity after administration of the sympathoneural imaging agents ^{123}I-metaiodobenzylguanidine (Satoh et al., 1997; Braune et al., 1998, 1999; Yoshita et al., 1998; Satoh et al., 1999; Druschky et al., 2000; Ohmura, 2000), [N-methyl-^{11}C]meta-hydroxyephedrine (Berding et al., 2003), and 6-[^{18}F]fluorodopamine (Goldstein et al., 2000); virtually absent entry of norepinephrine, the sympathetic neurotransmitter, and dihydroxyphenylalanine and dihydroxyphenylglycol, indices of norepinephrine synthesis and turnover, into the cardiac venous drainage (Goldstein et al., 2000). Myocardial tissue obtained at autopsy of patients with Parkinson's disease contains decreased tyrosine hydroxylase immunoreactivity, a marker of cardiac sympathetic denervation (Orimo et al., 2001, 2002).

The sympathetic denervation in Parkinson's disease seems to be relatively selective for the heart, because ^{123}I-metaiodobenzylguanidine- and 6-[^{18}F]fluorodopamine-derived radioactivity remain unchanged in most other body organs (Goldstein et al., 2000; Reinhardt et al., 2000; Taki et al., 2000), and levels of norepinephrine in antecubital venous plasma are normal (Senard et al., 1993; Goldstein et al., 2002).

The ability of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to produce Parkinsonism and nigrostriatal neurotoxicity has supported the concept of Parkinson's disease resulting from exposure to an environmental toxin. In contrast with extensive literature about central neural dopaminergic neurotoxicity by systemically administered MPTP, relatively little is known about possible toxicity to peripheral catecholamine-producing cells. MPTP treatment has been reported not to deplete adrenomedullary catecholamines (Stoddard et al., 1994). Plasma levels of the norepinephrine metabolite methoxyhydroxyphenylglycol fall relatively little (Bankiewicz et al., 1986). On the other hand, MPTP-treated mice have decreased cardiac accumulation of ^{123}I-metaiodo-

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ABBREVIATIONS: MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

benzylguanidine (Takatsu et al., 2000) and decreased auricular myocardial concentrations of norepinephrine (Luthman and Sundstrom, 1990), consistent with cardiac sympathetic denervation from neurotoxic injury.

The extent and severity of MPTP neurotoxicity are well known to vary substantially across species and strains (Luthman and Sundstrom, 1990). Although MPTP exposure unquestionably evokes Parkinsonism in humans and other primates (Langston et al., 1983; Langston and Ballard, 1983; Ballard et al., 1985; Bankiewicz et al., 1986; Skirboll et al., 1990; Eberling et al., 1997), whether in primates MPTP produces cardioselective sympathetic denervation as in Parkinson's disease has been unknown. This study used 6-[^{18}F]fluorodopamine positron emission tomographic scanning and plasma levels of catecholamines and their deaminated metabolites to assess cardiac and overall sympathetic innervation in rhesus monkeys with severe Parkinsonism from systemic MPTP injection. The results were compared with those in untreated animals or in a positive control monkey treated with 6-hydroxydopamine, which is well known to abolish sympathetic terminal innervation and markedly reduce cardiac 6-[^{18}F]fluorodopamine-derived radioactivity (Goldstein et al., 1991).

Materials and Methods

Subjects. The animal research protocol was approved by the Animal Care and Use Committee of the National Institute of Neurological Disorders and Stroke. A total of six adult male rhesus monkeys (*Macaca mulatta*; body mass 4–6 kg) were studied. Animals were housed singly with a 12-h light/dark cycle and fed Purina monkey chow twice daily with water ad libitum.

MPTP-Induced Parkinsonism. Two monkeys had 6-[^{18}F]fluorodopamine scanning before drug treatment; three had the scanning after chronic Parkinsonism produced in the remote past by systemic MPTP, with no injection within the past 2 years; one had the scanning before MPTP administration, 2 weeks after a series of four doses, when the animal was not yet Parkinsonian, and again about a month later, after another four doses of MPTP, when the animal had severe Parkinsonism; and one had the scanning before and 1 week after systemic administration of 6-hydroxydopamine at a previously identified sympatholytic dose (Goldstein et al., 1991).

Administration of MPTP i.v. produces bilateral damage to the substantia nigra pars compacta and a bilateral Parkinsonian syndrome. A Parkinsonian rating scale was used to quantify the clinical status of the monkeys. The scale includes ratings of 10 Parkinsonian features (tremor, posture, locomotion, hypokinesia, bradykinesia, balance, fine and gross motor skills, startle response, and freezing) and drug-related side effects (hyperkinesia, psychological disturbance, vomiting, and diarrhea). Scores on a 40-point scale were used to classify the monkeys as stage 1 to stage 4, with stage 1 representing mild Parkinsonism, and stage 4 severe bilateral Parkinsonism. All the MPTP-treated monkeys in this study had stage 4 bilateral Parkinsonism. Administration of 6-hydroxydopamine i.v. does not produce Parkinsonian features, because of the blood-brain barrier for catecholamines.

6-[^{18}F]Fluorodopamine Scanning. MPTP-treated animals and controls underwent cardiac sympathetic neuroimaging by 6-[^{18}F]fluorodopamine positron emission tomographic scanning, in a manner similar to that applied in humans (Goldstein et al., 1997a). Briefly, the animal, while under monitored general anesthesia with isoflurane and artificially ventilated, was positioned in an Advance scanner (General Electric, Milwaukee, WI), with the thorax or head in the gantry. 6-[^{18}F]Fluorodopamine (dose in most cases 0.25 mCi) dissolved in approximately 10 ml of normal saline was infused intrave-

nously at a constant rate for 3 min. Dynamic 3-dimensional thoracic scanning was performed for at least 30 min, followed by a static three-dimensional imaging of the head for 15 min.

Plasma Catechols. To assess overall sympathetic innervation, plasma levels of catechols were measured in three untreated monkeys, three monkeys with severe Parkinsonism after remote treatment with MPTP, one monkey before and after development of MPTP-induced Parkinsonism, and one monkey after 6-hydroxydopamine injection. Plasma catechols were assayed as described previously (Holmes et al., 1994).

Results

Untreated monkeys had intense 6-[^{18}F]fluorodopamine-derived radioactivity in the left ventricular myocardium, as well as the liver, spleen, nasopharyngeal mucosa, thyroid gland, and submandibular and parotid salivary glands (Fig. 1; Table 1). Parkinsonian monkeys treated with MPTP in the remote past had myocardial concentrations 6-[^{18}F]fluorodopamine-derived radioactivity that did not differ from those in untreated monkeys (Fig. 2).

In the monkey studied before MPTP administration, after the last of a series of four MPTP injections, before establishment of Parkinsonism (acute phase), and about a month later after another series of four MPTP injections, when the animal was severely Parkinsonian (subacute phase), myocardial 6-[^{18}F]fluorodopamine-derived radioactivity was increased in the acute phase and decreased in the subacute phase (Figs. 1 and 3). Analogous increases in radioactivity were also noted in sympathetically innervated structures of the head (Fig. 1, middle). Plasma levels of catecholamines and their deaminated metabolites were decreased at both time points (Fig. 4).

In the monkey treated with a single dose of 6-hydroxydopamine, 6-[^{18}F]fluorodopamine-derived radioactivity in the
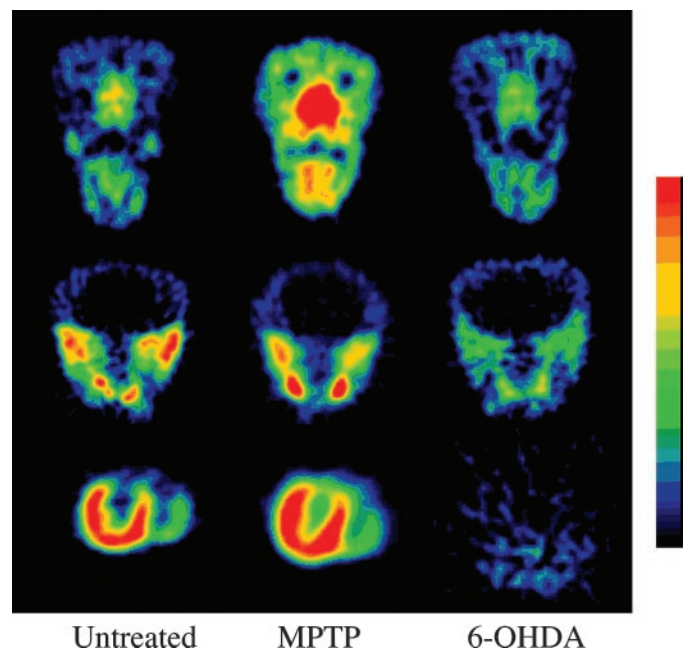

Fig. 1. Coronal positron emission tomographic scans of the head and transverse scans of the heart in an untreated monkey (left), a monkey 1 week after a 1-week series of four injections of MPTP (middle), and a monkey 1 week after a single injection of 6-hydroxydopamine (6-OHDA, right). Images of the head are from 15-min static scans beginning 30 min after injection of 6-[^{18}F]fluorodopamine. Images of the heart are averaged across the first 30 min after initiation of the injection.

TABLE 1

Tissue concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity in the scanning interval 5 to 10 min after initiation of 3-min injection of 6-[^{18}F]fluorodopamine

Numbers in parentheses indicate numbers of animals.

Group	Heart	Liver	Salivary	Thyroid	NP	LV Chamber
Untreated (2)	2,565	1,850	1,164	463	801	1,155
MPTP acute (1)	4,355	3,787	1,233	480	809	2,337
MPTP subacute (1)	1,859	1,342	2,038	847	1,164	1,018
MPTP remote (3)	3,128	3,350	1,205	485	722	878
6-OHDA (1)	1,129	643	746	306	607	1,237

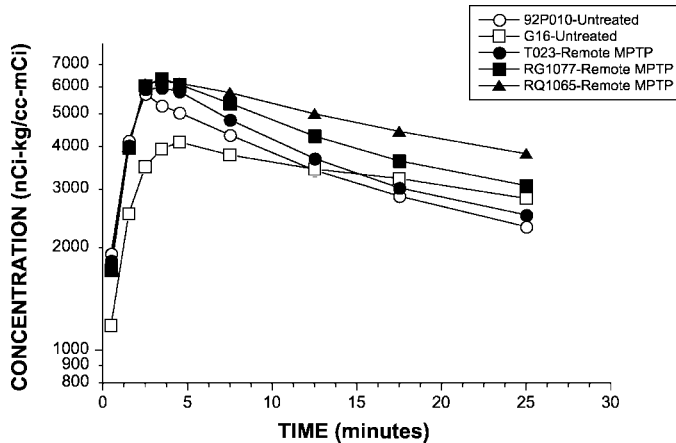LV, left ventricle; NP, nasopharyngeal mucosa; 6-OHDA, 6-hydroxydopamine.

Fig. 2. Left ventricular mean concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity during and after a 3-min injection of 6-[^{18}F]fluorodopamine into untreated monkeys (open circles and squares), and severely Parkinsonian monkeys treated more than 2 years previously with MPTP (filled circles, squares, and triangles).
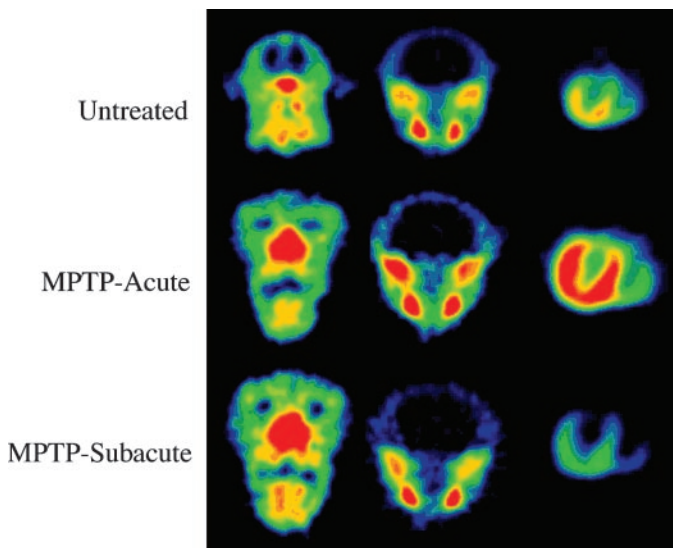

Fig. 3. Coronal positron emission tomographic scans of the head and transverse scans of the heart in an untreated monkey (left), the same monkey 1 week after a series of four injections of MPTP, before establishment of Parkinsonism (MPTP-acute), and the same monkey after a subsequent 5-week series of four more injections of MPTP (MPTP-subacute). Images of the head are from 15-min static scans beginning 30 min after injection of 6-[^{18}F]fluorodopamine. Images of the heart are averaged across the first 30 min after initiation of the injection.

left ventricular myocardium could not be distinguished from that in the chamber, due to both decreased uptake and accelerated loss of radioactivity in the tissue (Fig. 5). There was also decreased radioactivity in sympathetically innervated

structures in the head. The curve relating myocardial 6-[^{18}F]fluorodopamine-derived radioactivity with time differed clearly between this animal and another tested before and after MPTP-induced Parkinsonism, because although the two animals had similarly decreased radioactivity immediately after 6-[^{18}F]fluorodopamine administration, subsequently the MPTP-treated monkey had a decreased rate of loss of the radioactivity, whereas the 6-hydroxydopamine-treated monkey had an increased rate of loss. Thus, by 25 min after initiation of the injection of 6-[^{18}F]fluorodopamine, the myocardial radioactivity concentration in the MPTP-treated monkey was almost 4 times that in the 6-hydroxydopamine-treated monkey.

Plasma levels of norepinephrine, epinephrine, dihydroxyphenylglycol, and dihydroxyphenylacetic acid were all much lower in the acute and subacute phases after MPTP than in untreated monkeys (Fig. 4), the values similar to those after 6-hydroxydopamine treatment. In contrast, in the remote phase, plasma levels of these catechols were only slightly lower than in untreated animals.

Discussion

In this study, unexpectedly, MPTP-treated monkeys with severe, chronic Parkinsonism had about the same amount of cardiac 6-[^{18}F]fluorodopamine-derived radioactivity and concurrently measured plasma levels of catecholamines and their deaminated metabolites as did untreated monkeys. Even in the animal with evidence for loss of cardiac sympathetic innervation subacutely after eight MPTP injections over several weeks, the loss was quantitative, not qualitative. The findings therefore did not mimic those in Parkinson's disease in humans, where most patients have evidence for loss of cardiac sympathetic nerves (Goldstein et al., 2000).

In complete contrast, a monkey treated with 6-hydroxydopamine as a positive control had markedly decreased 6-[^{18}F]fluorodopamine-derived radioactivity throughout the left ventricular myocardium. The two neurotoxins therefore exerted quite different effects on cardiac sympathetic innervation.

Another unexpected finding was that, compared with values in untreated animals, the monkey that received MPTP treatment within a few weeks before 6-[^{18}F]fluorodopamine scanning had very low plasma levels of catecholamines and their deaminated metabolites, yet increased cardiac 6-[^{18}F]fluorodopamine-derived radioactivity. Curves relating cardiac 6-[^{18}F]fluorodopamine-derived radioactivity with time indicated slower loss of radioactivity in MPTP-treated animals. A quite similar pattern of low plasma norepinephrine levels, increased cardiac 6-[^{18}F]fluorodopamine-derived radioactivity, and slowed loss of radioactivity occurs in
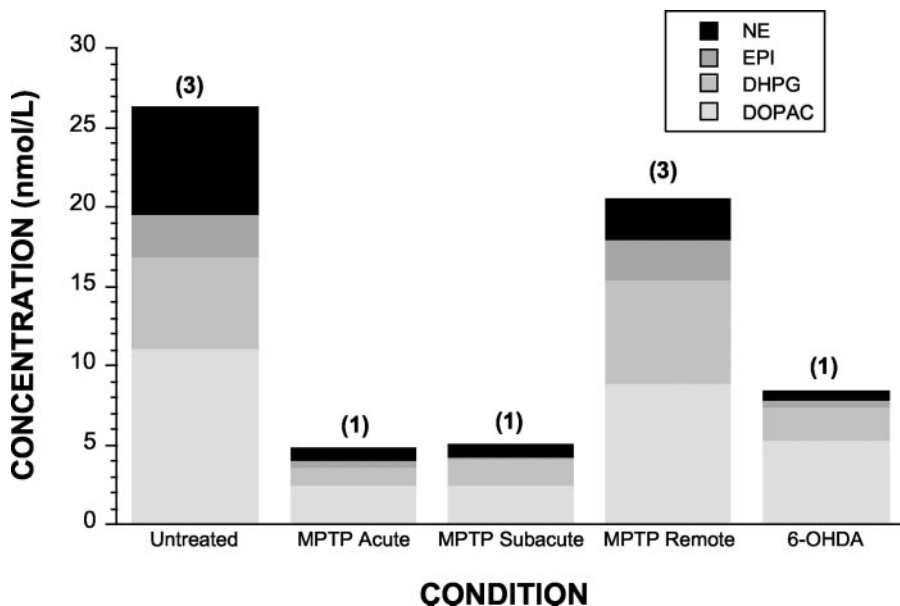
Fig. 4. Plasma levels of catecholamines (norepinephrine, NE; epinephrine, EPI) and deaminated metabolites of catecholamines (dihydroxyphenylglycol, DHPG; dihydroxyphenylacetic acid, DOPAC) in monkeys that were untreated; treated with MPTP acutely, subacutely, or remotely; or treated with 6-hydroxydopamine (6-OHDA). Numbers above bars indicate the numbers of animals.
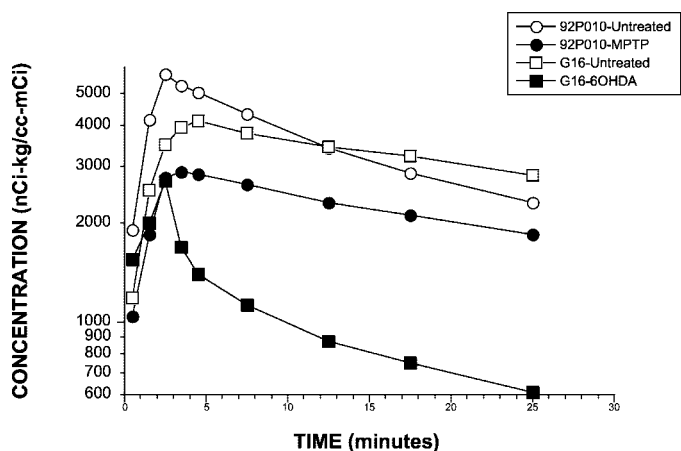

Fig. 5. Left ventricular concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity during and after a 3-min injection of 6-[^{18}F]fluorodopamine in untreated monkeys (92P010, open circles; G16, open squares), monkey 92P010 after production of severe Parkinsonism by repeated injections of MPTP over 5 weeks (filled circles), and monkey G16 1 week after administration of 6-hydroxydopamine (filled squares).

healthy volunteers and in anesthetized dogs during i.v. infusion of trimethaphan to block ganglionic neurotransmission (Goldstein et al., 1990, 1993, 1997b). The results, and similarities to those during ganglion blockade in other studies, lead us to propose early neurotoxic effects of MPTP at the level of preganglionic or ganglionic neurotransmission, resulting in decreased exocytotic release of norepinephrine from intact cardiac sympathetic terminals. By an analogous mechanism, MPTP would decrease adrenomedullary secretion concurrently, resulting in low plasma epinephrine levels.

After repeated administration of MPTP over several weeks in one monkey, plasma levels of catechols remained very low, whereas cardiac 6-[^{18}F]fluorodopamine-derived radioactivity fell to subnormal levels. We interpret this pattern in terms of a subacute phase involving actual loss of cardiac sympathetic terminals. Because of continued slow loss of cardiac 6-[^{18}F]fluorodopamine-derived radioactivity from remaining terminals, the extent of the extent of downward displacement of the time-activity curve probably underestimated the ex-

tent of decrease in neuronal uptake of 6-[^{18}F]fluorodopamine. The pattern in this subacute phase bore a striking resemblance to that in healthy volunteers and in anesthetized dogs after treatment with desipramine to block the cell membrane norepinephrine transporter (Goldstein et al., 1990, 1993, 1997b). Desipramine exerts two major effects on sympathetic neuroeffector function. One is the classical blockade of neuronal reuptake of norepinephrine; the second, perhaps generally less well appreciated but clearly established, is decreased central sympathetic outflow (Finberg et al., 1990; Szabo and Schultheiss, 1990; Esler et al., 1991; Lavian et al., 1991). The results, and similarities to those after desipramine in other studies, lead us to propose that the subacute phase after MPTP injection involves a postganglionic lesion, with decreased activity of the cell membrane norepinephrine transporter and coupled with persistence of a preganglionic or ganglionic lesion producing decreased nerve traffic-dependent release from sympathetic terminals. The 6-[^{18}F]fluorodopamine scanning results cannot distinguish between cardiac sympathetic denervation and inhibition of the cell membrane norepinephrine transporter in this phase.

Over the course of many months or years from the last administration of MPTP, sympathetic and adrenomedullary cells seem to recover or regrow, so that cardiac 6-[^{18}F]fluorodopamine-derived radioactivity and plasma levels of catecholamines eventually approximately normalize. Slightly increased cardiac 6-[^{18}F]fluorodopamine-derived radioactivity and slightly decreased plasma levels of catechols in this phase might reflect a residual preganglionic lesion, corresponding to chronic Parkinsonism. The finding of long-term recovery of peripheral catecholamine-producing cells fits with evidence for recovery of behavioral and central dopaminergic function in primates by a year after MPTP injection (Elsworth et al., 2000).

6-Hydroxydopamine rapidly destroys sympathetic nerve terminals, as confirmed by virtually undetectable 6-[^{18}F]fluorodopamine-derived radioactivity at a time that would correspond to the acute phase after MPTP injection. Because they are catecholamines, neither 6-hydroxydopamine nor 6-[^{18}F]fluorodopamine penetrates the blood-brain barrier. In

fact, as demonstrated in the present study, 6-[^{18}F]fluorodopamine scanning reveals the central nervous system by negative contrast. After sympatholysis by 6-hydroxydopamine, not only was the peak myocardial concentration of 6-[^{18}F]fluorodopamine-derived radioactivity decreased but also the radioactivity declined further, rapidly, to even lower levels, confirming previous reports in nonprimate laboratory animals (Chang et al., 1990; Goldstein et al., 1991). In marked contrast, as noted above, after MPTP cardiac 6-[^{18}F]fluorodopamine-derived radioactivity declined quite slowly. If lack of entry of 6-hydroxydopamine into the brain explained the difference in time-activity curves for cardiac 6-[^{18}F]fluorodopamine-derived radioactivity, then one would deduce that MPTP decreases exocytotic release from sympathetic nerves because of a neurotoxic effect in the central nervous system. Whether MPTP destroys brainstem catecholaminergic neurons descending to spinal preganglionic neurons remains unknown.

The cardiac sympathetic neuroimaging and plasma catecholamine findings in the primate MPTP model differed importantly from those reported previously in clinical Parkinson's disease. In Parkinson's disease, loss of cardiac sympathetic innervation is an early finding (Druschky et al., 2000; Ohmura, 2000; Reinhardt et al., 2000; Takatsu et al., 2000), without evidence for a premonitory phase involving a preganglionic lesion; sympathetic denervation is relatively selective for the heart, with normal plasma levels of catecholamines (Goldstein et al., 2000; Takatsu et al., 2000; Taki et al., 2000); and cardiac sympathetic denervation progresses over time, with loss of terminals in the left ventricular free wall or apex occurring faster than loss in the basal anteroseptal myocardium (Li et al., 2002). Finally, although after heart transplantation some cardiac sympathetic reinnervation can occur (Kaye et al., 1993), no report to date has noted evidence for recovery of cardiac sympathetic innervation in humans with Parkinson's disease.

In patients with MPTP-induced Parkinsonism, the movement disorder can worsen over years, associated with further loss of 6-[^{18}F]fluorodopa-derived radioactivity in the nigrostriatal system (Vingerhoets et al., 1994). This might reflect prolonged neurotoxicity, rather than simply an additive effect of aging (Cordes et al., 1994). Whether patients with MPTP-induced Parkinsonism have evidence for cardiac sympathetic denervation remains unknown.

Neither MPTP nor 6-hydroxydopamine provides a completely satisfactory animal model of peripheral catecholaminergic dysfunction in Parkinson's disease. Systemic administration of MPTP is inadequate, because in the acute phase there is a preganglionic lesion resulting in low plasma levels of catecholamines and increased retention of catecholamines; in the subacute phase there may be decreased cardiac neuronal uptake of catecholamines but if so this occurs without accelerated loss; in the chronic phase there is recovery. Systemic administration of 6-hydroxydopamine also is inadequate, because the blood brain barrier for catecholamines prevents sufficient entry of the neurotoxin into the central nervous system to produce Parkinsonism.

This study involved only a very small number of animals. In designing the experiment, we had to take into account not only statistical power but also the expense and scarcity of 6-[^{18}F]fluorodopamine scanning, competition with other clinical and preclinical research protocols involving 6-[^{18}F]fluorodopamine scanning, and financial and ethical limitations on treating and maintaining primates with MPTP-induced severe Parkinsonism. These considerations led to an extraordinarily constrained experiment, consisting mainly of demonstrations, with inadequate numbers for statistically meaningful comparisons.

In summary, nonhuman primates treated with MPTP seem to undergo phases of peripheral catecholaminergic dysfunction. First to develop, over the course of a few weeks from a single injection, is a preganglionic lesion, resulting in decreased exocytotic release of catecholamines from intact cells and if anything increased retention of cardiac 6-[^{18}F]fluorodopamine-derived radioactivity. Over the course of months of repeated treatment, some loss of cardiac sympathetic terminals takes place, with persistence of the preganglionic lesion, resulting in a noticeable but not total loss of cardiac 6-[^{18}F]fluorodopamine-derived radioactivity and continued low plasma levels of catecholamines. In a long-term recovery phase, both cardiac 6-[^{18}F]fluorodopamine-derived radioactivity and plasma levels of catecholamines revert toward normal. The acute phase corresponds with behavioral signs of early Parkinsonism, the subacute and remote phases with established Parkinsonism.

The field of neurotoxin-induced Parkinsonism, as a model of the clinical condition, would benefit from identification of a substance that destroys cardiac sympathetic noradrenergic nerves and also penetrates the blood-brain barrier to destroy nigrostriatal dopamine cells as early effects.

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