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Short- and long-term changes in striatal and extrastriatal dopamine uptake sites in the MPTP-treated common marmoset

Kanna K. Gnanalingham [a], Nicole A. Milkowski [b], Lance A. Smith [a], A. Jackie Hunter [b], Peter Jenner [a,*], C. David Marsden [c]

[a] *Parkinson's Disease Society Experimental Research Laboratories, Pharmacology Group, Biomedical Sciences Division, King's College, London, UK*
[b] *SmithKline Beecham Pharmaceuticals, Harlow, UK*
[c] *University Department of Clinical Neurology, National Hospital for Neurology, Queen Square, London, UK*

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Abstract

The 'short-term' (15–30 days) and 'long-term' (18–42 months) effects of the systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on [^{3}H]mazindol binding to dopamine uptake sites was investigated in the common marmoset. In the 'short-term' MPTP-treated group, [^{3}H]mazindol binding was reduced in the caudate-putamen (by −82 to −98% with respect to controls), substantia nigra pars compacta (−71 to −84%), ventral tegmental area (−72%) and nucleus accumbens (−54%). [^{3}H]Mazindol binding in the globus pallidus, frontal cortex and substantia nigra pars reticulata was much lower and was unaffected by MPTP treatment. In the 'long-term' MPTP-treated group, [^{3}H]mazindol binding was still greatly reduced in the substantia nigra pars compacta (by −76 to −89%), ventral tegmental area (−71%) and most of the caudate-putamen (−69 to −98%), although the reduction in [^{3}H]mazindol binding in the nucleus accumbens (−27%) and rostroventral caudate nucleus (−69%) was less than in the 'short-term' MPTP-treated group. The motor deficits induced by MPTP treatment in the common marmoset are largely reversible with increasing survival times (Ueki et al., 1989, Neuropharmacology 28, 1089). In the present study, the apparent 'recovery' in [^{3}H]mazindol binding in the rostroventral caudate nucleus and nucleus accumbens may indicate regeneration of dopamine neurone terminals in these regions and this may contribute to the behavioural recovery seen in this primate model of Parkinson's disease.

Keywords: MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine); [^{3}H]Mazindol binding; Autoradiography; Basal ganglion; Motor recovery; (Marmoset)

1. Introduction

Administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to human and non-human primates produces many of the behavioural, biochemical and neuropathological changes associated with idiopathic Parkinson's disease (Davis et al., 1979; Burns et al., 1983; Langston et al., 1984; Close et al., 1985; Jenner et al., 1984; Schneider et al., 1987; Pifl et al., 1988). Thus, in MPTP-treated common marmosets there is severe hypo/bradykinesia, rigidity, a flexed posture and loss of vocalisation, although tremor is less apparent (Close et al., 1985; Jenner et al., 1984). In the midbrain, there is severe loss of tyrosine hydroxylase positive neurones in the substantia nigra pars compacta but a partial loss in the ventral tegmental area (Waters et al., 1987). Correspondingly, dopamine levels are grossly depleted in the caudate-putamen and partial losses occur in the nucleus accumbens (Rose et al., 1989a,b). The noradrenergic nucleus, locus coeruleus is unaffected in MPTP-treated marmosets (Waters et al., 1987; Rose et al., 1993).

Unlike in idiopathic Parkinson's disease, however, MPTP-treated marmosets show a gradual recovery of motor function following subacute MPTP treatment. At 12–18 months post-MPTP treatment the motor activity of these animals is similar to that of untreated animals (Ueki et al., 1989; Rose et al., 1989a). Behavioural recovery has been reported in other species

* Corresponding author. Pharmacology Group, Biomedical Sciences Division, King's College, Manresa Road, London SW3 6LX, UK. Tel. 071-333 4716, fax 071-376 4736.

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of MPTP-treated primates (Eidelberg et al., 1986; Kurlan et al., 1991), although Degryse and Colpaert (1986) have reported a progressive worsening of motor deficits in a 20-year-old MPTP-treated cynomolgus monkey. The mechanisms underlying behavioural recovery are not well understood. We have previously reported that behavioural improvement in MPTP-treated marmosets is associated with a recovery of tyrosine hydroxylase positive neurones in the substantia nigra pars compacta (Waters et al., 1987) and of dopamine levels in the caudate-putamen and more especially the nucleus accumbens (Rose et al., 1989a,b). In the marmoset, although dopamine turnover is initially increased in the caudate-putamen and nucleus accumbens, this is not apparent at 3–4 months post-MPTP treatment, when there is behavioural recovery (Rose et al., 1989a,b). Consequently, the apparent 'recovery' of dopamine levels may reflect increased synthesis/release of dopamine by the surviving dopaminergic terminals and/or a regeneration of terminals. Indeed, in a preliminary study, we found an inverse correlation between the loss of [^{3}H]mazindol binding in the caudate nucleus of the MPTP-treated marmosets and the time elapsed after MPTP treatment (Gnanalingham et al., 1993).

In the present study, we have investigated in detail the relationship between the changes in striatal and extrastriatal [^{3}H]mazindol binding to dopamine uptake sites in common marmosets, at 'short-term' (15–30 days) and 'long-term' (18–42 months) following MPTP treatment.

2. Materials and methods

2.1. MPTP treatment

Adult common marmosets (*Callithrix jacchus*; 3–8 years of age) of both sexes were utilised in this study. Six animals were used as controls. Ten animals were treated with MPTP hydrochloride for 5 days (total dose 8–12 mg/kg s.c.).

2.2. Preparation of brain sections

At various time points after MPTP treatment (15–30 days, the 'short-term MPTP' group and at 18–42 months, the 'long-term MPTP' group; $n = 5$) the marmosets were killed by anaesthetic overdose (sodium pentobarbitone; 100 mg/kg i.p.). The brains were rapidly removed, frozen in isopentane at $-40°$ C and finally stored at $-70°$ C. Several of the animals were also part of a 2-deoxyglucose study, investigating cerebral glucose metabolism (manuscript in preparation). This involved the administration of 50 μCi/kg [^{14}C]2-deoxyglucose (in 0.9% saline i.v.), 45 min before a lethal dose of sodium pentobarbitone (100 mg/kg i.p.).

Coronal sections through the basal ganglia of the marmoset brain were cut using a cryostat (10 μM; Bright Instruments; $-20°$ C), thaw mounted onto subbed slides (with 5% gelatin and 0.5% chromic potassium) and stored at $-70°$ C. Some sections were also stained with cresyl violet to aid the identification of brain regions being investigated.

2.3. [^{3}H]Mazindol autoradiography

[^{3}H]Mazindol binding was carried out as described previously (Javitch et al., 1985; Gnanalingham et al., 1993). On the day of the experiment, the frozen sections were allowed to thaw and dried in a stream of cool air. To 'wash-out' the [^{14}C]2-deoxyglucose, the sections were prewashed for 2×5 min in ice-cold 50 mM Tris-HCl buffer (pH 7.4), preincubated for a further 2×8 min in fresh buffer and dried in a stream of cold air (Crossman et al., 1984; Robertson et al., 1990). The brain sections were then incubated for 50 min at 4° C in 50 mM Tris-HCl buffer (pH 7.9) containing 300 mM NaCl, 5 mM KCl, 50 nM desipramine hydrochloride (to block noradrenaline uptake sites) and 4 nM [^{3}H]mazindol. Incubations were terminated by washing sections in 2×1 min ice-cold Tris-HCl buffer (pH 7.4) and a further rinse in distilled water. Non-specific binding was determined in the presence of 10 μM mazindol (approximately 30% non-specific binding in the caudate-putamen) (Javitch et al., 1985). Non-specific binding observed with mazindol is comparable with that of the structurally dissimilar dopamine uptake inhibitor, GBR 12909 (Shimizu and Prasad, 1991).

The wet sections were rapidly dried under a stream of cool air and exposed together with ^{3}H standards (Amersham) to tritium hyperfilm (Amersham), for 4–6 weeks at 3–4° C. At the end of the exposure period the autoradiographs were developed, fixed (D19 and unifix-Kodak) and analysed densitometrically (Imaging Research, Ontario, Canada).

Brain regions at the following rostro-caudal levels were analysed (Stephan et al., 1980): level 1 (> A 12.5) – frontal cortex; level 2 (A 11.5) – rostral caudate-putamen and nucleus accumbens; level 3 (A 8.5) – main body of putamen and head of caudate; level 4 (A 8.0) – lateral and medial segments of globus pallidus; level 5 (A 5.5) – substantia nigra pars compacta, ventral tegmental area and substantia nigra pars reticulata.

2.4. Statistics

The results for [^{3}H]mazindol binding were analysed by one-way analysis of variance (ANOVA) and post-hoc Duncan's multiple range test.

2.5. Materials

Materials used were supplied by the following companies: [^{3}H]mazindol (25 Ci/mmol) from Dupont New England Nuclear; MPTP hydrochloride from Research Biochemicals; desipramine hydrochloride from Sigma. Mazindol was a gift from Sandoz (UK). All other chemicals were obtained from standard commercial sources.

3. Results

Due to a shortage of brain tissue, saturation analysis of [^{3}H]mazindol binding was not carried out. However, in accordance with previous observations (Alexander et al., 1992), it is assumed that changes in [^{3}H]mazindol binding in the MPTP treatment groups reflect differences in the density of dopamine uptake sites and not affinity.

In control brain, high levels of specific [^{3}H]mazindol binding were found in the caudate and putamen (Figs. 1 and 2). Moderate levels were detected in the nucleus accumbens and substantia nigra pars compacta, while the substantia nigra pars reticulata, ventral tegmental area and frontal cortex demonstrated lower levels of specific [^{3}H]mazindol binding (Table 1 and Figs. 1 and 2). In the lateral and medial segments of globus pallidus negligible levels of specific [^{3}H]mazindol binding were observed (Table 1).

In the 'short-term' MPTP-treated group, [^{3}H]-mazindol binding was severely reduced in all subregions of the caudate and putamen (−82% to −98%; $P < 0.01$; Figs. 1 and 2). Similar losses, though less severe, were also observed in the nucleus accumbens (−54%; $P < 0.01$), substantia nigra pars compacta (−71 to −84%; $P < 0.01$) and ventral tegmental area (−72%; $P < 0.05$; Table 1 and Figs. 1 and 2). [^{3}H]Mazindol binding in the frontal cortex, lateral and medial segments of globus pallidus and the substantia nigra pars reticulata was not significantly affected by MPTP treatment (Table 1).

In the 'long-term' MPTP-treated group, [^{3}H]-mazindol binding was also reduced in the caudate-putamen (−69 to −98%; $P < 0.01$), nucleus accumbens (−27%; $P < 0.01$), substantia nigra pars compacta (−76 to −89%; $P < 0.01$) and ventral tegmental area (−71%; $P < 0.05$) (Table 1 and Figs. 1 and 2). However, in the 'long-term' MPTP-treated group, [^{3}H]mazindol binding in the nucleus accumbens

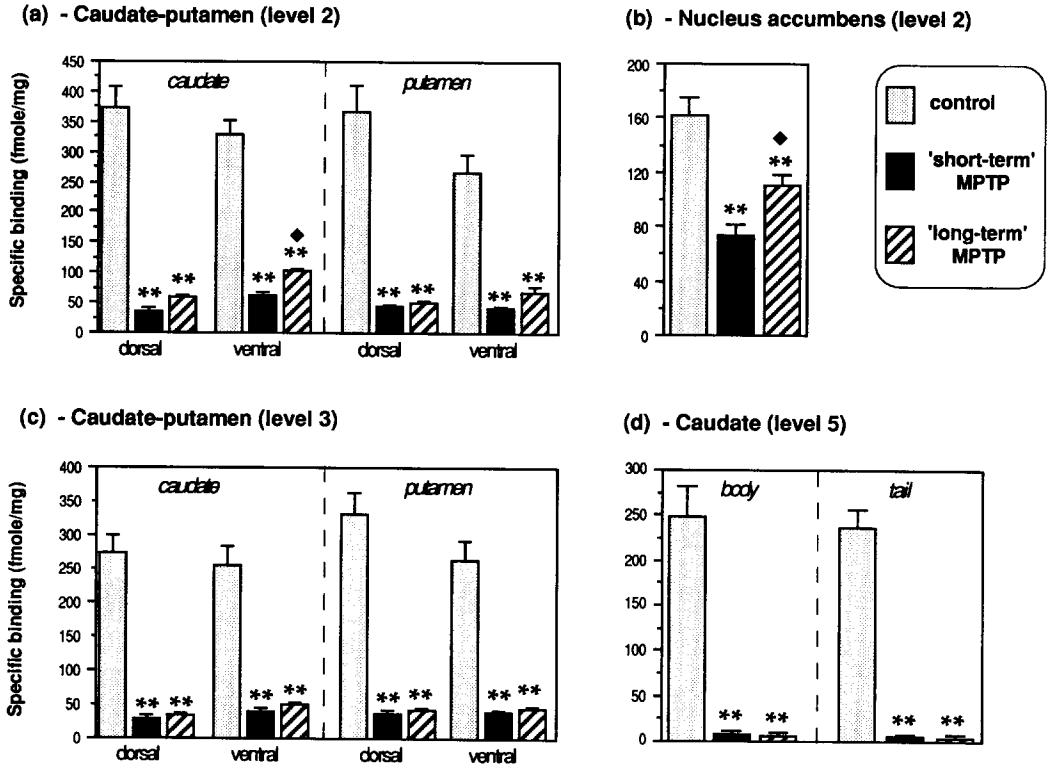

Fig. 1. Effect of MPTP treatment on specific [^{3}H]mazindol binding (expressed in fmol/mg tissue) at 4 nM concentration in the caudate, putamen (levels 2, 3 and 5) and nucleus accumbens (level 2). Non-specific binding was defined in the presence of 10 μM mazindol. The MPTP-treated marmosets were killed at 15–30 days ('short-term' MPTP group) or 18–42 months post-MPTP treatment ('long-term' MPTP group). The results are the mean ± S.E.M. values for groups of 5–6 animals; $^{**}P < 0.01$ vs. control group; $P < 0.05$ vs. 'short-term' MPTP group; one-way ANOVA and post-hoc Duncan's multiple range test.

(−27%) and rostroventral caudate (−69%; level 2) was significantly higher than the corresponding values for the 'short-term' MPTP group (−54%, nucleus accumbens and −82%, rostroventral caudate; $P < 0.05$; Figs. 1 and 2).

The percent loss in [^{3}H]mazindol binding (expressed as percent control values) in the various subregions of the caudate-putamen and nucleus accumbens of the 'short-term' MPTP-treated group positively correlated with the corresponding values in the 'long-term' MPTP group ($P < 0.001$; Fig. 3).

4. Discussion

Although, the MPTP-treated primate mimics many of the features of idiopathic Parkinson's disease, there are reports of a gradual and variable behavioural re-

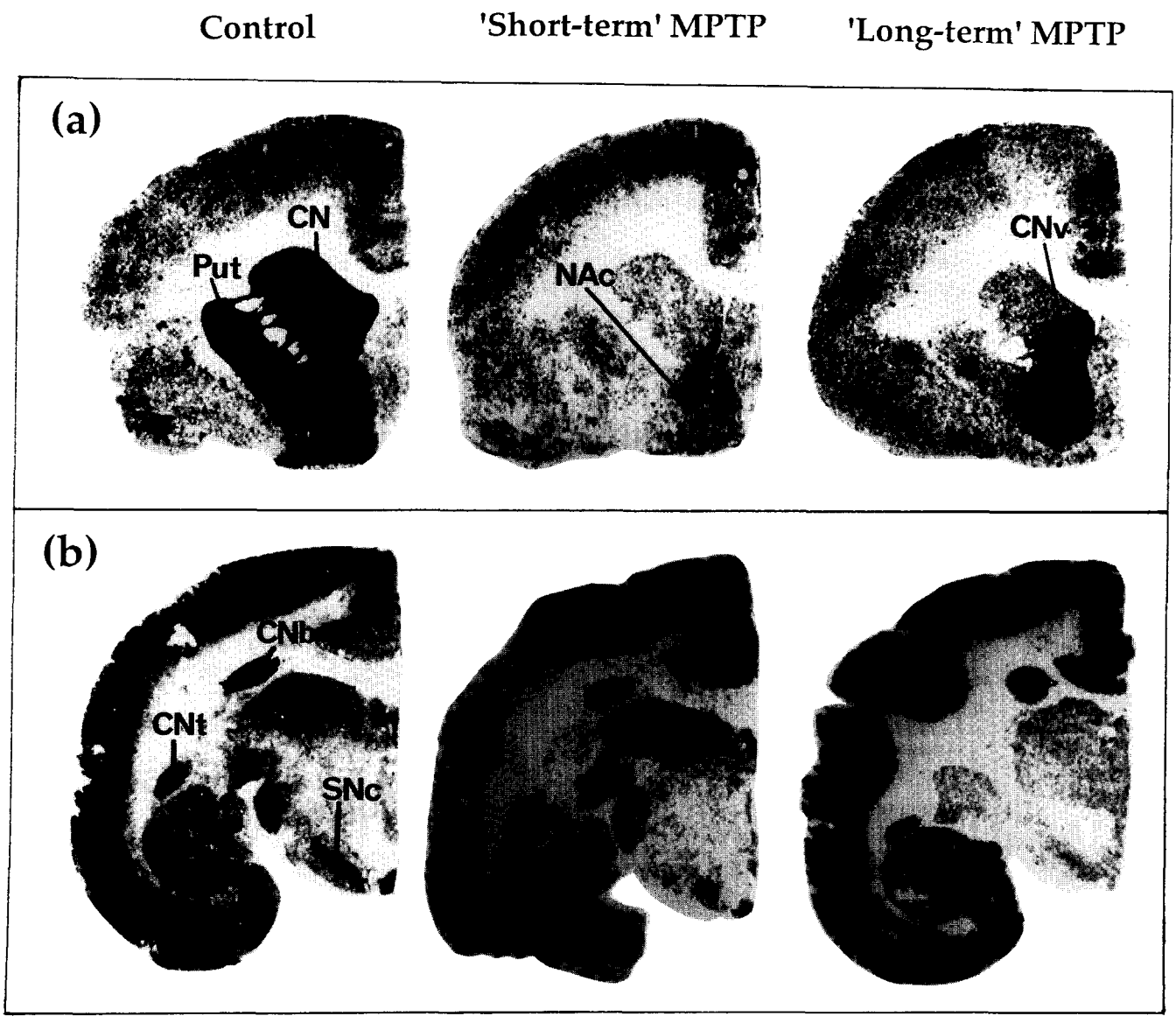

Fig. 2. Direct reversal prints of [^{3}H]mazindol binding autoradiographs taken from control and MPTP-treated marmosets at 20 days ('short-term' MPTP) and at 33 months post-MPTP treatment ('long-term' MPTP). The effect of MPTP treatment on [^{3}H]mazindol binding in the caudate-putamen, nucleus accumbens (a – level 2; A11.5) and substantia nigra pars compacta/ventral tegmental area complex (b – level 5; A5.5) are shown. At 20 days post-MPTP, there is pronounced loss of [^{3}H]mazindol binding in the caudate-putamen and substantia nigra pars compacta/ventral tegmental area complex, but more partial losses in the nucleus accumbens. At 33 months post-MPTP, although [^{3}H]mazindol binding remains reduced in the caudate-putamen, substantia nigra pars compacta/ventral tegmental area complex and nucleus accumbens, the loss in the ventral caudate nucleus and the nucleus accumbens is less than at 20 days post-MPTP. (Abbreviations used: CN – caudate nucleus; CNb – body of caudate nucleus; CNt – tail of caudate nucleus; CNv – ventral caudate nucleus; NAc – nucleus accumbens; Put – putamen; SNc – substantia nigra pars compacta.)

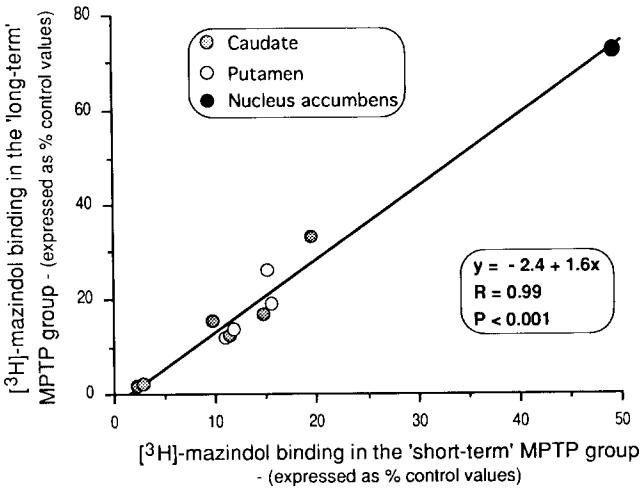

Fig. 3. Correlation between the percent loss in [^{3}H]mazindol binding (expressed as percent control values) in the various subregions of the caudate-putamen and nucleus accumbens of the 'short-' and 'long-term' MPTP-treated groups ($n = 11$; $r = 0.99$; $P < 0.001$). The control values for the nucleus accumbens and caudate-putamen were 162 and 250–372 fmol/mg tissue, respectively.

covery in both MPTP-treated monkeys as well as in human cases of MPTP intoxication (Rose et al., 1989a; Ueki et al., 1989; Kurlan et al., 1991; Eidelberg et al., 1986; Langston et al., 1983; Davis et al., 1979). The mechanism(s) underlying this phenomenon is/are poorly understood.

In the MPTP-treated marmoset, there was severe depletion of [^{3}H]mazindol binding in the caudate-putamen and the substantia nigra pars compacta/ventral tegmental area complex (particularly in the lateral substantia nigra pars compacta). However, the decrease in [^{3}H]mazindol binding was smaller or not apparent in other extrastriatal areas including the nucleus accumbens, substantia nigra pars reticulata, lateral and medial segments of globus pallidus and frontal cortex. Evidently, these extrastriatal areas with known dopaminergic innervation are more variably affected in the MPTP-treated marmoset, an observation consistent with corresponding studies in the MPTP-treated marmoset and other species of monkeys (Mitchell et al., 1985; Pifl et al., 1990, 1992; Parent et al., 1990; Alexander et al., 1992). Moreover, in the 'long-term' MPTP-treated group, [^{3}H]mazindol binding in the rostroventral caudate nucleus (level 2) and more especially in the nucleus accumbens was increased with respect to the 'short-term' MPTP-treated group. These findings confirm and extend our earlier observations (Gnanalingham et al., 1993), and are consistent with the near-complete recovery in locomotor activity and motor disability scores of MPTP-treated marmosets, at 12–18 months post-MPTP treatment (Ueki et al., 1989; Waters et al., 1987).

Interestingly, the percent loss in [^{3}H]mazindol binding (expressed as percent control values) in the various subregions of the caudate-putamen and nucleus accumbens of the 'short-term' MPTP-treated group positively correlated with the corresponding values in the 'long-term' MPTP group. Indeed, the gradient of this correlation was greater than 1, indicating that brain regions such as the rostroventral caudate and nucleus accumbens with smaller losses in [^{3}H]mazindol binding (and by implication a substantial population of surviving dopaminergic nerve terminals), also exhibited greater recovery in [^{3}H]mazindol binding. The 'long-term' recovery in [^{3}H]mazindol binding in these brain regions suggests an increase in dopamine uptake sites probably due to dopaminergic terminal regeneration and/or axonal sprouting. Such an interpretation is consistent with the observation that in MPTP-treated marmosets at 3–4 months post-MPTP, the levels of

Table 1
Effect of MPTP treatment on specific [^{3}H]mazindol binding (expressed in fmol/mg tissue ± S.E.M.) at 4 nM concentration

Brain region	Control	MPTP-treated (% change from control)	
		Short-term	Long-term
1. Frontal cortex	43 ± 11	45 ± 6	35 ± 8
4. Globus pallidus – lateral segment	8 ± 2	7 ± 1	6 ± 2
4. Globus pallidus – medial segment	9 ± 3	14 ± 3	8 ± 4
5. Substantia nigra pars compacta – medial	119 ± 21	35 ± 0 [b] (−71)	29 ± 6 [b] (−76)
– lateral	81 ± 30	10 ± 3 [b] (−84)	7 ± 5 [b] (−89)
5. Substantia nigra pars reticulata – medial	37 ± 16	12 ± 2	7 ± 4
– lateral	37 ± 17	13 ± 5	13 ± 7
5. Ventral tegmental area	58 ± 15	16 ± 6 [a] (−72)	17 ± 7 [a] (−71)

Non-specific binding was defined in the presence of 10 μM mazindol. The MPTP-treated marmosets survived for 15–30 days (the 'short-term' MPTP group) or 18–42 months (the 'long-term' MPTP group). The results are the mean values for groups of 5–6 animals; [a] $P < 0.05$, [b] $P < 0.01$ compared to control group; one-way ANOVA and post-hoc Duncan's multiple range test.

dopamine in the caudate-putamen (11–16% of controls) and more especially the nucleus accumbens (73% of controls) are greater than that at 10 days post-MPTP treatment (caudate-putamen, 1% and nucleus accumbens, 17%) (Rose et al., 1989a). In the same study, dopamine turnover was unaffected in the caudate-putamen and nucleus accumbens at 3–4 months post-MPTP treatment (Rose et al., 1989a). However, the survival times of the animals in the 'long-term' MPTP-treated group of the present study are considerably greater (18–42 months) than in the study by Rose et al. (1989a). Consequently, it is not entirely certain whether the regeneration of dopaminergic neurone terminals (as suggested by the present findings) contributes to the improvement in dopamine levels, apparent as early as 3–4 months post-MPTP. Nevertheless, there appears to be recovery in dopamine function especially in the nucleus accumbens, which in rodent studies has been implicated in the generation of locomotor activity (Arnt, 1987). Thus, recovery above a 'critical threshold' level in dopaminergic function in the nucleus accumbens may underlie the behavioural recovery seen in the MPTP-treated monkey, although other hypotheses such as compensatory changes in post-synaptic neurones that receive dopamine innervation and/or recruitment of alternative motor pathways may also contribute to this phenomenon (Eidelberg et al., 1986).

Surprisingly, in the 'long-term' MPTP-treated group there was no recovery in [^{3}H]mazindol binding in the substantia nigra pars compacta/ventral tegmental area complex, despite the reported recovery of neuronal cell bodies in these regions in the MPTP-treated marmoset (Waters et al., 1987; Gnanalingham et al., 1993). Although this suggests that the recovery in dopamine uptake sites is more likely in dopamine neurone terminals than cell bodies, the greater variability of [^{3}H]mazindol binding in the substantia nigra pars compacta and ventral tegmental area may have masked any recovery. Moreover, as assessed by tyrosine hydroxylase staining, not all the perikarya in the substantia nigra pars compacta of control marmosets are dopaminergic, although MPTP treatment also affects this neuronal population (Waters et al., 1987). Consequently, a lack of recovery in [^{3}H]mazindol binding in the substantia nigra pars compacta/ventral tegmental area complex of the 'long-term' MPTP group may indicate recovery in non-dopaminergic neurones in these nuclei.

With respect to the present findings, two recent observations may be of relevance. Firstly, it has been reported that the most pronounced differences in dopamine levels between symptomatic and asymptomatic MPTP-treated monkeys are seen in the extrastriatal areas including the ventral tegmental area, globus pallidus and nucleus accumbens (Pifl et al., 1990, 1992). Therefore, in the 'long-term' MPTP-treated marmosets a return to relatively 'normal' dopamine function in the nucleus accumbens may underlie their more 'normal' behavioural patterns. Secondly, in MPTP-treated squirrel monkeys, bilateral 6-hydroxydopamine lesions of the locus coeruleus reduces the recovery in behaviour, dopamine levels in the caudate-putamen and dopaminergic neurones in the substantia nigra pars compacta (Mavridis et al., 1991). While, the mechanism(s) underlying this effect is not known, this clearly implicates an important role for the noradrenergic system in the evolution of MPTP toxicity. In the MPTP-treated marmoset the locus coeruleus is unaffected, although in MPTP-treated squirrel monkeys and in macaques variable destruction of the locus coeruleus has been reported (Waters et al., 1987; Rose et al., 1993; Mitchell et al., 1985; Forno et al., 1986). Thus, in the MPTP-treated marmoset an intact locus coeruleus may aid recovery in dopamine function and behaviour. Moreover, both these observations also suggest that the variability in the behavioural recovery of MPTP-treated monkeys between different studies may reflect differences in the effects of MPTP in the locus coeruleus and/or on dopamine levels extrastriatally (Kurlan et al., 1991; Eidelberg et al., 1986; Degryse and Colpaert, 1986). Conversely, the progressive nature of idiopathic Parkinson's disease may indicate greater dopamine losses in the extrastriatal areas and more frequent pathological changes in the locus coeruleus of the parkinsonian brain (Agid et al., 1987; Jellinger, 1986).

In conclusion, the present study demonstrates that in the MPTP-treated marmoset there is recovery in dopamine uptake sites in the rostroventral caudate nucleus and nucleus accumbens, at longer survival times. This is consistent with the recovery in dopamine levels in these regions and with the behavioural recovery seen in this primate model.

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