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TRANSIENT DEPLETION OF NUCLEUS ACCUMBENS DOPAMINE CONTENT MAY CONTRIBUTE TO INITIAL AKINESIA INDUCED BY MPTP IN COMMON MARMOSETS

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Abstract—Acute treatment of common marmosets with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) caused an initial profound akinesia and other motor deficits. However, over the following months akinesia gradually disappeared although the animals remained clumsy and poorly coordinated. At 10 days following MPTP treatment there was a profound decrease in the dopamine, HVA and DOPAC content of the caudate nucleus, putamen and nucleus accumbens. By 3–4 months following MPTP treatment the animals had largely recovered from their akinesia, but the caudate nucleus and putamen dopamine, HVA and DOPAC content remained low. In contrast, the dopamine content of the nucleus accumbens had returned towards normal and the metabolite levels were higher than at 10 days. No overall alterations in 5HT or 5HIAA levels were observed at either time point. The transient and reversible nature of dopamine loss in the nucleus accumbens may contribute to the initial profound akinesia exhibited by common marmosets treated with MPTP. The restoration of dopamine levels in the nucleus accumbens may be partially responsible for the subsequent recovery of motor function that occurs in MPTP-treated marmosets.

Administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to man and non-human primate species induces destruction of nigral dopamine containing cells accompanied by parkinsonian motor deficits [1–6]. In the common marmoset MPTP initially induces akinesia, rigidity, postural abnormalities and occasionally postural tremor [7]. Histological examination of the marmoset brain shows MPTP to markedly reduce the dopamine cell content in substantia nigra with smaller variable effects on the ventral tegmental area [8, 9]. However, despite obvious initial neurotoxicity, motor function gradually improves over the following weeks, particularly the akinesia component of the parkinsonian syndrome. Others have also suggested that functional recovery occurs following MPTP treatment of macaque monkeys [10].

Why many aspects of motor activity should recover after acute MPTP administration is not clear. The effects of MPTP on nigral dopamine cells are permanent, as judged by a persistent reduction in caudate-putamen dopamine content and [^{3}H]dopamine uptake into synaptosomal preparations of the putamen [7, 11]. One explanation is that there is an increase in striatal dopamine turnover as a compensatory mechanism by remaining dopamine neurones [11]. Thus, some weeks following MPTP treatment of common marmosets, when motor function was improving, the ratio of dopamine metabolites to dopamine was increased compared to earlier time points [11]. However, there was also a profound acute decrease in dopamine levels in the nucleus accumbens in MPTP-treated marmosets, equivalent to that occurring in caudate-putamen [11]. This was surprising in view of the histological evidence of limited damage to the ventral tegmental area, and biochemical evidence, in vervet monkeys, showing that the HVA : dopamine ratio increased in caudate-putamen two months following MPTP treatment, but not in the nucleus accumbens [6, 9]. This discrepancy between the limited degree of cell loss in the ventral tegmental area and the profound decrease in dopamine content of the nucleus accumbens is of interest. Acute dopamine depletion in this area may contribute to the initial profound akinesia induced by MPTP in common marmosets, but the relative preservation of ventral tegmental neurones may indicate their subsequent capacity for functional recovery.

In this study we have compared the changes in dopamine content of the caudate nucleus, putamen and nucleus accumbens, at a time when common marmosets exhibit profound akinesia, with changes subsequently, when motor activity has recovered from the effects of MPTP treatment.

MATERIALS AND METHODS

MPTP treatment. Thirteen male or female common marmosets (*Callithrax jaccus*) weighing between 287–350 g were treated with MPTP (1–4 mg/kg i.p. daily) over a period of 6–8 days. Animals were treated with individual dose regimes so as to render them markedly parkinsonian. The mean cumulative dose of MPTP administered was 9 ± 2 mg/kg (range 7 to 12 mg/kg). A further eleven male or female common marmosets (initial weight

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290–305 g) received vehicle injection over the same time period.

Animals were treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine base (MPTP; Aldrich Chemical Co., Gillingham, U.K.) or MPTP hydrochloride (Research Biochemicals Inc., Nattick, MA). MPTP base was dissolved in a minimum quantity of 70% ethanol and diluted to volume with distilled water. MPTP hydrochloride was dissolved in 0.9% sodium chloride solution.

Behavioural assessment. The effects of MPTP treatment were assessed by observer rating. Motor deficits exhibited by individual animals were recorded and the overall degree of parkinsonism of each animal assessed on a 0–5 scale of increasing severity (0 = normal; 1 = normal movement but quiet, easily handled and less spontaneous activity; 2 = able to move freely but little spontaneous activity, clumsy and poorly coordinated movements, little or no checking behaviour, freezing episodes; 3 = able to move but very clumsy and little coordination, virtually no spontaneous activity; blink reflex diminished, little vocalization, stooped posture, some postural tremor; 4 = some akinesia and bradykinesia, no spontaneous movement, loss of vocalization and blink reflex, exaggerated startle reflex, stooped posture, postural tremor, rigidity of limbs and trunk, seborrhea; 5 = totally akinetic, drooling, no spontaneous feeding or drinking, constipation, exaggeration of all components of lower scores). The behavioural effects induced by MPTP were observed at intervals during the post-treatment period prior to killing for biochemical assessment at 10 days and 3–4 months. At each time some of the control group were also killed for comparison with MPTP-treated animals.

Biochemical determinations. At 10 days and 3–4 months after MPTP administration, animals were anaesthetized using pentobarbitone (100 mg/kg i.p.) and decapitated. The brains were quickly removed and stored at −70° until microdissection. Brains were sliced and putamen, caudate and nucleus accumbens were microdissected at −20°. The tissues were stored at −70° until biochemical assay.

Concentrations of dopamine 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxytryptamine (5HT) and 5-hydroxyindoleacetic acid (5HIAA) were determined by high pressure liquid chromatography with electrochemical detection (HPLC-ECD).

The system employed consisted of a Waters 510 pump, a Spectra Physics 8780 automated sampler and injector equipped with a 100 μl sample loop. The amperometric detector was a BAS LC-3A, with a thin layer electrochemical cell fitted with a glassy-carbon working electrode and an Ag/AgCl reference electrode. The working potential was 0.8 V. Chromatographic peaks were integrated using a Spectra Physics 4270 integrator. Chromatography was performed on a Spherisorb ODS-2 reverse-phase C18 column (5 μm particle size; dimensions 250 × 4 mm; Phase Separations). The mobile phase consisted of 0.1 M sodium phosphate containing 1 mM EDTA, 0.74 mM octane sulphonic acid and 17.5% methanol. The pH was adjusted to 3.1 with 3 M phosphoric acid. All chromatography was performed at 10°.

Samples were homogenized in 0.4 M perchloric acid containing 1 mM EDTA and 0.5 mM sodium metabisulphite (homogenizing acid). An aliquot of the homogenate was added to a solution of dihydroxybenzylamine (DHBA) in homogenizing acid in a 9:1 volume:volume ratio. The homogenates were centrifuged at 1800 *g* for 30 min at 4° in a Sorvall RC-3B refrigerated centrifuge. Fifty μl of the supernatant was used for HPLC analysis of monoamines and their metabolites. Concentrations of the monoamines and their metabolites were calculated using the internal standard (DHBA) method of quantification. Recoveries were calculated from spiked cerebellar homogenates and were found to be greater than 90% for all compounds. The detection limit for the assay was 50 pg per injection for all compounds.

RESULTS

Behavioural effects of MPTP treatment

Administration of MPTP to common marmosets initially induced profound akinesia accompanied by rigidity of the limbs and trunk and postural abnormalities. On occasions postural tremor was observed. Animals exhibited a loss of vocalization and blink reflex. In this period animals required hand feeding. When able to feed spontaneously, freezing episodes were observed. During this initial period up to 10 days following MPTP treatment, the animal showed scores between 3–5 (average 3.8 ± 0.4) for motor disability.

Subsequently, spontaneous locomotion recovered such that after 3–4 months animals could feed normally and responded with rapid movements when challenged. However, all animals still showed motor deficits induced by MPTP. When observed within the home cage there was less spontaneous movement or chewing movements than shown by control animals. Also noticeable was the poor ability to move from perch to perch or from cage floor to a perch; movement was carried out in a poorly coordinated and clumsy manner. Rigidity was no longer apparent and vocalization and blink reflexes had returned. At 3–4 months following MPTP treatment, the motor disability score for the animals ranged between 1 and 3 (average 2.2 ± 0.4).

Alterations in biochemical parameters (Tables 1–3)

At 10 days following MPTP treatment the dopamine content of the caudate nucleus and putamen was reduced to less than 2% of levels obtained in control animals. Similarly there were marked reductions in the concentration of the dopamine metabolites HVA and DOPAC. By 3–4 months following the start of MPTP treatment there had been some recovery in the levels of dopamine in both the caudate nucleus and putamen but these remained greatly reduced to 11–16% of levels obtained in control animals. Similarly there had been some recovery in the levels of HVA and DOPAC in these structures but again they remained decreased compared to control animals. The (HVA + DOPAC)/dopamine ratio was slightly increased in the caudate nucleus at 10 days and at 3–4 months but this did not reach statistical significance; the ratio of

Table 1. Alterations in neurochemical parameters in the caudate nucleus at 10 days and 3–4 months induced by acute MPTP treatment of common marmosets

Parameter (μg/g tissue)	10 days		3–4 months	
	Control	MPTP	Control	MPTP
DA	14.17 ± 1.30	0.22 ± 0.09*	16.75 ± 2.55	1.79 ± 0.86*†
DOPAC	1.84 ± 0.25	0.18 ± 0.02*	1.06 ± 0.22	0.20 ± 0.08*
HVA	8.10 ± 1.06	0.01 ± 0.00*	10.01 ± 1.78	2.20 ± 0.90*†
5-HT	0.13 ± 0.03	0.14 ± 0.04	0.65 ± 0.09	0.50 ± 0.07
5-HIAA	0.27 ± 0.02	0.18 ± 0.03	1.18 ± 0.08	0.93 ± 0.17
Ratio (HVA + DOPAC)/DA	0.70 ± 0.05	1.87 ± 0.63	0.67 ± 0.09	1.24 ± 0.35
Ratio 5-HIAA/5-HT	2.65 ± 0.42	2.24 ± 0.66	1.86 ± 0.15	1.78 ± 0.28

The values shown are the mean (± SE) of values for 4–7 individual animals.
* $P < 0.05$ compared to control values.
† $P < 0.05$ compared to values obtained at 10 days after MPTP treatment.
Analysis of variance followed by Student's *t*-test.

Table 2. Alterations in neurochemical parameters in the putamen at ten days and 3–4 months induced by acute MPTP treatment of common marmosets

Parameter (μg/g tissue)	10 days		3–4 months	
	Control	MPTP	Control	MPTP
DA	13.04 ± 0.62	0.17 ± 0.06*	15.15 ± 1.64	2.47 ± 0.08*†
DOPAC	1.76 ± 0.15	0.16 ± 0.03*	0.99 ± 0.28	0.20 ± 0.08*
HVA	10.81 ± 1.03	0.01 ± 0.01*	6.13 ± 0.82	1.65 ± 0.05*
5-HT	0.10 ± 0.01	0.21 ± 0.06	0.55 ± 0.08	0.57 ± 0.17
5-HIAA	0.31 ± 0.07	0.24 ± 0.05	0.62 ± 0.15	0.79 ± 0.22
Ratio (HVA + DOPAC)/DA	0.96 ± 0.05	1.22 ± 0.33	0.46 ± 0.03	0.53 ± 0.11
Ratio 5-HIAA/5-HT	2.76 ± 0.38	1.40 ± 0.24*	1.08 ± 0.11	1.16 ± 0.18

The values shown are the mean (± SE) of values for 4–7 individual animals.
* $P < 0.05$ compared to control values.
† $P < 0.05$ compared to values obtained at 10 days after MPTP treatment.
Analysis of variance followed by Student's *t*-test.

Table 3. Alterations in neurochemical parameters in the nucleus accumbens at 10 days and 3–4 months induced by acute MPTP treatment of common marmosets

Parameter (μg/g tissue)	10 days		3–4 months	
	Control	MPTP	Control	MPTP
DA	10.37 ± 1.12	1.82 ± 0.40*	10.14 ± 0.80	7.36 ± 0.83*†
DOPAC	1.41 ± 0.23	0.04 ± 0.03*	2.26 ± 0.32	1.21 ± 0.23*†
HVA	9.71 ± 2.12	0.17 ± 0.12*	8.32 ± 0.44	4.56 ± 1.46†
5-HT	0.87 ± 0.18	1.27 ± 0.09	0.26 ± 0.26	0.85 ± 0.04
5-HIAA	2.10 ± 0.24	1.21 ± 0.23	0.33 ± 0.26	0.31 ± 0.09
Ratio (HVA + DOPAC)/DA	1.09 ± 0.15	0.21 ± 0.12*	1.14 ± 0.13	0.74 ± 0.12†
Ratio HIAA/5-HT	2.61 ± 0.83	0.99 ± 0.19	0.27 ± 0.27	0.42 ± 0.13

The values shown are the mean (± SE) of values for 4–7 individual animals.
* $P < 0.05$ compared to control values.
† $P < 0.05$ compared to values obtained at 10 days after MPTP treatment.
Analysis of variance followed by Student's *t*-test.

(HVA + DOPAC)/dopamine was not altered in the putamen at these time points.

In the nucleus accumbens the levels of dopamine, HVA and DOPAC were also dramatically reduced 10 days following MPTP treatment; dopamine concentrations fell to less than 18% of control values. There was also a marked decrease in the (HVA + DOPAC)/dopamine ratio. However, by 3–4 months the levels of dopamine had returned to approximately 73% of those observed in control animals and there were significant increases in the level of both HVA and DOPAC compared to the 10 day time point. The (HVA + DOPAC)/dopamine ratio had returned to control values by 3–4 months.

There were no changes in the levels of 5HT or 5HIAA in caudate nucleus, putamen or nucleus

accumbens at either 10 days or 3–4 months, although there was a decrease in the 5HIAA/5HT ratio in the putamen at 10 days.

DISCUSSION

The administration of MPTP to common marmosets results in the destruction of dopamine cells in the zona compacta of substantia nigra, but causes less marked and more variable damage to the dopamine containing cells of the ventral tegmental area [8, 9]. There appears to be no damage to the locus coeruleus or raphe nuclei in the young adult marmosets employed in these experiments. These data suggested that destruction of the nigro-striatal pathway is a major factor in the induction of motor deficits by MPTP treatment of young common marmosets. It should be noted that in other species of monkey, particularly older animals, MPTP may cause cell loss both in the ventral tegmental area and locus coeruleus [12–16].

Administration of MPTP to common marmosets induces a variety of parkinsonian features some of which gradually disappear. One mechanism of recovery may be compensation by remaining dopamine neurones in caudate-putamen, resulting in increased dopamine turnover as shown by an increased ratio of (HVA + DOPAC)/dopamine [11]. We also found an increase in metabolite:dopamine ratio at 4–6 weeks after MPTP treatment of marmosets. However, this was not evident at 3–4 months after MPTP in the present study. This suggests that remaining nigro-striatal dopamine neurones are unable to maintain any compensatory increase in dopamine turnover, and that this mechanism alone cannot explain the recovery of motor function shown by MPTP-treated marmosets. Another mechanism of recovery is suggested by the present observation that the dopamine content of the nucleus accumbens is dramatically decreased shortly after MPTP treatment (despite the evidence for a limited loss of mesolimbic dopamine neurones), but that 3–4 months later, when motor defects have improved, there is considerable recovery of dopamine content in this region.

At the time that akinesia was grossly apparent at 10 days following MPTP treatment there were marked falls in the levels of dopamine and its metabolites both in the caudate-putamen, and in nucleus accumbens. When the gross akinesia had disappeared at 3–4 months there was some increase in the dopamine content of the caudate-putamen, but this was still dramatically reduced compared to that of control animals. Whether this small increase in caudate-putamen dopamine content contributes to the reversal of akinesia is not clear. However, the absence of increased dopamine turnover at this time suggests it to be unlikely.

In contrast to the caudate-putamen, by 3–4 months the dopamine content of the nucleus accumbens had recovered almost to normal. Similarly, there were increases in the levels of HVA and DOPAC and the ratio of (HVA + DOPAC)/dopamine had returned to control values. This suggests that the initial decrease and subsequent recovery of the nucleus accumbens dopamine turnover more closely parallels the time course of appearance and reversal of akinesia induced by MPTP than changes in caudate-putamen dopamine function. It may be, therefore, that in the common marmoset the nucleus accumbens plays a key role in the generation of locomotion as occurs in rodent species.

Why there is an initial but reversible decrease in nucleus accumbens dopamine content is not clear. In rats and mice the administration of MPTP (or MPP^+) causes an acute release of dopamine [17–19] and impairment of dopamine synthesis due to inhibition of tyrosine hydroxylase activity [20, 21] and depletion of biopterin [22]. Indeed, in mice MPTP also causes a reversible impairment of 5HT metabolism in striatum [23] which is consistent with the decrease in 5HT turnover observed in the putamen at the 10 day time point in this study. There may, therefore, be some impairment of mesolimbic dopamine function either due to the inhibition of dopamine synthesis or to some persistent amine depleting action of MPTP as occurs in rodent species.

In conclusion, while nigral cell death may contribute to persistent motor deficits induced by MPTP in common marmosets, the initial akinesia induced by MPTP appears linked to a transient fall in nucleus accumbens dopamine content. In the common marmoset at least, the disruption of normal dopaminergic function in the nucleus accumbens appears to play a key role in the generation of parkinsonian motor deficits.

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