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Amphetamine-induced circling behaviour in MPTP-lesioned mice

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This study was designed to examine the effect of intrastriatal administration of MPTP on (+)-amphetamine-induced circling behaviour in mice. The results demonstrate that (+)-amphetamine elicits circling behaviour in MPTP-lesioned animals. MPTP produced a 70% depletion of striatal dopamine concentration.

In response to amphetamine administration, mice, lesioned unilaterally in one striatum with 6-hydroxydopamine, will circle to the damaged side (Ungerstedt 1968, 1971; Von Voigtlander & Moore 1973; Costall & Naylor 1975). Amphetamine is believed to elicit this circling behaviour by releasing a reserpine-insensitive, newly synthesized pool of dopamine (DA) from DA nerve terminals in the intact striatum (Weissman et al 1966; Chiueh & Moore 1973; Fung & Uretsky 1982). This mouse circling model has been widely used to study compounds with striatal dopaminergic activity.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has recently been recognized as a neurotoxin that destroys dopaminergic nigrostriatal pathways in man (Davis et al 1979; Langston et al 1983) and several animal species (Hallman et al 1984; Heikkila et al 1985; Fuller & Steranka 1985; Langston 1985). It has been shown that repeated systemic administration of MPTP (11 injections) to mice caused a 90% reduction in striatal DA content (Heikkila et al 1985). The present study was designed to determine if a single intrastriatal administration of various doses of MPTP would induce significant nigrostriatal damage in mice to elicit circling behaviour in reponse to the systemic administration of amphetamine.

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Methods

MPTP-induced lesions of the right striatum in mice. Male ICR mice (Sasco, Omaha), 25–32 g, were anaesthetized with chloral hydrate (430 mg kg^{-1} i.p.). Chilled NaCl 0·9% (saline) (4 μl), containing 10, 20 or 30 μg of MPTP hydrochloride (Research Biochemicals, Inc.) was injected into the right striatum of the mouse over 4 min, using a stereotaxic instrument (David Kopf) with a 10 μl Hamilton syringe. Saline was injected into the control animals. The solution was injected into the

centre of the corpus striatum which was 3·5 mm below the skull surface, 2·2 mm lateral to the midline and 5 mm anterior to the occipital suture (Fung & Schwarz 1983). The incision was closed with a wound clip.

Assessment of circling behaviour. Five days after surgery, mice were allowed to adapt in 2 litre round bottom flasks for 30 min. (+)-Amphetamine sulphate (4 mg kg^{-1}, i.p.) was injected and circling behaviour determined. The number of 360 degree turns to the right (ipsilateral) or left (contralateral) were recorded manually for 2 min at 10 min intervals for 50 min. Net ipsilateral circling (towards the lesioned side) was determined by subtracting the turns to the left from the turns to the right. The ipsilateral/contralateral ratio of turns in these MPTP-lesioned mice was 10/1.

Biochemical assay of dopamine. Animals were decapitated, brains removed and striatal tissues dissected. Samples from two mice were pooled and homogenized in 1 ml 0·4 M perchloric acid. The excess perchlorate was precipitated with 0·1 ml of KOH-HCOOH buffer, and the samples were centrifuged at 4800*g* for 15 min and the supernatant was decanted to Bio-Rad columns packed with Sephadex G-10.

The lesioned or intact striata of the mice were isolated according to Earley & Leonard (1978) and the DA content was determined spectrofluorometrically (Chang 1964).

Results and discussion

The present studies show that intrastriatal administration of MPTP in mice produced a 70% reduction in striatal DA concentration in lesioned mice compared with control values (DA content μg g^{-1} MPTP-treated mice 2·6 ± 0·2, control 9·4 ± 0·2, n = 5; $P < 0·01$ by Student's *t*-test). This suggests a neurotoxic effect of MPTP on striatal dopaminergic neurons. Similarly, systemic administration of MPTP in rodents has been shown to produce nerve cell destruction in the substantia nigra with long-lasting depletion of DA (Markey et al 1984; Fuller & Steranka 1985; Heikkila et al 1985; Jarvis & Wagner 1985; Wallace et al 1984). Thus, in response to the systemic administration of amphetamine, this imbalance of DA concentration in the lesioned mice resulted in net ipsilateral circling when compared to saline-treated controls (Fig. 1). None of the MPTP-lesioned mice died after surgery nor did they show any signs of gross motor deficit. Since (+)-amphetamine can still induce circling in these MPTP-lesioned mice 21 days after lesioning, the induction of circling behaviour by MPTP appears to be persistent.

The mouse striatum after the injection of MPTP is similar to the striatum of patients with Parkinson's disease with marked degeneration of dopaminergic neurons in the substantia nigra. Therefore, the mouse with MPTP-induced nigrostriatal (Langston et al 1983; Markey et al 1984) lesions can serve as a useful animal model for studying dopaminergic agonists effective in the treatment of Parkinson's disease.

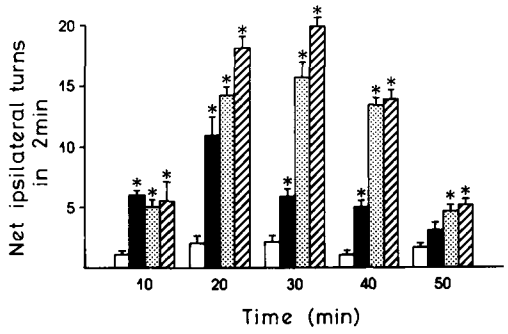

FIG. 1. Time-course of ipsilateral circling in mice lesioned in right striatum with MPTP. Circling behaviour was determined 10 min after the administration of (+)-amphetamine (4 mg kg^{-1} i.p.). Each value is the mean ± standard error of the mean of 5 animals. Open columns = control, solid columns = mice lesioned with 10 μg MPTP, dotted columns = mice lesioned with 20 μg MPTP, hatched columns = mice lesioned with 30 μg MPTP. *$P < 0·01$ (Student's *t*-test).

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