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Short communication

Unilateral intranigral injection of MPTP in the rat induces contraversive turning

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Unilateral injection of MPTP into the pars compacta of the substantia nigra in rats induced contraversive turning immediately after the injection. Contraversive turning decreased, and reversed its direction after about 30 min. Ipsiversive turning was still present 24 h after the injection of MPTP. These results suggest that MPTP has an initial stimulatory effect on dopaminergic neurons followed by a depression of the activity of these cells.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Substantia nigra; Turning

1. Introduction

Drug abusers who had self-injected synthetic heroin contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed severe signs of Parkinson's disease due to the selective destruction of the dopaminergic nigrostriatal pathway by MPTP (Langston, 1985). MPTP given systemically also destroys dopaminergic neurons and/or terminals in several animal species including primates and rodents. MPTP neurotoxicity is attributed to its metabolism in the brain by MAO-B (see Langston, 1985). However, the brains of rodents, especially of rats, seem to be more resistant to the toxic effects of the drug than the brains of primates. This has been attributed to a more rapid metabolic clearance of MPTP and its metabolites from the brains of rodents (Johannesen et al., 1985). Thus, intranigral injection of MPTP in the rat failed to produce lasting damage to the dopaminergic nigral cells (Chiueh et al.,

1984). In our experiments we tried to determine the acute effects of unilateral injection of MPTP into the substantia nigra pars compacta (SNC) in rats.

2. Materials and methods

Male BD IX rats (200–250 g; N = 8) received a unilateral injection of 50 $\mu\text{g}/1 \mu\text{l}$ (290 mmol) MPTP (Janssen Pharmaceuticals) through chronic cannulas implanted in the SNC. Control rats (N = 8) received a saline solution whose molarity was adjusted to 290 mmol. Turning in both groups was automatically recorded with the animals in a square box (50 \times 50 cm). Recordings were made for 30 min immediately after the injection and again, 24 h later, for 30 min.

3. Results

Intranigral injection of MPTP induced strong contraversive turning (away from the site of injection) whereas injection of the saline solution induced a short initial period of ipsiversive turning

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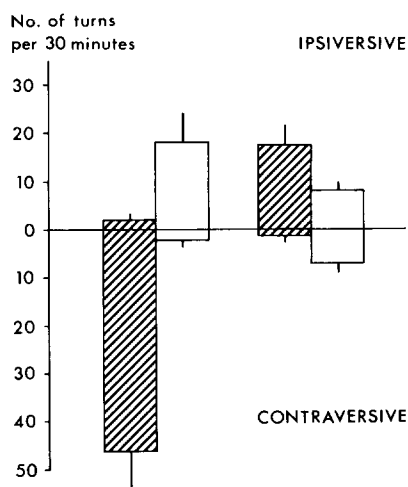


Fig. 1. Ipsiversive and contraversive turning immediately (left side) and 24 h (right side) after unilateral infusions of MPTP (hatched bars) and saline (plain bars) into the pars compacta of the substantia nigra. Mean values are shown ± 1 S.E.M.

(see fig. 1). Drug-induced contraversive turning decreased slowly and reversed its direction after 20-40 min: the rats began to turn ipsiversively. Spontaneous ipsiversive turning was still present 24 h after the intranigral injection of MPTP. Rats in the control group injected with saline did not turn preferentially in either direction when observed 24 h after the injection. Half of the MPTP-injected rats were again tested for spontaneous turning behavior 7 days after the injection; they no longer showed asymmetry in turning behavior.

Light microscopic inspection of the injection site revealed a small lesion at the immediate center of the injection site but no systematic degeneration of dopaminergic cell bodies in the SNC.

4. Discussion

Our results suggest that the drug has an initial stimulatory effect on dopaminergic cells, followed by a depression of the activity of these cells. Support for this hypothesis comes from the work of Pileblad and coworkers (1985) who found a transient increase followed by a marked retardation of dopamine synthesis and turnover after subcutaneous injection of MPTP in mice. In these latter experiments, as different species and differ-

ent route of application of the drug were used, the peak increase in dopamine turnover occurred between 60 and 100 min after drug injection in contrast to the immediate induction of contraversive turning observed in our experiments.

Similar results, contra- or ipsiversive turning after injection of MPTP into the SNC and contraversive turning after injection of the drug into the substantia nigra pars reticulata (SNR) in rats, have already been described by Sirinathsinghji (1985). His results resemble the results obtained after the injection of dopamine or a dopamine-agonist into the SNC or SNR (Kelly et al., 1984), thus favouring a dopamine agonist-like action of MPTP. Ipsiversive turning after injection of dopamine or a dopamine agonist into the SNC is then explained as being due to stimulation of dopamine autoreceptors which inhibit the cellular activity of dopaminergic nigral cells. How dopamine or a dopamine agonist induce contraversive turning when injected into the SNR is still open to discussion (see Kelly et al., 1984).

Our results seem to eliminate a dopamine agonist action of MPTP. Instead of ipsiversive turning after injection of MPTP into the SNC, we first observed contraversive turning, followed by ipsiversive turning. The discrepancy between our results and those of other authors (see above) could be explained by assuming that, in our rats, MPTP spread from the site of injection in the SNC to the SNR where it stimulated yet unknown structures, mimicking the effects of dopamine and inducing contraversive turning. Still, we would like to point out that the start of contraversive turning in our rats immediately followed the injection of MPTP into the SNC, and that the contraversive turning was of short duration and the ipsiversive turning which followed the contraversive turning was still present 24 h after injection. This suggests that MPTP has a longer lasting depressive effect on dopaminergic nigral neurons.

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References

- Chiueh, C.C., S.P. Markey, R.S. Burns, J.N. Johannessen, A. Pert and I.J. Kopin, 1984, Neurochemical and behavioral effects of systemic and intranigral administration of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the rat, *European J. Pharmacol.* 100, 189.
- Johannessen, J.N., C.C. Chiueh, R.S. Burns and S.P. Markey, 1985, Differences in the metabolism of MPTP in the rodent and primate parallel differences in sensitivity to its neurotoxic effects, *Life Sci.* 36, 219.
- Kelly, E., P. Jenner and C.D. Marsden, 1984, Behavioural effects mediated by unilateral nigral dopamine receptor stimulation in the rat, *Exp. Brain Res.* 55, 243.
- Langston, J.W., 1985, Mechanism of MPTP toxicity: more answers, more questions, *Trends Pharmacol. Sci.* 6, 375.
- Pileblad, E., B. Fornstedt, D. Clark and A. Carlsson, 1985, Acute effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on dopamine metabolism in mouse and rat striatum, *J. Pharm. Pharmacol.* 37, 707.
- Sirinathsingji, D.J.S., 1985, Behavioural effects in the rat after acute unilateral intranigral infusions of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *Brain Res.* 339, 366.