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RAPID COMMUNICATIONS

ORAL VERSUS PARENTERAL EFFICACY OF 1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE (MPTP): DIFFERENTIAL EFFECTS ON DEPLETION OF HEART NOREPINEPHRINE AND OF STRIATAL DOPAMINE IN MICE

Ray W. Fuller and Susan K. Hemrick-Luecke

Lilly Research Laboratories, Eli Lilly and Company,
Lilly Corporate Center, Indianapolis, IN 46285, U.S.A.

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MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) has been implicated as the cause of severe and irreversible Parkinsonian symptoms in drug abusers who self-administered MPTP inadvertently due to its presence as a contaminant in a sample of a meperidine analog sold on the street as a narcotic drug (1). MPTP causes destruction of nigrostriatal dopamine neurons in primates, leading to symptoms that closely resemble those in idiopathic Parkinson's disease in humans (2,3). In mice, MPTP causes persistent depletion of striatal dopamine and its metabolites after repeated administration of only a few doses, although Parkinsonism-like movement disorders are not observed (4-6). In mice, MPTP has been given parenterally, e.g. intravenously (4), intraperitoneally (5) or subcutaneously (6). MPTP given parenterally can also cause rapid and reversible depletion of heart norepinephrine after only a single dose in mice (7). The effect on striatal dopamine (8,9), but apparently not the effect on heart norepinephrine (10), requires the conversion of MPTP to MPP+ (1-methyl-4-phenylpyridinium) through the action of monoamine oxidase type B. In order for striatal dopamine to be depleted, that conversion has to occur in brain. MPP+ formed peripherally presumably would not cross the blood-brain barrier, since MPP+ given systemically does not deplete striatal dopamine (11), though it does deplete heart norepinephrine just as MPTP does (10). Here we compare effects of oral and subcutaneous administration of MPTP on striatal dopamine and cardiac norepinephrine in mice.

MATERIALS AND METHODS: Male CRL/CFW mice weighing 20-30 g (Charles River Breeding Laboratories, Portage, MI) were given MPTP HCl, synthesized by Dr. David W. Robertson in the Lilly Research Laboratories, either by subcutaneous injection or by oral gavage. Hearts were removed from mice killed 24 hr after a single dose of MPTP, and striata were removed from mice killed 1 week after the last of 4 daily doses of MPTP. Tissues were frozen on dry ice and stored at -15° C prior to analysis. Dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were measured in striatum and norepinephrine was measured in heart by liquid chromatography with electrochemical detection (12,13).

RESULTS: Fig. 1 compares oral and subcutaneous routes of administration of MPTP in the depletion of heart norepinephrine. Both routes led to significant decreases in heart norepinephrine 24 hr after the dose, and the potency of the drug was indistinguishable regardless of route of administration. The 3 and 10 mg/kg doses each depleted heart norepinephrine to essentially the same extent whether given by oral gavage or by subcutaneous injection.

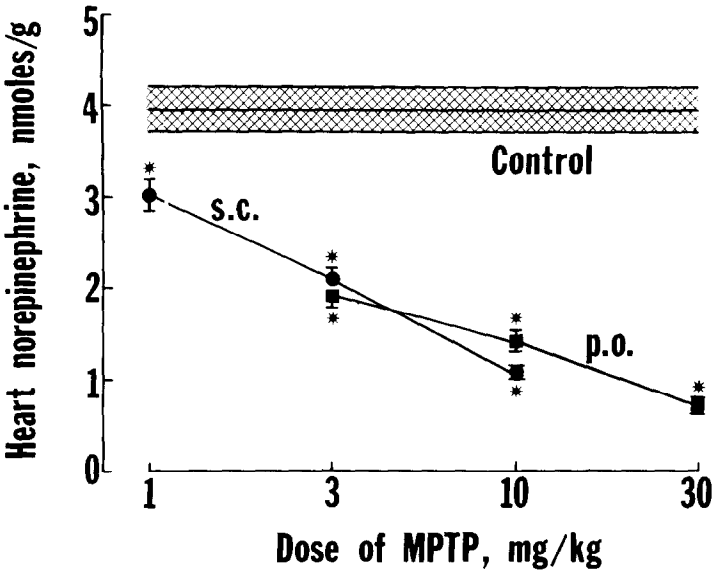

Fig. 1. Depletion of heart norepinephrine by a single dose of MPTP given subcutaneously (•) or orally (▪). Mean values ± standard errors for 5 mice in each treated group and 6 mice in the control group are shown. Asterisks indicate statistically significant ($P<.05$) difference from the control group.

In marked contrast are the persistent effects on striatal dopamine and its metabolites (Table 1). In that case, MPTP given subcutaneously produced marked depletion after four daily doses of 20 mg/kg each, whereas MPTP given orally caused no depletion at doses of 20, 40, 80, or 160 mg/kg.

DISCUSSION: A plausible explanation of our results is that MPTP given orally is metabolized completely or nearly completely to MPP+ before reaching the systemic circulation. In that case, MPP+ (being a quaternary compound) would not be able to cross the blood-brain barrier to exert a neurotoxic action on striatal dopaminergic terminals. However, MPP+ injected systemically does deplete cardiac norepinephrine levels (10). Thus orally administered MPTP may be converted so extensively to MPP+ prior to reaching the systemic circulation that no effect on striatal dopamine results, but depletion of cardiac norepinephrine occurs through the action of MPP+. That possibility is compatible with our results, though additional data such as direct measurement of MPTP and MPP+ levels would be required to verify such an hypothesis.

The influence of route of administration is pertinent to the consideration of an environmental neurotoxin as a possible etiologic factor in idiopathic Parkinson's disease (14). If MPTP itself were present in the environment, then exposure by oral ingestion may not be adequate for MPTP to cause Parkinson's disease if our results in mice are predictive. The importance of route of administration also has implications for the testing of possible neurotoxic hazards of MPTP analogs (15). If exposure is likely to be via inhalation or cutaneous contact, for instance, then testing neurotoxicity by oral administration or intravenous injection may have limited relevance. Recently, Wilkening et al. (15) reported that an N-methylpyrrole analog of MPTP was not neurotoxic when given orally to monkeys. We have found (unpublished data) that this analog caused persistent depletion of striatal dopamine at

Table 1. Persistent depletion of striatal dopamine by subcutaneous but not by oral administration of MPTP

Treatment group	N	Striatal dopamine and metabolites, nmoles/g		
		Dopamine	DOPAC	HVA
Subcutaneous				
Control	10	66.5 ± 1.9	6.17 ± .23	6.95 ± .39
MPTP (20 mg/kg)	10	27.5 ± 1.9* (-59%)	2.95 ± .13* (-52%)	3.91 ± .20* (-44%)
Oral				
Control	6	70.3 ± 1.9	6.35 ± .28	5.94 ± .31
MPTP (20 mg/kg)	6	71.9 ± 4.2	6.37 ± .22	7.00 ± .59
MPTP (40 mg/kg)	6	68.3 ± 3.8	6.31 ± .41	6.34 ± .38
MPTP (80 mg/kg)	6	70.5 ± 1.0	6.83 ± .23	7.10 ± .12
MPTP (160 mg/kg)	5†	65.8 ± 10.5	6.08 ± .76	5.85 ± .47

* Significant decrease from control ($P<.05$).
† One of six treated mice died after the second injection.

MPTP was administered at 20 mg/kg s.c. and at 20, 40, 80 and 160 mg/kg p.o. Mice were killed one week after the last of 4 daily doses. Mean values ± standard errors for the number of mice (N) are given.

least as great as that caused by MPTP in mice when the compounds were given s.c. at 20 mg/kg, although that dose was ineffective when given orally.

A detailed and thorough study of the factors involved in the differences among MPTP effects depending on routes of administration may give additional insight into mechanisms involved in its various actions.

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