PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **180**, 567-571 (1985)

DUODENAL ULCER INDUCED BY MPTP (1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE)

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Abstract. Experiments in rats revealed that the parkinsonian drug 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) given in multiple daily doses either per os (p.o.) or subcutaneously (s.c.) induced in a dose-dependent manner solitary or double ("kissing") duodenal ulcers in the rat. MPTP also diminished cerebral concentrations of DOPAC and the duodenal ulcers were prevented by pretreatment with dopamine agonists (e.g., bromocriptine, lergotrile) or monoamine oxidase inhibitors (e.g., pargyline, l-deprenyl). High doses of MPTP also caused gastric erosions and motility changes resembling parkinsonism (e.g., akinesia, rigidity, forward bending of trunk). This chemical decreased gastric secretion of acid and pepsin, as well as pancreatic bicarbonate, trypsin and amylase. Thus, MPTP causes duodenal ulcers that are possibly associated with impaired defense in the duodenal bulb (e.g., decreased availability of duodenal and pancreatic bicarbonate).

Recently, MPTP was reported to cause Parkinson's disease in humans (1) and primates (2). The chemical is an analogue derived from the synthetic analgesic alphaprodine and it has been taken by heroin users (1). This motility disorder is accompanied by a degeneration of the dopaminergic nigrostriatal pathway and a decrease in the concentration of dopamine and its metabolites dihydroxy-phenylacetic acid (DOPAC) and homovanillic acid (HVA) (2-4). The behavioral and neurochemical changes were also detected in rodents (3-6).

Structural similarities exist between dopamine and the duodenal ulcerogens cysteamine and propionitrile (7,8). Dopamine agonists (e.g., bromocriptine, lergotrile, apomorphine derivatives) or the precursor tyrosine prevented, while dopamine antagonists (e.g., haloperidol, pimozide, (+) butaclamol) aggravated the cysteamine-induced duodenal ulcer (8-10). Chemically induced duodenal ulcers resemble human duodenal ulcers by structural and functional criteria and may serve as animal models of the disease (11). Independent human studies revealed that dopamine infusion inhibited gastric acid secretion (12, 13) and suggested that untreated patients with Parkinson's disease (a dopamine deficiency syndrome) had increased incidence of peptic ulcer while schizophrenics had (with possible dopamine excess or receptor hyperactivity) decreased ulcer disease (for review see 11,14). Thus, since dopamine has been implicated in the pathogenesis of duodenal ulceration, we tested the hypothesis that MPTP may cause duodenal ulcer in rats.

Materials and Methods. Female Sprague-Dawley rats (150-200g), were maintained

0037-9727/85 $1.50

on unlimited access to Purina laboratory chow and tap water. MPTP was initially obtained as free base (Aldrich) solubilized in 0.1N HCl and titrated back to about pH 5.0. MPTP-HCl (Research Biochemicals, Inc., Wayland, Mass.) was dissolved in deionized water. Doses listed refer to free base. MPTP was administered p.o. or s.c. in a single or multiple daily doses up to 4 days. Volume of vehicle at administration was 0.2-0.5ml. Rats were killed on the fifth day and the incidence of duodenal ulcers was evaluated as described previously (9-11). In addition, severity (surface in mm^2 of duodenal ulcer on the anterior wall of duodenum) was expressed as mean ± standard error of the mean.

In the pharmacologic modulation experiments, rats of all groups were injected with MPTP, 2mg/100g s.c. x3 daily for 4 days and killed on the fifth day. Bromocriptine (Sandoz), lergotrile (Eli Lilly) (each 1mg/100g), pargyline (Abbott) (0.2mg/100g) or L-deprenyl (gift of Prof. J. Knoll) (0.1mg/100g) was administered p.o. 30 min before each dose of MPTP.

For secretory studies rats with chronically implanted gastric fistula were prepared and gastric as well as duodenal/pancreatic secretions were collected for 8 hr after MPTP, 5mg/100g s.c. in mildly restrained animals as described previously.(15).

For biochemical experiments, groups of rats were injected with MPTP, 5mg/100g s.c. and were decapitated 1,4 or 8 hr later. Brain was rapidly removed and homogenate prepared for the measurements of dopamine, DOPAC and HVA with a recent method involving high-performance liquid chromatography with electrochemical detection (HPLC-EC) (16).

Each control and experimental group consisted of 3-4 animals and every experiment was performed at least twice. The results were pooled and expressed as mean ± standard error of mean. Incidence (positive/total: number of rats having duodenal ulcer/total number of animals) was evaluated statistically with the Fisher-Yates Exact Probability Test. Severity of duodenal ulcers was evaluated for statistical significance with two-tailed Student's t-test for unpaired comparisons.

Results and Discussion. Dose-response studies with MPTP administered p.o. or s.c. in multiple doses for 2-3 days revealed motor disorders (e.g., akinesia, rigidity, forward bending of trunk, tremor) resembling Parkinson's disease and solitary or double ("kissing") duodenal ulcers in the proximal duodenum (Fig. 1). When relatively high doses of MPTP were administered to rats, resulting in 60-100% mortality, multiple gastric erosions and ulcers that were larger and deeper than the usual superficial stress ulcers were noted. Gastric ulcers were thus seen only with high doses of MPTP and the incidence of gastric lesions was parallel with mortality, e.g., about 65% in the group receiving MPTP at 7.5mg/100g s.c. once

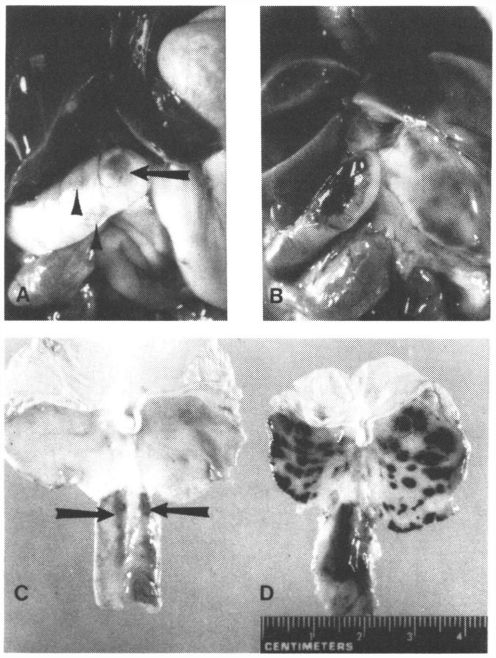

Figure 1 Ulcers that developed in rats given MPTP: (A) In situ view of an early duodenal ulcer (horizontal arrow) on the anterior wall of proximal duodenum. Serosal reaction to two adjacent mild ulcers (vertical arrows) is also visible on the anterior and posterior walls. (B) Severe, extensive and hemorrhagic ulcer on the anterior wall of duodenum ("Anteperforationem"). Hemorrhagic gastric ulcers are transparent on the serosa of stomach. (C) Mucosal view of early duodenal ulcers (arrows) on the anterior and posterior wall of duodenum. (D) Two severe, hemorrhagic duodenal ulcers and multiple bleeding gastric ulcers in glandular stomach and antrum.

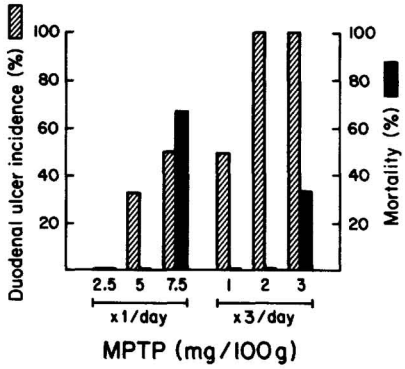

Figure 2 Dose-dependent duodenal ulcerogenic effect of MPTP injected s.c. to group of rats (n=6). The chemical was administered either once or 3 times daily (as indicated) for 4 days and survivors were killed on fifth day.

daily for 4 days (Figs. 1,2). The incidence of both neurologic and gastrointestinal disorders increased with multiple daily doses of MPTP. Thus, a single large dose was rarely ulcerogenic in the duodenum. On the other hand, in groups of rats (n=6), 2.5, 5 or 7.5 mg/100g s.c. once daily for 4 days produced duodenal ulcers in 0, 33 or 50% of the animals, respectively. The incidence of duodenal ulcers following 1, 2 or 3mg/100g s.c. 3 times daily for 4 days was 50, 100 or 100%, while the mortality remained low, i.e., 0, 0 or 33%, respectively (Fig. 2) and no gastric ulcers were visible.

The pharmacologic modulation experiments revealed that administration (30 min before each dose of MPTP) of dopamine agonists bromocriptine or lergotrile, significantly decreased the severity of duodenal ulcers (Table 1). The inhibitors of monoamine oxidase (MAO) pargyline or l-deprenyl, significantly inhibited both the incidence and intensity of MPTP-induced ulcers. Thus, this effect of MAO inhibitors is similar to the prevention of neurotoxicity and parkinsonism induced by MPTP in mice and primates (17-19) and suggests a MAO-sensitive generation of toxic metabolites of MPTP.

The secretory studies in fasted rats with chronic gastric fistula interestingly showed that the total 8 hr gastric acid and pepsin output were decreased to 24 and 60% of controls, re-

Table 1
Effect of dopamine agonists and monoamine oxidase inhibitors on MPTP-induced duodenal ulcer in the rat

Group	Treatment (A)	Duodenal ulcer (B)		
		Incidence		Severity
		(Pos./Tot.)	(%)	(mm^2)
1.	Vehicle	13/14	93	8.3 ± 2.1
2.	Bromocriptine	4/6	67	2.0 ± 9.7*
3.	Lergotrile	3/6	50	2.5 ± 1.5*
4.	Pargyline	1/6*	17*	0.2 ± 0.2**
5.	l-Deprenyl	0/6**	0**	0**

(A) Rats of all groups were injected with MPTP, 2mg/100g s.c. x3 daily for 4 days and killed on the fifth day. Dopamine agonists or MAO inhibitors were administered p.o. 30 min before each dose of MPTP.

(B) Cumulative duodenal ulcer incidence and severity listed on the fifth day.

* $p < 0.05$; ** $p < 0.005$

spectively, by MPTP (5mg/100g s.c.). Outputs of pancreatic bicarbonate, amylase and trypsin were also diminished to 67, 16 and 17% of controls. Thus, duodenal ulcers cannot be ascribed to gastric acid hypersecretion but, at least in part, may be associated with decreased neutralization of the acid remaining in the duodenal bulb. Furthermore, recent duodenal myoelectric recordings in fasted rats revealed virtually a complete lack of myoelectric spike potentials for about 4 hr after a single s.c. dose of MPTP, suggesting a markedly decreased motility in and emptying from the proximal duodenum. Thus, a motility disorder as it has been shown in the duodenal ulcer induced by cysteamine or propionitrile (20,21) may contribute to the duodenal ulcerogenic effect of MPTP. The pathogenesis probably involves localized hyperacidity in the duodenal bulb because of decreased neutralization and impaired duodenal emptying of acid, and possibly vascular effects, especially decreased blood flow.

In recent biochemical experiments when the levels of catecholamines and their metabolites were measured by HPLC-EC, MPTP (5mg/100g s.c.) decreased in 1 hr brain concentrations of DOPAC to 65% of controls while it did not modify noradrenaline. Biochemical and neuropharmacologic studies are in progress to further characterize the role of monoamines in duodenal ulceration caused by this dopamine neurotoxin.

Acknowledgment

These studies were supported by grant AM-25229 and Research Career Development Award AM-00600 (S.Sz.) from the National Institutes of Health. Bromocriptine, lergotrile and pargyline were gifts from the Sandoz, Eli Lilly and Abbott Companies, respectively, while l-deprenyl was kindly provided by Prof. J. Knoll (Budapest, Hungary). We also thank Dr. Y. Ohkubo who provided assistance in some of the biochemical experiments. Our preliminary results were published in abstract form (Fed Proc 43: 945, 1984; 44: 733,1985).

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Received July 30, 1985.
P.S.E.B.M. 1985, Vol. 180.
Accepted October 3, 1985.