Effects of Phenylalaninol on Centrally Induced Gastric Acid Secretion

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The effects of phenylalaninol (D-isomer) on gastric acid secretion and gastric ulcer were studied in rats. The compound reduced the gastric acid secretion stimulated by intracisternal thyrotropin releasing hormone and intravenous 2-deoxy-D-glucose, but not that stimulated by subcutaneous carbachol or histamine. Phenylalaninol prevented stress- and indomethacin-induced gastric ulcers. We conclude that phenylalaninol inhibits ulcer formation mainly by central inhibition of gastric acid secretion.

Keywords phenylalaninol; gastric acid secretion; gastric ulcer; central nervous system

Ephedrine and amphetamine stimulate the central nervous system and have been found to inhibit stress ulcers in rats.[1] We have reported that methamphetamine can inhibit gastric acid secretion, which is an important factor in the formation of gastrointestinal ulcers.[2] *N*-Benzyl-phenylalaninol and *N*,*N*-dimethyl-phenylalaninol have been reported to inhibit inflammation.[3] These suggest that phenylpropylamine derivatives have many pharmacological activities. The effects of phenylalaninol and its derivatives that we synthesized on gastric acid secretion, glucose level, fibrinolysis and coagulative activity in blood were measured to find novel pharmacological active compounds. Phenylalaninol remarkably inhibited gastric acid secretion, but had no other effects. Because there have been few studies of the effect of this substance on the gastrointestinal tract, we will report and discuss the effect of phenylalaninol on gastric acid secretion and gastric ulcer in rats.

Materials and Methods

Gastric Acid Secretion Male Wistar rats used weighed 210—280 g, and were anesthetized with urethane (1.25 g/kg i.p.) after a 24 h fast. Gastric acid secretion was measured as previously described.[4] The trachea was exposed and cannulated. A dual polyethylene gastric cannula[5] was inserted into the gastric lumen after ligation of the pylorus and esophagus. The stomach was perfused with 10 ml of saline solution (pH 7.0) through the inlet tube of the gastric cannula and the perfusate was collected from the outlet tube of the cannula. It was titrated for acid content using pH stat with 0.01 N NaOH solution. These procedures were repeated at intervals of 20 min. The first fraction was discarded. 2-Deoxy-D-glucose (2DG, 200 mg/kg) was given intravenously immediately after the first two assays. Data were not used if the total acid output of the second plus third fractions after 2DG was less than 15 μeq HCl/40 min. Carbachol (0.05 mg/kg) and histamine (10 mg/kg) were given subcutaneously. Thyrotropin releasing hormone (TRH, 1 μg/10 μl) was given by intracisternal injection. Phenylalaninol and cimetidine were given by i.p. injection 1 h after the 2DG, carbachol and histamine, or 20 min before the TRH injection. The total acid output of the second plus third fractions after the administration of phenylalaninol or cimetidine was expressed as μeq HCl/40 min in 2DG-, carbachol- and histamine-treated rats. In animals given TRH assays were continued for 2 h after the injection of TRH, and the total acid output was expressed as μeq HCl/2 h.

Gastric Ulcer Male Wistar rats weighing 220—260 g were used after a 24 h fast. The stomachs were removed 6 h after administration of indomethacin (40 mg/kg i.p.) or 17 h after the restraint plus water-immersion stress.[6] The gastric mucosal lesions were measured as described previously.[4] Phenylalaninol and cimetidine were given intragastrically 30 min before the injection of indomethacin or stress-load.

Drugs Phenylalaninol (D-isomer, Fuji Chemical Industries), carbachol (Wako), cimetidine (Aldrich), 2DG (Nakarai), histamine (Wako), indomethacin (Merck) and TRH (Peptide Institute Inc.) were used. Cimetidine and indomethacin were suspended in 0.5% carboxymethylcellulose solution, and the others were dissolved in saline solution.

Statistics The results are expressed as mean ± S.E. The significance of results was determined with multiple-comparison test (Bonferroni) after one way variance analysis.

Results and Discussion

Table I shows the effects of phenylalaninol on gastric acid secretion stimulated by TRH, 2DG, carbachol and histamine. Although phenylalaninol significantly and dose-dependently (3—100 mg/kg) inhibited gastric acid secretion stimulated by intracisternal TRH and intravenous 2DG, this was not the case with carbachol-stimulated secretion. Even the highest dose of phenylalaninol did not significantly influence the gastric acid secretion stimulated by histamine, although cimetidine at 10 mg/kg significantly inhibited gastric acid secretion stimulated by TRH. Cimetidine inhibited 2DG-, carbachol- and histamine-induced acid secretion, but not significantly because of the small number of rats. Phenylalaninol inhibited the gastric acid secretion induced by intracisternal TRH as well as intravenous 2DG which stimulates the hypothalamus.[7] These results suggest that phenylalaninol inhibits gastric acid secretion mainly by affecting the central nervous system. Although the mechanism by which the highest dose of phenylalaninol enhanced carbachol-induced gastric acid secretion is not known, phenylalaninol might influence the

TABLE I. Effects of Phenylalaninol and Cimetidine on Gastric Acid Secretion Stimulated by TRH, 2DG, Carbachol and Histamine

Compound	Dose mg/kg i.p.	TRH (μeq HCl/2 h)	2DG (μeq HCl/40 min)	Carbachol (μeq HCl/40 min)	Histamine (μeq HCl/40 min)
Control		98.8 ± 15.0 (14)	43.7 ± 6.0 (14)	44.9 ± 13.4 (7)	51.0 ± 14.6 (7)
Phenylalaninol	3	41.3 ± 9.2[a] (6)	—	—	—
	10	36.3 ± 8.4[a] (6)	24.8 ± 12.3 (4)	46.6 ± 13.1 (4)	—
	30	27.4 ± 2.5[b] (6)	11.4 ± 4.1 (4)	48.6 ± 10.7 (4)	—
	100	—	8.3 ± 0.9[a] (4)	103.4 ± 3.9[a] (4)	65.0 ± 4.4 (4)
Cimetidine	10	40.2 ± 3.9[a] (6)	16.1 ± 3.4 (4)	5.6 ± 0.9 (4)	4.4 ± 1.2 (4)

a) $p<0.05$, *b*) $p<0.01$ *vs.* control. Parentheses indicate the number of rats used.

TABLE II. Effects of Phenylalaninol and Cimetidine on Gastric Ulcers

Compound	Dose mg/kg *p.o.*	Stress ulcer (mm)	Indomethacin ulcer (mm)
Control		29.1±2.6 (11)	24.1±3.9 (17)
Phenylalaninol	30	6.8±2.3[a] (6)	4.8±1.1[a] (6)
	100	1.3±0.9[a] (6)	1.1±0.3[a] (6)
Cimetidine	30	5.9±2.0[a] (6)	9.1±2.0 (6)
	100	4.3±2.8[a] (6)	5.0±2.5[a] (6)

a) $p<0.01$ *vs.* control. Parentheses indicate the number of rats used.

peripheral cholinergic system.

Table II summarizes the effects of phenylalaninol and cimetidine on the experimental gastric lesions. Phenylalaninol dose-dependently (30, 100 mg/kg) prevented stress- and indomethacin-induced ulcers, at the doses which inhibited gastric acid secretion.

From the present study it may be concluded that phenylalaninol inhibited ulcer formation mainly by central inhibition of gastric acid secretion.

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