

## Stimulation of Gastrin Release in Dogs by Individual Amino Acids (40072)

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Although it is well established that placing mixtures of amino acids into the stomach increases serum gastrin concentration, there are only a few studies of the effects of individual amino acids (1). In this study 21 L-amino acids were instilled into gastric fistulas in dogs and the effect on serum gastrin concentration was noted.

**Methods and materials.** *Dogs.* Two or more months before the tests were started, three dogs (18–24 kg) had a Thomas type cannula (2) placed in the stomach to form a gastric fistula.

**Amino acids.** Amino acids were bought from Calbiochem, La Jolla, CA. With the exception of tryptophan which was used at 50 mM concentration, all other amino acids were used at 100 mM. The osmolarity of all amino acid solutions and of the 150 mM NaCl control solution was adjusted to 360 mOsm kg<sup>-1</sup> with mannitol and the pH was adjusted to 7.4 with 1 M NaOH. As a standard stimulant for acid secretion and gastrin release, 12% liver extract (Liver Concentrate Powder, Reheis Chemical, Phoenix, AR) was used at pH 7.4.

**Procedure.** After an 18-hr fast, the gastric fistula was opened and the stomach washed with water. The test solution was then instilled into the gastric fistula by peristaltic pump at a rate of 10 ml min<sup>-1</sup> for 30 min. The solution remaining in the stomach was drained for 2 min.

**Serum gastrin.** Samples of blood were drawn from a leg vein at 0, 15, and 30 min after starting the infusion of the test solution. Blood was allowed to clot at 5°, serum was removed within 2 hr and stored at -20° until the assay was performed. Serum gastrin was measured by radioimmunoassay using antibody 1296 as previously described (3). The mean of the increment above basal of the 15 and 30 min values was taken as the gastrin response in each test.

**Statistics.** Each amino acid and liver extract was tested three times in each dog and saline

was tested 12 times in each dog. The order of tests was randomized. The significance of differences between the mean response to saline and to the other test substances was tested by analysis of variance. The results in the table are expressed as means plus or minus between-dog standard errors.

**Results.** Only four of the amino acids caused a significantly greater increase in serum gastrin than saline: cysteine, phenylalanine, tryptophan, and hydroxyproline (Table I). The increase in serum gastrin in response to the most potent amino acids (cysteine and phenylalanine) was not significantly different from that produced by liver extract. The fluid drained from the stomach at the end of the 30-min period of perfusion with amino acids had a pH above 4.0 in all instances. The volume of fluid recovered from the stomach was significantly greater than the saline control after instillation of cysteine, tryptophan, and liver extract (Table I).

**Discussion.** Before radioimmunoassay of gastrin was available, it was assumed that any agent which when perfused into an antral pouch evoked secretion of acid from a Heidenhain pouch did so by releasing gastrin. Using this method, Elwin (4) found that all of the amino acids he tested, namely, glycine,  $\alpha$ -alanine,  $\beta$ -alanine, sarcosine, phenylalanine, and lysine produced statistically significant stimulation of acid secretion. Similarly, Konturek and coworkers (5) found that all of the 18 amino acids which they tested by this method stimulated acid secretion but only phenylalanine produced a significant increase in serum gastrin. Using intragastric titration in human subjects, Byrne and coworkers (6) found that tryptophan and phenylalanine caused an increase in serum gastrin and stimulated acid secretion; aspartic acid, leucine, cysteine, serine, histidine, alanine, methionine, and valine stimulated acid secretion but did not cause an increase in serum gastrin; and isoleucine, lysine, arginine, glutamic acid, threonine, glycine, hydroxyproline, and

TABLE I. MEAN ( $\pm$ SE) INCREMENT ABOVE BASAL OF SERUM GASTRIN AND MEAN ( $\pm$ SE) VOLUME RECOVERED FROM THE STOMACH AFTER INFUSING VARIOUS SUBSTANCES INTO THE STOMACH AT 10 ML MIN<sup>-1</sup> FOR 30 MIN.

Infusate	Increment in gastrin (pg ml <sup>-1</sup> )	Volume recovered (ml)
$\alpha$ -alanine	23 $\pm$ 9	51 $\pm$ 28
$\beta$ -alanine	12 $\pm$ 4	62 $\pm$ 12
arginine	20 $\pm$ 5	113 $\pm$ 32
aspartic acid	19 $\pm$ 6	113 $\pm$ 41
asparagine	24 $\pm$ 9	40 $\pm$ 10
cysteine	62 $\pm$ 14*	202 $\pm$ 38*
glutamic acid	22 $\pm$ 4	139 $\pm$ 32
glutamine	3 $\pm$ 7	63 $\pm$ 14
glycine	17 $\pm$ 5	98 $\pm$ 42
histidine	20 $\pm$ 7	52 $\pm$ 9
hydroxyproline	29 $\pm$ 8*	113 $\pm$ 30
isoleucine	4 $\pm$ 5	72 $\pm$ 25
leucine	12 $\pm$ 5	149 $\pm$ 26
lysine	18 $\pm$ 5	155 $\pm$ 30
methionine	12 $\pm$ 3	59 $\pm$ 15
phenylalanine	53 $\pm$ 19*	100 $\pm$ 17
proline	17 $\pm$ 8	82 $\pm$ 18
serine	22 $\pm$ 5	61 $\pm$ 10
threonine	22 $\pm$ 6	79 $\pm$ 16
tryptophan	39 $\pm$ 7*	293 $\pm$ 23*
valine	20 $\pm$ 4	66 $\pm$ 11
liver extract	51 $\pm$ 8*	281 $\pm$ 40
saline	15 $\pm$ 4	86 $\pm$ 23

\* Significantly greater than saline control,  $P < 0.05$ .

proline neither stimulated acid secretion nor caused an increase in serum gastrin. The picture that emerges from all of these studies is that while many amino acids stimulate acid secretion only a few release gastrin. The discrepancy between acid secretion and release of gastrin is probably not attributable to inadequate sensitivity of the radioimmunoassay for gastrin because earlier studies showed that doses of exogenous gastrin that produced threshold acid responses also produced detectable increases in immunoassayable gastrin in blood (7). Some mechanisms other than release of gastrin by which amino acids might stimulate acid secretion include: (a) Amino acids may stimulate acid secretion by initiating a neural reflex comparable to that elicited by distention (8); (b) Solutions of amino acids may act in part by directly stimulating the oxyntic glands they are bathing (9); (c) Amino acids may release from the stomach and/or intestine (10) hormonal stimulants of acid secretion other than gastrin. The additional hormone(s) may be related to gastrin but not immunoreactive to antibodies

to gastrin or may be unrelated. (d) Amino acids absorbed into the blood may stimulate acid secretion (11).

In an earlier study, we (10) found that infusion of liver extract into the duodenum of antrectomized dogs did not cause an increase in serum gastrin so we presume that the increases found in the present study are mainly of antral origin.

Although the only two amino acids which slowed gastric emptying, cysteine and tryptophan, also released gastrin, the other two amino acids which released gastrin, phenylalanine and hydroxyproline, did not affect gastric emptying. Stephens *et al.* (12) also found that tryptophan delayed gastric emptying; they could not test cystine adequately because it caused vomiting under their test conditions, an effect we did not encounter.

**Summary.** Solutions of 21 different L-amino acids were instilled into the gastric fistulas of three dogs. Only 4 of the amino acids produced an increase in serum gastrin significantly greater than that evoked by saline: cysteine, phenylalanine, tryptophan, and hydroxyproline.

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