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Research Article

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To determine whether this rise in plasma G-17 concentration could account for some or all of the acid secretory response, several doses of synthetic human G-17-I were infused intravenously into the same subjects. During i.v. G-17-I infusion, the stomach was continuously infused with isotonic saline. By graphically relating plasma G-17 concentration during i.v. G-17 infusion to concomitant acid secretion, it was determined that a 13-pmol/liter rise in plasma G-17 concentration could increase acid secretion 14.8 meq/h. Therefore, the rise in plasma G-17 concentration during intragastric amino acid infusion could have produced all of the observed acid secretory response. This suggests that gastrin heptadecapeptide is the major physiologic mediator of the human acid secretory response to meals containing mixed amino acids.

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Role of Gastrin Heptadecapeptide in the Acid Secretory Response to Amino Acids in Man

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ABSTRACT Amino acids and peptides release gastrin and stimulate gastric acid secretion. However, the relation between gastrin release and acid secretory response is unclear. An isotonic mixed amino acid solution (casein hydrolysate) was continuously infused into the stomach of eight healthy human subjects. Acid secretion, measured by *in vivo* intragastric titration, increased 12.8 meq/h over the response to intragastric infusion of isotonic saline. Plasma gastrin heptadecapeptide (G-17) concentration, measured by specific radioimmunoassay, increased 13 pmol/liter during intragastric amino acid infusion.

To determine whether this rise in plasma G-17 concentration could account for some or all of the acid secretory response, several doses of synthetic human G-17-I were infused intravenously into the same subjects. During *i.v.* G-17-I infusion, the stomach was continuously infused with isotonic saline. By graphically relating plasma G-17 concentration during *i.v.* G-17 infusion to concomitant acid secretion, it was determined that a 13-pmol/liter rise in plasma G-17 concentration could increase acid secretion 14.8 meq/h. Therefore, the rise in plasma G-17 concentration during intragastric amino acid infusion could have produced all of the observed acid secretory response. This suggests that gastrin heptadecapeptide is the major physiologic mediator of the human acid secretory response to meals containing mixed amino acids.

INTRODUCTION

Amino acids and peptides are the most potent components of food in stimulating gastric acid secretion (1). Meals containing amino acids and peptides can

elicit acid secretion by at least five mechanisms. First, these meals cause gastric distention, which elicits secretion by stimulating cholinergic reflexes in the body and fundus of the stomach (2). Second, amino acids and peptides stimulate endogenous release of various species of gastrin from the antrum and small intestine and thereby cause a rise in the circulating concentration of these secretagogues (3, 4). Third, amino acids in the gastric lumen of animals can react directly with parietal cells to induce acid secretion (5). Fourth, upon entering the small intestine, peptides and amino acids may release non-gastrin acid secretagogues from intestinal endocrine cells ("intestinal phase") (6, 7). Fifth, amino acids given intravenously stimulate acid secretion without releasing gastrin (7). To what extent these mechanisms are involved in the human acid secretory response to meals containing amino acids is unknown. For example, although intragastric amino acids release gastrin and stimulate acid secretion, it has never been demonstrated that the rise in circulating gastrin concentration is responsible for any of the acid secretory response to amino acids. It was the purpose of these experiments to determine whether the rise in circulating gastrin heptadecapeptide (G-17)¹ concentration can account for any or all of the acid secretory response to mixed amino acids in man.

METHODS

Overview of methods and rationale. An amino acid solution continuously infused into the stomach stimulated acid secretion and led to a rise in plasma G-17 concentration. As a control, saline continuously infused into the stomach stimulated acid secretion (though less than amino acids) but did not cause a rise in plasma G-17 concentration. On separate days, several *i.v.* doses of G-17-I were superimposed

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¹Abbreviation used in this paper: G-17, gastrin heptadecapeptide.

on the intragastric saline infusion; the resulting plasma G-17 concentration was related graphically to the acid secretory response. From this plot we determined how much acid secretion could have resulted from the rise in plasma G-17 concentration that was associated with intragastric amino acid infusion. This value was then compared with observed acid secretion in response to amino acids.

Subjects. Eight healthy subjects with no history of gastrointestinal disorder were each studied on three mornings, and experiments were performed in random order. Five subjects were men and three were women, with a mean age of 29 yr (range 22–45 yr). Basal acid output and peak acid output to 0.04 mg/kg histamine acid phosphate subcutaneously were 2.1 ± 0.7 and 27.9 ± 1.7 (mean \pm SEM) meq/h, respectively. No subject was taking any medication, and all gave written informed consent.

Intubation and measurement of acid secretion. In all experiments a radio-opaque triple-lumen nasogastric tube was used. Tubes 1 and 3 terminated 14 cm proximal to the tip of tube 2. After a 10-h fast, the triple-lumen tube was positioned under fluoroscopic guidance with the tip of tube 2 in the gastric antrum. Through tube 1, either an amino acid or saline solution at pH 5.0 was infused into the stomach, and acid secretion was measured by *in vivo* intragastric titration. Every 3 min a gastric sample was aspirated through tube 2. pH was determined and the sample immediately returned to the stomach. Through tube 3, 0.5 N sodium bicarbonate was infused as needed to maintain gastric pH at 5.0. The number of milliequivalents of bicarbonate added is equal to the number of milliequivalents of acid secreted (8).

Intragastric saline and amino acid infusion. To initiate the experiment, we injected 200 ml of saline (300 mosmol/kg), adjusted to pH 5.0, into the stomach as a bolus, and a constant intragastric saline infusion was then begun at a rate of 400 ml/h (Brinkman Peristaltic Pump, Desaga, Inc., Heidelberg, West Germany). After 90 min, intragastric saline infusion was stopped, the stomach emptied, and the volume recorded. At this point, a volume of mixed amino acid solution (300 mosmol/kg) (casein hydrolysate, Stuart Pharmaceuticals Div., Wilmington, Del.) equal to the volume just emptied was injected into the stomach and a constant intragastric amino acid infusion was begun at a rate of 400 ml/h. Intragastric amino acid infusion was continued for 180 min (i.e., from 90 to 270 min). Gastric volume was also measured by aspiration and reinfusion at 180 min and by aspiration at 270 min. During the 270-min experiment, 0.15 M NaCl was slowly infused intravenously.

Intravenous G-17 infusion. On two additional mornings, G-17 dose-response studies were carried out while the stomach was being continuously infused with saline for the entire 270-min experiment. As described above, a 200-ml saline bolus was injected into the stomach and saline was infused intragastrically at 400 ml/h. During a 90-min control period, 0.15 M NaCl was slowly infused intravenously. After the control period, a 90-min *i.v.* infusion of one of four G-17-I doses was begun. At 180 min, a second 90-min *i.v.* infusion of another of the four G-17-I doses was initiated. Each subject, therefore, received four different G-17-I doses over two mornings. Gastric volume was measured as above at 90, 180, and 270 min.

Preparation and dosage of G-17-I. Synthetic human G-17-I (Imperial Chemical Industries, Ltd., Cheshire, England) was diluted to 25 ml with 0.15 M NaCl in 1% human albumin and infused intravenously by a Harvard syringe pump (Harvard Apparatus Co., Inc., Millis, Mass.). Doses were 4.0, 10.0, 25.0, and 62.5 pmol/kg·h and were given in random order. These doses were selected be-

cause they seemed likely to produce plasma G-17 concentrations in the physiologic range. Since the plasma half-life of G-17-I is approximately 6 min, a steady plasma G-17 concentration should be reached within 30–45 min (3). For this reason, plasma G-17 concentration was measured every 15 min during the latter half of each 90-min *i.v.* infusion of G-17 or saline.

Plasma G-17 and gastrin measurement. Through a separate indwelling 19-gauge needle, 12 ml of venous blood was drawn into oxalate tubes from the arm opposite the *i.v.* G-17 or saline infusion. Plasma, obtained immediately by centrifugation, was stored at -20°C until assayed. Plasma G-17 concentration was measured by radioimmunoassay using L6, an antibody which has almost absolute specificity for heptadecapeptide gastrins I and II. The characteristics of this antibody have been described in detail recently (9). Coded samples were run in duplicate at 1:10 dilution and read against a standard curve of G-17 diluted in 5% gastrin-free serum prepared by charcoal extraction, and then samples were decoded.

RESULTS

Acid secretion and plasma G-17 concentration during intragastric saline and amino acid infusion. As shown in Fig. 1 (upper panel), during intragastric saline infusion, acid secretion was higher in the first 15 min than in any subsequent period, possibly because of greater gastric distention immediately after the initial 200-ml saline bolus. By 30 min, acid secretion had reached a near steady rate. Between 45 and 90 min, acid secretion averaged 1.6 meq/15 min. When intragastric amino acid infusion was substituted for saline at 90 min, the rate of acid secretion increased and reached a near steady level within 45 min. Between 150 and 270 min, acid secretion averaged 4.8 meq/15 min. This represented a rise in acid secretion of 3.2 meq/15 min (or 12.8 meq/h) over the rate of acid secretion in response to the saline control.

Plasma G-17 concentration did not change from basal levels during intragastric saline infusion (Fig. 1, lower panel). On the other hand, during intragastric amino acid infusion, plasma G-17 concentration increased from a control level of 15 pmol/liter to 31 pmol/liter by 150 min and remained near this level for the next 120 min. Between 150 and 270 min, plasma G-17 concentration averaged 28 pmol/liter, a rise of 13 pmol/liter over control. Since we were limited in the number of blood specimens we could obtain, the pattern of rise in plasma G-17 concentration was not determined.

Thus, mean acid secretion increased 3.2 meq/15 min and plasma G-17 concentration increased 13 pmol/liter with amino acid infusion. In the eight individual subjects, acid secretion in response to amino acids (expressed as a percent of peak histamine response) was correlated closely with the concomitant rise in plasma G-17 concentration ($r = 0.92, P < 0.001$).

Acid secretion and plasma G-17 concentration

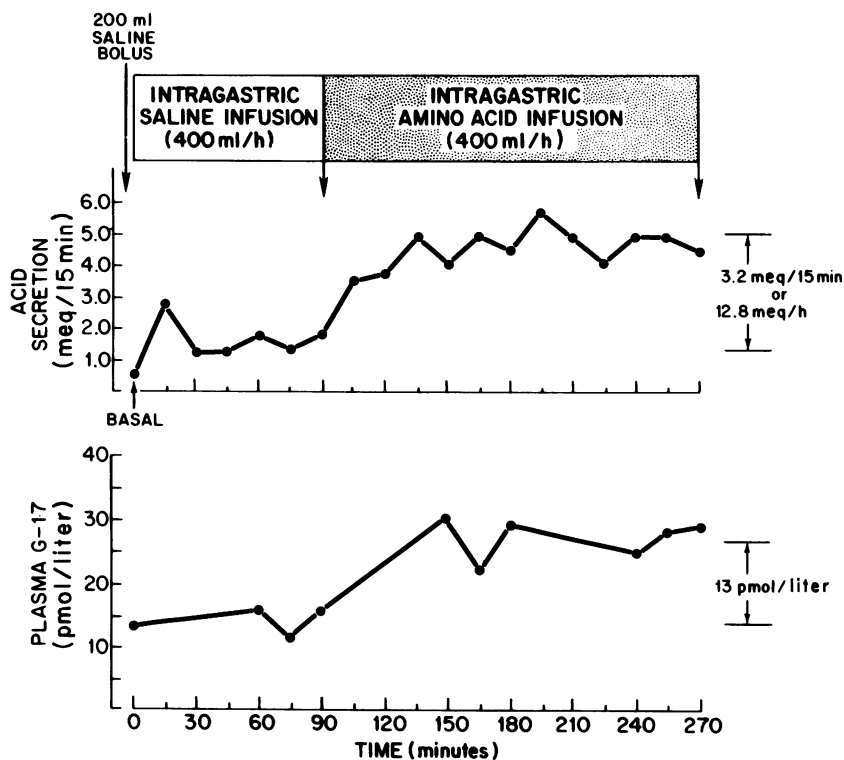


FIGURE 1 Mean acid secretion (upper panel) and plasma G-17 concentration (lower panel) in response to intragastric saline or amino acid infusion in eight subjects. Mean increments in acid secretion and plasma G-17 concentration over saline control in response to intragastric amino acid infusion are shown in brackets on the right. These were obtained by subtracting mean acid secretion and plasma G-17 concentration between 45 and 90 min (control) from mean acid and G-17 values between 150 and 270 min. Basal acid secretion (0.5 meq/15 min) is shown.

during *i.v.* G-17-I infusion. As shown in the upper panel in Fig. 2, acid secretion rates were quite steady during the latter half of each 90-min *i.v.* G-17-I infusion. Plasma G-17 concentration was also relatively constant during this period, as shown in the lower panel of Fig. 2. Infusion of 4.0 pmol of G-17/kg·h increased acid secretion significantly ($P < 0.05$) without leading to a significant rise in plasma G-17 concentration. In seven of eight subjects, acid secretion increased when this dose of G-17 was superimposed on intragastric saline infusion (Table I).

The relationship between rise in plasma G-17 concentration during *i.v.* G-17-I infusion and the corresponding rise in acid secretion, in milliequivalents per hour, is shown in Fig. 3. Each point represents the mean rise (\pm SEM) for each G-17-I dose. From this curve, the anticipated acid secretory response to a given rise in plasma G-17 concentration can be determined.

Predicted acid secretory response to rise in plasma G-17 concentration induced by amino acids. Plasma

G-17 concentration rose 13 pmol/liter during intragastric amino acid infusion (Fig. 1). As shown by the dashed line in Fig. 3, this rise in plasma G-17 concentration would be expected to increase acid secretion by 14.8 meq/h, whereas the actual increase during amino acid infusion was 12.8 meq/h. In other words, the rise in plasma G-17 concentration could have accounted for all of the acid secretory response to amino acids.

Gastric volume. The volumes of gastric contents were not significantly different whether saline or amino acids were infused into the stomach (74 ± 8 and 83 ± 9 ml [mean \pm SEM], respectively, $P > 0.15$). Likewise, when *i.v.* G-17-I was superimposed on intragastric saline infusion, gastric volume did not change significantly ($P > 0.45$ for each G-17-I dose). Since the rate of intragastric infusion of saline and amino acids was the same (400 ml/h), similar intragastric volumes imply that gastric emptying rates during intragastric saline and amino acid infusion were approximately the same.

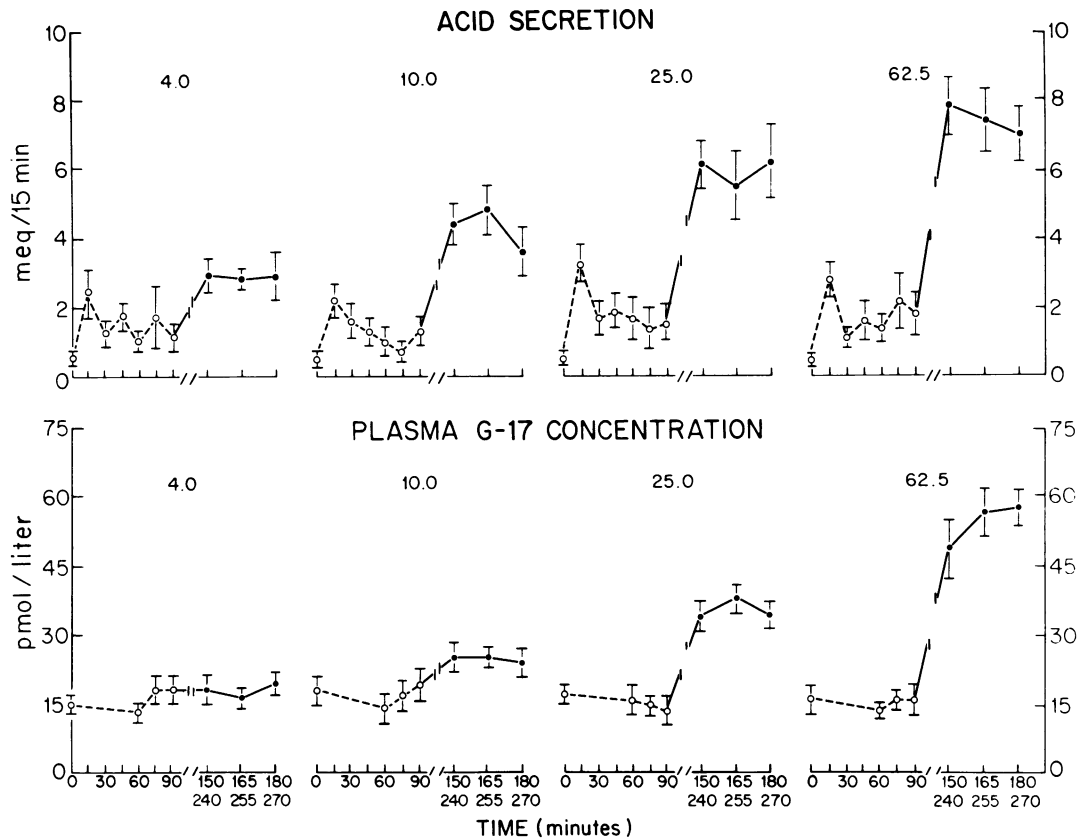


FIGURE 2 Mean (\pm SEM) acid secretion (upper panel) and plasma G-17 concentration (lower panel) in response to i.v. G-17 infusion in eight subjects. After a 90-min i.v. saline infusion (control), G-17-I doses of 4.0, 10.0, 25.0, and 62.5 pmol/kg·h were infused for 90 min (i.e., from 90 to 180 min or from 180 to 270 min). Control values are shown as open circles and dashed lines. Acid secretion and plasma G-17 concentration during i.v. G-17-I infusion, shown as solid circles and solid lines, are given for the latter half of each 90-min G-17-I infusion.

DISCUSSION

It was the purpose of these experiments to determine the potential role of G-17 in the human acid secretory response to meals containing amino acids. A constant intragastric infusion of mixed amino acids was employed instead of a normal eaten meal for several reasons. First, when a meal is eaten, G-17 levels rise rapidly and begin to fall within 30 min (9). Second, during and after a meal, gastric volume and the volume, pH, and osmolarity of chyme entering the small intestine are not constant. Third, food also contains fat and carbohydrate, which can release inhibitors of acid secretion from the small intestine. Because of these complex changes occurring during and after eating, it is impossible to determine what role a particular stimulant, such as G-17, plays in the overall secretory response.

Intragastric infusion of an isotonic mixed amino acid solution produced plasma G-17 concentrations

TABLE I
Increase (over Saline Control) in Acid Secretion (Δ Acid) and Plasma G-17 Concentration (Δ G-17) during i.v. Infusion of 4.0 pmol of G-17/kg·h in Eight Subjects

Patient	Δ Acid meq/h	Δ G-17 pmol/liter
T. H.	9.2	4
K. J.	17.4	6
J. H.	10.1	-5
S. D.	-2.7	0
A. C.	1.8	5
P. B.	0.5	-9
C. P.	4.8	7
D. M.	4.3	2
Mean \pm SEM	5.7 \pm 2.3*	1 \pm 2†

* The difference between rate of acid secretion during G-17 infusion and saline control was significant ($P < 0.05$).

† The difference between plasma G-17 concentration during G-17 infusion or saline control was not significant ($P > 0.6$).

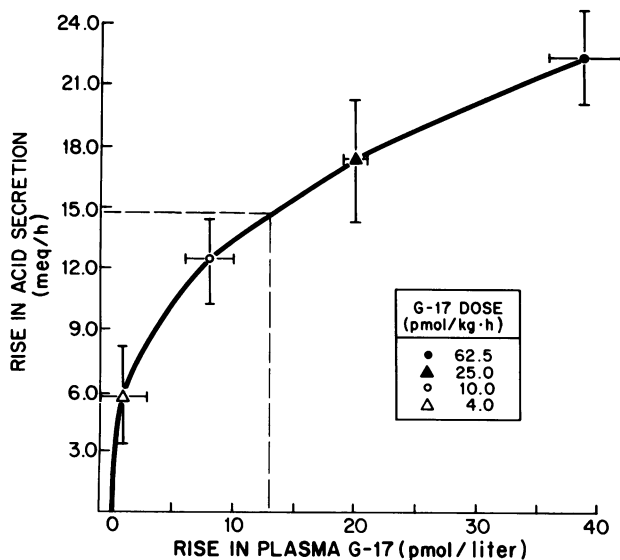


FIGURE 3 Mean (± 1 SEM) rise in acid secretion versus mean (± 1 SEM) rise in plasma G-17 concentration in response to i.v. infusion of the four G-17-I doses. Points were obtained by subtracting in individual subjects control values (i.e., mean acid secretion between 45 and 90 min and mean plasma G-17 concentration between 60 and 90 min) from levels during the latter half of each 90-min G-17-I infusion. A rise in plasma G-17 concentration in response to amino acids (13 pmol/liter) would be predicted to increase acid secretion 14.8 meq/h (dashed line). Observed acid secretion increased 12.8 meq/h (see Fig. 1).

and acid secretory rates that were stable. Likewise, continuous i.v. infusion of human G-17-I produced nearly constant plasma G-17 levels and acid secretory rates. Gastric volume equilibrated at approximately 80 ml during intragastric amino acid infusion and intragastric saline infusion (with or without i.v. G-17-I). Maintaining gastric pH at 5.0 prevented acid from entering the small intestine and stimulating release of at least some enterogastrones, such as secretin, which might inhibit acid secretion.

By infusing several doses of G-17-I intravenously during intragastric saline infusion, the relationship between plasma G-17 concentration and acid secretion could be defined in the presence of a standard degree of gastric distention. From this curve, the fraction of the acid secretory response to amino acids that could be attributed to endogenous G-17 release was determined. There were three possibilities. First, the plasma G-17 concentration achieved during amino acid infusion might be enough to explain all of the rise in acid secretion induced by amino acids. This would make it unnecessary to invoke other mechanisms of stimulation, such as direct effect on parietal cells or an intestinal phase of acid secretion. Second, the G-17 level reached during amino acid infusion

might account for none or only part of the observed rise in acid secretion noted after amino acid infusion, which would indicate that amino acids stimulate acid secretion entirely or partly by mechanisms other than endogenous G-17 release. Third, the plasma G-17 concentration achieved with amino acids might be sufficient to cause more acid secretion than was observed during intragastric amino acid infusion; this would suggest that amino acids also released inhibitors of acid secretion that blunted the expected secretory response to G-17.

We found that all the increase in acid secretion (over control) in response to amino acids could be accounted for by the resulting rise in plasma G-17 concentration. Although neither a direct stimulatory effect of amino acids on parietal cells nor an intestinal phase of acid secretion can be excluded by these experiments, there is no reason to postulate a major role for these nongastrin mechanisms in the human acid secretory response to mixed amino acids. If these mechanisms are involved, they must be opposed by inhibitors of acid secretion released by amino acids. Although secretin release would be inhibited at pH 5.0 (10), amino acids might have released cholecystokinin or gastric inhibitory polypeptide from the small intestine (11, 12). Both cholecystokinin and gastric inhibitory polypeptide, when given exogenously, can antagonize gastrin-stimulated acid secretion (13, 14).

In summary, after intragastric infusion of a mixed amino acid solution, all the increase in acid secretion over saline distention control could be accounted for by the corresponding rise in plasma G-17 concentration. This makes it likely that gastrin heptadecapeptide is the major physiological mediator of the human acid secretory response to meals containing mixed amino acids.

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