Intravenous Infusion of L-Isomers of Phenylalanine and Tryptophan Stimulate Gastric Acid Secretion at Physiologic Plasma Concentrations in Normal Subjects and after Parietal Cell Vagotomy

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ABSTRACT To determine whether intravenous infusion of individual amino acids stimulated gastric acid secretion in man, graded doses of phenylalanine, tryptophan, glycine, alanine, histidine, and NaCl control were infused on separate days in nine healthy subjects. Intravenous infusion of phenylalanine and tryptophan significantly stimulated gastric acid secretion to 50 and 52%, respectively, of the acid secretory response to intragastric peptone. Intravenous alanine and histidine were without effect, whereas glycine produced a slight response. Serum gastrin concentrations did not significantly change during intravenous amino acid infusion, except in response to 0.1 M phenylalanine. However, the increase in serum gastrin occurred 2 h after acid secretion had significantly increased in response to the 0.025 M phenylalanine infusion. Plasma amino acid concentrations were measured during intravenous amino acid infusion and in response to a steak meal in five of the subjects. At a time when acid secretion was significantly increased during intravenous infusion of phenylalanine and tryptophan, plasma amino acids were similar to, or less than, that observed after the steak meal, suggesting that circulating levels of these three amino acids have a physiologic effect on gastric secretion in man. Intravenous infusion of a combination of graded doses of phenylalanine plus a continuous infusion of 0.01 M tryptophan shifted the dose-response curve to the left and resulted in a significantly greater response than to either amino acid alone. In five subjects with parietal cell vagotomy, intravenous phenylalanine and tryptophan stimulated acid secretion, whereas histidine was without effect, similar to normal subjects.

These studies indicate that intravenous infusion of small amounts of phenylalanine (0.025 M, 3.1 mmol/h) and tryptophan (0.01 M, 1.25 mmol/h) stimulated gastric acid secretion at plasma concentrations similar to those observed after a steak meal, suggesting a physiologic role for circulating levels of these amino acids on gastric acid secretion. Because acid secretion increased at a time when serum gastrin was unchanged and since there was no correlation between changes in serum gastrin and acid secretion, the responses to phenylalanine and tryptophan are probably mediated by a nongastrin-related mechanism(s). Since both phenylalanine and tryptophan stimulated secretion in vagotomized subjects, the response is vagally independent. These observations suggest that circulating levels of these two amino acids have either a direct or indirect effect on or near the human parietal cell.

INTRODUCTION

In man and dog, intravenous infusion of a mixture of L-amino acids increased gastric acid secretion to ~30–40% of the maximal acid response to either pentagastrin or histamine (1–5). Furthermore, in man, equal amounts of a mixture of L-amino acids perfused either into the duodenum or infused intravenously result in equivalent increases in gastric acid secretion (1, 2). The mechanism of action of circulating amino acids

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on parietal cell function is not known. Since serum gastrin does not increase with either intraduodenal or intravenous amino acid infusion (1–3), it has been postulated that the intestinal phase of gastric acid secretion may be due at least in part to the direct or indirect effect of circulating amino acids on or near the parietal cell (2, 6). After removal of the gastric antrum, small bowel, colon, and pancreas, Marino and Landor (7) observed that an intravenous infusion of a mixture of L-amino acids stimulated gastric acid secretion in the vagotomized dog. This observation further supports the hypothesis that amino acids may have a direct effect on or near the canine parietal cell.

The effect of intragastric instillation of individual amino acids on serum gastrin and acid secretion has been examined in both animals and man. In man, Taylor et al. (8) observed that intragastric instillation of phenylalanine and tryptophan significantly increased gastric acid secretion and serum gastrin, while 16 other L-amino acids tested were without significant effect. However, in dogs, Konturek et al. (9) observed that gastric acid secretion increased in response to perfusion of a Heidenhain pouch with L-isomers of essential and nonessential amino acids and that this was unaccompanied by any significant change in serum gastrin. These findings indicated that individual L-amino acids were capable of increasing gastric acid secretion when they came in direct contact with the oxyntic gland mucosa by a gastrin-independent mechanism. The effects of intravenous administration of individual amino acids in man have not been previously reported.

The purposes of this study were to determine whether intravenous infusion of L-isomers of individual amino acids stimulate gastric acid secetion in man, and if the response to intravenous infusion of individual amino acids occurred within the range of plasma amino acid concentrations observed after a standard steak meal. The effect of individual amino acid infusion in subjects with parietal cell vagotomy was studied to determine if vagal innervation was necessary for a secretory response.

METHODS

Subjects. Nine normal subjects, five male and four female, (age 30.8±3.5 yr) were studied. All were in good health with no history of gastrointestinal disorders or other medical problems. In addition, five subjects (age 55±5.0 yr) were studied 34.8±5.6 mo after parietal cell vagotomy. Each had evidence of duodenal ulcer at surgery with no evidence of ulcer recurrence. Completeness of vagotomy was documented by a negative response to insulin-induced hypoglycemia (10) within 2 wk of study.

Written informed consent was obtained and these experiments were approved by the Human Subjects Committee, University of California, San Diego. Tests were performed in the morning at least 12 h after an overnight fast.

Test substances. L-isomers of five amino acids were selected: phenylalanine, tryptophan, histidine, glycine, and alanine. Sterile, pyrogen-free pure synthetic L-amino acids were used (Ajinomoto U. S. A., Inc., New York).

The amino acids were prepared for intravenous infusion under sterile conditions in a laminar flow hood. Each amino acid was carefully weighed and dissolved with sterile water in a 1,000-ml sterilized volumetric flask. Aliquots of this solution were then transferred to four 1,000-ml sterile, evacuated bottles (a gift of American McGaw, Irvine, CA) and diluted with water and 23.4% sodium chloride (Mogul Corp., Chargin Falls, OH) to make the desired concentrations of 0.0125, 0.025, 0.05 and 0.1 M of glycine, histidine, phenylalanine, and alanine, respectively; and 0.005, 0.01, 0.02, and 0.04 M of tryptophan. It was not possible to solubilize tryptophan at a concentration > 0.04 M. Each solution was isoosmolar with plasma and contained 310 mosmol/kg. Glacial acetic acid was added to the histidine solution to adjust the pH to 6.8, and sodium chloride and sterile water were added to obtain the final desired concentrations. The solutions were filtered through a 0.8-μm filter (Millex-PF; Millipore/Continental Water Systems, Bedford, MA) and a 0.22-μm sterilizing filter (Millex-GS; Millipore/Continental Water Systems) and 125 ml was transferred into sterile, evacuated bottles and autoclaved at 122°C for 20 min. Since tryptophan is not heat stable, it was sterilized by filtration only.

Sterility testing was done by using the Add-A-Check System (Millipore/Contiential Water Systems) that utilizes a 0.45-μm bacterioretentive filter to enhance detection of low levels of contamination. All cultures were found to be negative in this test. Pyrogen testing was performed on multiple bottles of each set of amino acid solutions by using the Limulus amebocyte lysate test (Limulus, Mallinckrodt, Inc., Science Products Div., St. Louis, MO) (11). All pyrogen tests were found to be negative. Sterile 0.15 M sodium chloride (Travenol Laboratories, Inc., Deerfield, IL) served as a control.

On 5 separate d each subject received an individual amino acid intravenously over a 4-h period at a rate of 125 ml/h (IVAC Corp., La Jolla, CA). Infusion was begun with the lowest dose and then was doubled every hour so that each subject received four doses of an individual amino acid on a single day. The doses of phenylalanine, alanine, glycine, and histidine were 1.56, 3.13, 6.25, and 12.5 mmol/h, and tryptophan doses were 0.62, 1.25, 2.5, and 5 mmol/h. These doses were chosen to bracket the amount of the amino acid present in Freamine II (American McGaw), previously shown to be a potent gastric secretory stimulus in man (2). As a control, 0.15 M sodium chloride was infused at 125 ml/h throughout the 4 h.

Pentagastrin (Ayerst Laboratories, New York) and regular insulin (Eli Lilly & Co., Indianapolis, IN) were refrigerated at 4°C until used. Peptone (50 g/500 ml, Bactopeptone, Difco Laboratories, Inc., Detroit, MI) was prepared just before use in hot (90°C) distilled water and allowed to reach room temperature (22°C) before administration. The steak meal consisted of 142 g of ground sirloin steak, one piece of bread, 5 g butter, and 150 ml of water; the meal contained 49 g protein, 15 g fat, 14 g carbohydrate, and 405 kcal. The steak was fried and seasoned with salt and pepper to taste just before administration.

Experimental design. In the nine normal subjects, tests were randomized according to a table of random numbers and performed on separate days. There were usually 2–3-d intervals between tests.

On each day of secretory measurement, a radiopaque nasogastric tube (14–16 Fr) was fluoroscopically passed into the

middle of the gastric antrum. Gastric residuum was manually aspirated before a 30-min basal period began. Samples of gastric secretion were collected by continuous suction supplemented by manual aspiration every 5 min in 15-min periods. Volumes were measured to the nearest milliliter. Hydrogen ion concentration was measured in vitro by automatic titration to pH 7.0 of a 0.2-ml aliquot with 0.2 N NaOH (Radiometer America, Inc., Westlake, OH). Acid output was calculated as a product of volume times concentration.

On all days except for the day of pentagastrin testing, 10 ml of venous blood was drawn from an arm vein for measurement of serum gastrin and plasma amino acids at basal and hourly intervals. Blood was drawn through a heparin lock in the contralateral arm to the intravenous infusion. Serum gastrin measurements were kindly performed by Dr. John Walsh and Ms. June Ferrari by radioimmunoassay as previously described (12). All samples were measured in a single assay with antibody 1296, which measures both big gastrin (G-34) and heptadecapeptide gastrin (G-17) with an intraassay variation of 5%. The sensitivity of the assay is 10 pg/ml. Plasma amino acid measurements were determined by high performance liquid chromatography (HPLC)[1] (13).

Peptone meal and pentagastrin response. To determine each subject's gastric acid secretory response to a protein stimulus, 50 g of peptone in a volume of 500 ml (pH 5.5) was infused intragastrically over 4 min and gastric acid secretion measured by intragastric titration (14). One lumen of the nasogastric tube (Andersen AN 10, H. W. Andersen Products, Inc., Oyster Bay, NY) was attached to a mixing pump (SEPCO model 40, Scientific Equipment Products, Division of Baltimore Machine & Equipment, Inc., Baltimore, MD) that continuously mixed 30 ml of the intragastric contents past a reference pH electrode. Whenever the pH decreased below 5.5, 0.5 M NaOH was automatically infused through the smaller lumen of the nasogastric tube. The amount of NaOH infused was assumed to equal the amount of HCl secreted by the stomach (15).

Each subject's maximal gastric acid output to pentagastrin (6 μg/kg s.c.) was measured by standard methods (16). On the day of pentagastrin administration, gastric acid secretion was measured for a 30-min basal period and for 90 min after subcutaneous administration of pentagastrin.

Plasma amino acids. To determine physiologic changes in plasma amino acids, five subjects ate the cooked steak meal over 10 min. 10 ml of venous blood was obtained before and at four hourly intervals thereafter. The blood was added to tubes containing EDTA, centrifuged at 3,000 rpm, and the plasma removed and frozen (−4°C) until measurement of plasma amino acids by HPLC.

Reproducibility and step-doses vs. single dose. To examine reproducibility, gastric acid secretion in response to graded doses of phenylalanine was repeated in five subjects. To determine whether the effect of increasing step doses was cumulative, the responses to a 4-h infusion of a single dose of 0.025 M phenylalanine, 0.025 M histidine, and 0.01 M tryptophan was compared with the response to these doses infused intravenously on the single day step-dose test in five subjects.

Interaction between individual amino acids. The interaction between amino acid combinations was studied in five subjects. The responses to graded concentrations of phenylalanine (0.0125, 0.025, 0.05, and 0.1 M each infused for 1 h), tryptophan (0.01 M for 4 h), or histidine (0.025 M for 4 h) alone, or the combination of phenylalanine with histidine, or phenylalanine with tryptophan were compared.

Effect after vagotomy. Five subjects with complete parietal cell vagotomy were studied in the same manner as described for the normal subjects. In random order and on separate days each subject received: phenylalanine, tryptophan, histidine, sodium chloride control, and pentagastrin. Phenylalanine and tryptophan were chosen because they were each potent stimulants in normal subjects and histidine was used to represent the nonstimulatory amino acids in the normal group.

Statistical analysis. Statistical analysis was performed by using two-way analysis of variance and Bonferroni's t test (17). Differences were considered significant if $P < 0.05$, and results are expressed as means±1 SEM.

RESULTS

Effect of intravenous infusion of individual amino acids on gastric acid secretion. Both phenylalanine and tryptophan significantly stimulated gastric acid secretion to ~10 mmol/h (Fig. 1). The responses to 125 ml of 0.025–0.1 M (3.1–12.5 mmol) of phenylalanine and to 0.01–0.04 M (1.25–5.0 mmol) of tryptophan were significantly ($P < 0.01$) greater than the NaCl control (Fig. 1). There was a dose-response relationship with acid secretion reaching a plateau with 0.05 M phenylalanine and 0.1 M tryptophan. The responses to 0.025 and 0.05 M glycine were small, they were less than either phenylalanine and tryptophan, however, they were significantly greater than the saline control. Neither alanine nor histidine increased secretion. The 4-h total acid outputs during each infusion were: phenylalanine, 20.3±4.2; tryptophan, 17.8±4.2; glycine, 11.5±3.8; alanine, 8.9±1.9; histidine, 6.5±2.1; and NaCl control, 9.0±4.2 mmol/h. The total acid outputs to phenylalanine and tryptophan were significantly greater than the NaCl control. The response to NaCl alone, although slightly greater during the second hour, was not significantly different from the basal response.

The individual responses to each amino acid were normalized as a percentage of the maximal response (i.e, the sum of the highest four consecutive 15-min periods) to the peptone meal (22.2±3.9 mmol/h). Intravenous infusions of 0.05 M phenylalanine and 0.02 M tryptophan stimulated secretion to 50±12 and 52±15% of the response to the intragastric peptone meal; this was significantly greater than the NaCl control, 27.4±5.0. Alanine and histidine were similar to NaCl alone; 31.4±10.7 and 23.5±4.9%, respectively. Glycine was effective only at a concentration of 0.05 M when secretion increased to 38±6% of the maximal response to peptone. When the individual maximal responses (sum of the four highest 15-min periods) were normalized as a percentage of the maximal response to pentagastrin (28.9±4.1 mmol/h), phenylalanine stimulated acid secretion to 38.6±6.4%, tryptophan to 39.0±6.2%, and glycine to 31.4±4.3%. These values were each significantly different from saline

[1] *Abbreviation used in this paper:* HPLC, high performance liquid chromatography.

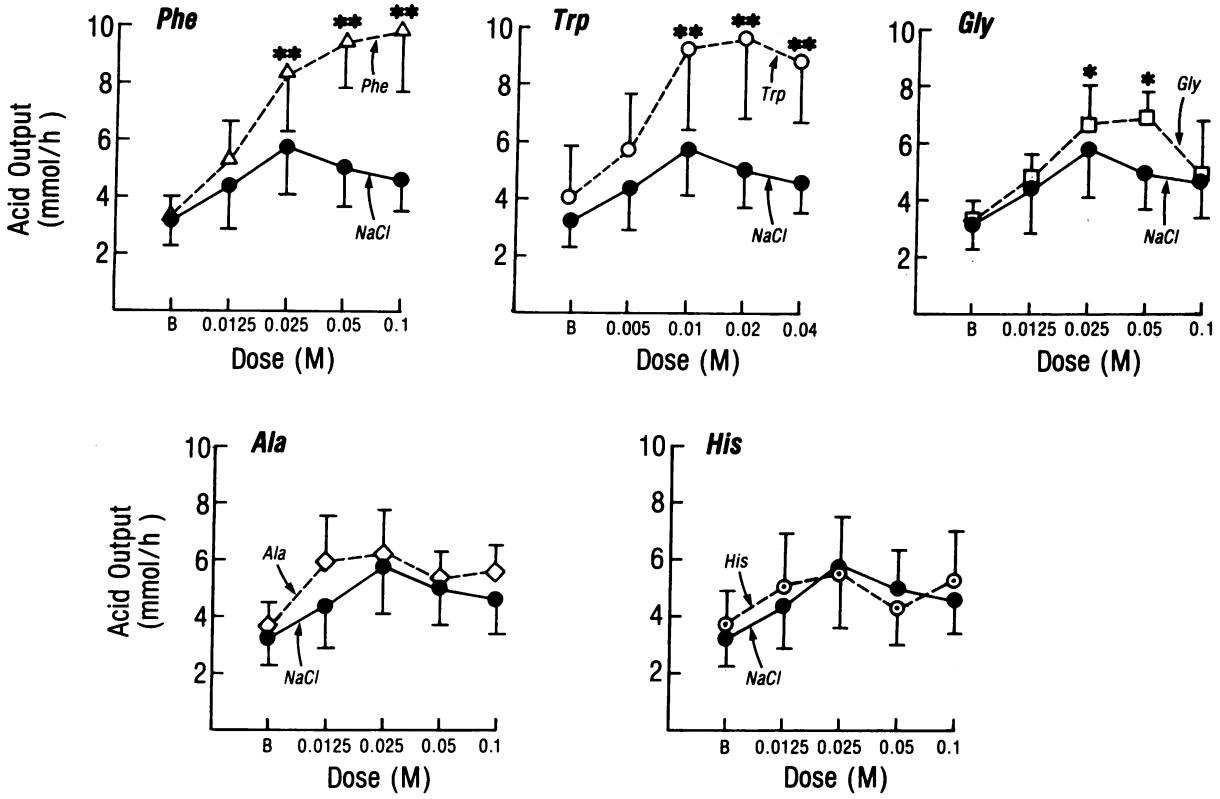

FIGURE 1 Mean (±SE) gastric acid secretory response (mmol/h) to intravenous infusion of graded doses of phenylalanine, tryptophan, glycine, alanine, histidine, and saline (NaCl) control in nine normal subjects. B indicates basal acid secretion. Each dose was infused in 125 ml over 1 h. The responses to 0.025–0.1 M Phe, 0.01–0.04 M Trp, and 0.025 and 0.05 M Gly were significantly different than the NaCl control. •• = $P < 0.01$ and • = $P < 0.05$. The responses to Ala and His were not significantly different than the NaCl control.

control (19.1±4.4%), whereas alanine (28.0±4.8%) and histidine (20.6±4.2%) were not different from the control test.

Reproducibility testing. We assessed the reproducibility of responses to graded doses of phenylalanine in five subjects. The dose-response curves on the two separate days were similar (Fig. 2). There was a significant correlation ($r = 0.71$) between the individual responses on the two test days. The mean coefficient of variation was 15.84±2.18%.

There was good agreement ($r = 0.74$; $P < 0.05$) between tests when the responses to step doses on a single day were compared with a single dose on a single day. Furthermore, the acid secretory responses to continuous intravenous infusion of a single dose of an individual amino acid did not progressively increase during the 4-h infusion. For example, the differences between the 2nd and 4th h responses to constant infusion of 0.025 M phenylalanine, 0.01 M tryptophan, and 0.025 M histidine were 0.6, 0.3, and 0.1 mmol/h, respectively.

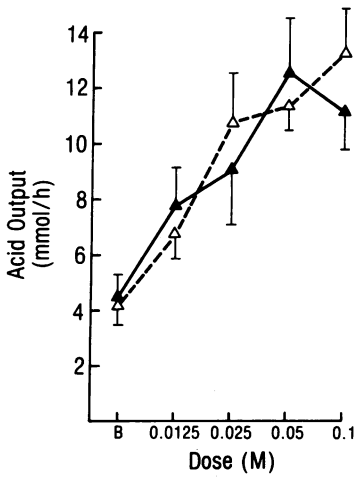

FIGURE 2 Reproducibility of phenylalanine dose-response test infused intravenously on two separate days in each of five normal subjects. The responses on separate days were not significantly different and were significantly correlated ($r = 0.71$).

Plasma amino acids. After the steak meal, plasma amino acids reached a peak during the 2nd h in 20 tests and in the 3rd h in 5 tests. Each of the amino acids significantly increased in response to the steak meal (Table I). As expected, intravenous infusion of each individual amino acid increased its respective plasma concentration. It was assumed that the change in plasma concentration during infusion of each dose of each amino acid occurred in a linear manner. Therefore, the individual mean plasma concentrations were determined by averaging the value before each dose with the plasma concentration at the end of each dose. After the steak meal, the mean peak plasma tryptophan was 115 nmol/ml, and the average of the two highest consecutive hourly concentrations were 94±7 nmol/ml (Table I). During 0.01 M tryptophan infusion, plasma tryptophan was 97 nmol/ml at a time when gastric acid secretion was significantly greater than that with basal and the NaCl control. Furthermore, after the steak meal, the peak plasma concentrations of phenylalanine and glycine were similar to or greater than the plasma concentrations during the 0.025-M infusions, when acid secretion was significantly increased. Plasma histidine increased from 80 to 316 nmol/ml during intravenous histidine infusion, greater than that observed after the steak meal, without altering secretion. During alanine infusion, plasma levels increased by only ~49 nmol/ml. However, alanine is recognized as one of the most metabolically active amino acids, it is rapidly removed from the plasma, and it may not even change in response to an amino acid-containing meal (17).

Since tryptophan and phenylalanine each significantly stimulated gastric acid secretion at plasma levels that were similar to or less than those that occurred after a physiologic stimulus, i.e. the steak meal, it is concluded that the response to circulating levels of these two amino acids is probably physiologic (18).

Serum gastrin. Serum gastrin concentrations were unchanged from basal and the saline control levels during intravenous infusion of amino acids, except in response to the highest, 0.01 M, dose of phenylalanine when it increased by 15.3±6.1 pg/ml (Fig. 3). This rise occurred 2 h after gastric acid secretion had significantly increased. The mean (±SE) changes in serum gastrin concentrations during the 0.05 M phenylalanine, 0.02 M tryptophan, and 0.05 M glycine infusions, when acid secretion had reached a plateau, were not significantly different than the change in serum gastrin concentrations in response to the saline control. Furthermore, during the intravenous amino acid infusions, there were no correlations between changes in serum gastrin concentrations and changes in gastric acid secretion (phenylalanine, $r = 0.350 \pm 0.216$; tryptophan, $r = 0.036 \pm 0.237$; glycine, $r = 0.072 \pm 0.211$; alanine, $r = -0.068 \pm 0.224$; histidine, $r = -0.236 \pm 0.157$; and NaCl, $r = 0.212 \pm 0.145$). Serum gastrin concentrations promptly and significantly increased 1 h after the steak meal and after the intragastric peptone meal (Fig. 3).

Combination studies. To examine the effects of the interaction of amino acids on acid secretion, a series of experiments were performed comparing the effect of graded doses of phenylalanine alone and combined with a continuous infusion of tryptophan (0.01 M) or histidine (0.25 M). The combination of tryptophan and phenylalanine shifted the dose-response curve to the left (Fig. 4). The maximal response to phenylalanine plus tryptophan was significantly greater than to phenylalanine alone and to tryptophan alone; 19.4±3.6,

TABLE I
Plasma Amino Acid Concentrations Before and During Intravenous Amino Acid Infusion and After Oral Steak Meal

Amino acid infused IV	Basal	0–60 min	61–120 min	121–180 min	181–240 min	Steak meal
			nmol/ml			
Phe	51±5	68±8	90±7*	103±14*	198±37*	85±7
Trp	49±5	66±6	97±8*	140±16*	244±38*	94±9
Gly	283±50	291±49	315±50*	417±75*	559±98	386±53
Ala	316±16	345±15	353±25	326±10	365±31	549±50
His	80±14	104±8	130±10	172±19	316±25	100±11

* Time period when gastric acid secretion was significantly greater than saline control.
Mean (±SE) plasma amino acid concentrations of phenylalanine, tryptophan, glycine, alanine, and histidine before (basal) and in response to intravenous infusion of each individual amino acid and after the steak meal. Each amino acid was infused in 125 ml for 1 h in increasing stepwise manner; doses of Phe, Gly, Ala, and His were 0.0125, 0.025, 0.05, and 0.1 M, respectively, and doses of Trp were 0.005, 0.01, 0.02, and 0.04 M. The steak meal contained 49 g protein and 405 kcal.

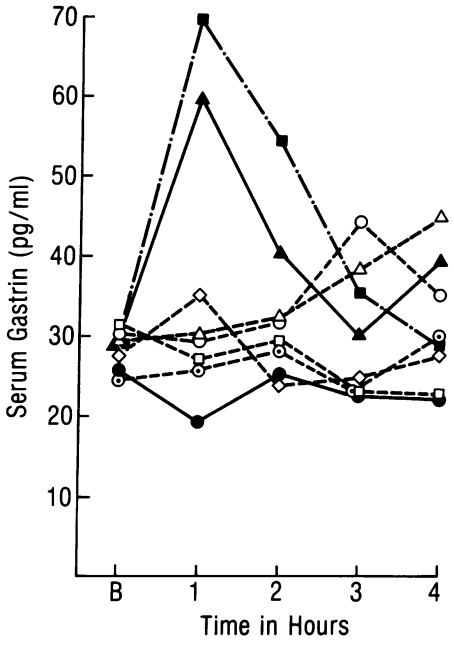

FIGURE 3 Mean hourly serum gastrin concentrations in response to oral steak meal (■), intragastric peptone (▲), intravenous infusion of graded doses (see legend to Fig. 1) of Phe (△), Trp (○), Gly (□), His (⊙), Ala (◇), and NaCl control (●). B indicates basal serum gastrin concentrations. After the steak meal and intragastric peptone, serum gastrin concentrations were significantly increased at the 1st and 2nd h. During the intravenous amino acid infusions, serum gastrin levels were not significantly different than those with the NaCl control except during the 4th h infusion during the highest dose (0.1 M) of Phe.

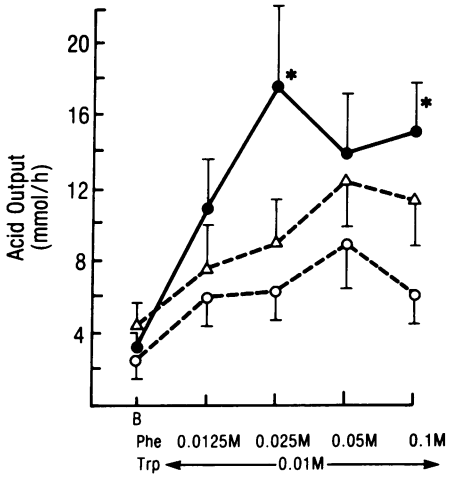

FIGURE 4 Mean (±SE) acid secretory response to graded concentrations of Phe (0.0125–0.1 M), (△) continuous 4-h infusion of 0.01 M Trp (○), and the combination of Phe plus Trp in five subjects (●). Each dose of Phe was infused intravenously for 1 h. The response to Phe plus Trp was significantly higher than the response to Phe alone at the indicated points. * indicates $P < 0.05$.

14.1±3.2, and 9.4±2.4 mmol/h, respectively. Histidine did not alter the response to phenylalanine. The maximal acid output to phenylalanine plus histidine was 12.7±2.5; to phenylalanine alone, 14.1±3.2; and to histidine alone; 8.6±0.6.

Effect after vagotomy. As in normal subjects, tryptophan and phenylalanine were significant stimulants in vagotomized subjects, whereas histidine was without effect (Fig. 5). However, in contrast with the responses in normal subjects, acid secretion continued to increase during infusion of the highest doses of phenylalanine and tryptophan rather than reaching a plateau (Fig. 1). Since vagal innervation affects both basal and maximal pentagastrin-stimulated secretion (19), the results were normalized as a percentage of maximal pentagastrin response minus basal response.

The basal acid outputs in vagotomized and normal subjects were 1.0±0.6 and 3.2±0.5 mmol/h, respectively ($P < 0.05$); and the maximal pentagastrin responses were 17.7±0.05 and 28.9±4.1 mmol/h, respectively. Maximal acid outputs to each amino acid and to saline, expressed as a percentage of maximal pentagastrin response in the subjects with vagotomy as compared with the normal subjects, were: phenylalanine 20.1±7.2 vs. 32.6±6.1; tryptophan, 26.8±8.3 vs. 30.4±5.0; histidine, 3.9±2.5 vs. 10.1±4.1; and saline, −3.2±3.2 vs. 8.8±3.9. The responses were not significantly different between the vagotomized and normal subjects (for each of the three amino acids $P > 0.2$).

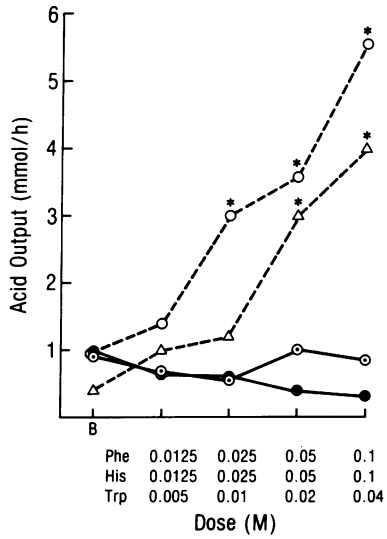

FIGURE 5 Mean acid output in response to graded concentrations of Phe (△), Trp (○), His (⊙), or NaCl (●) control in five subjects with parietal cell vagotomy. Each dose was infused intravenously in 125 ml for 1 h. * indicates $P < 0.05$ vs. NaCl control.

DISCUSSION

The results of this study indicate that (*a*) intravenous infusion of small amounts, i.e. <3.1 mmol/h, of phenylalanine and tryptophan significantly stimulated gastric acid secretion in man. Alanine and histidine were without effect; whereas glycine produced a smaller, yet significant, response. (*b*) The increase in acid secretion in response to phenylalanine, tryptophan, and glycine occurred at a time when plasma amino acid levels were similar to those observed after a steak meal, suggesting that the response may be physiologic. (*c*) The secretory responses to intravenous phenylalanine and tryptophan were independent of serum gastrin concentrations. (*d*) Vagal innervation of the parietal cell portion of the stomach was not required for the response to intravenous infusion of individual amino acids.

Gastric acid secretion in response to a maximal meal continues for ~3–4 h (20, 21), after the bulk of the meal has emptied from the stomach (22). It has been postulated that the prolonged secretory response to a meal is secondary to the intestinal phase of gastric secretion (23). Perfusion of the small intestine with either peptone or a mixture of amino acids increased gastric acid secretion to ~35% of the maximal response to pentagastrin (2, 24). Furthermore, an intravenous infusion of a mixture of L-amino acids produced an increase similar to intraduodenal infusion, suggesting that the response to intraduodenal amino acids could be largely accounted for by their effect after absorption (1–4, 6, 7). In Heidenhain pouch dogs, intravenous infusion of L-isomers of histidine, phenylalanine, glycine, tryptophan, and alanine increased acid secretion by 33–63% of the maximal histamine response without altering serum gastrin (25). Although the effect of intraduodenal infusion of individual amino acids was not examined in this study, intravenous infusion of phenylalanine or of tryptophan each increased acid secretion to ~39% and glycine to 31%, of the response to pentagastrin. Therefore, the response to intraintestinal amino acids may in largest part be due to the humoral effect after absorption.

Furthermore, phenylalanine and tryptophan each increased acid secretion to >50% of the response to an intragastric peptone meal containing > 235 mmol of amino acids (26). Feldman et al. (27) reported that a continuous intragastric infusion of mixed amino acids permitted to empty into the small intestine increased acid secretion by 13 mmol/h. In our subjects, 3.13 mmol of intravenous phenylalanine and 1.25 mmol of tryptophan increased gastric acid secretion by 5.2 and 5.3 mmol/h, respectively. Since the parietal cell mass was similar in these two different populations, phenylalanine and tryptophan could have accounted for ~40% (5.2/13) of the response to the amino acid mixture.

Grossman (18) defined a physiologic response to a hormone as that response that occurs with an exogenous infusion of the hormone that produces equal or lower blood levels than that produced by a physiologic stimulus. In this study, a standard steak meal was selected as an appropriate physiologic stimulus to measure changes in plasma amino acids. We do not intend to imply that the acid secretory response to a steak meal, which involves complex interactions of neural and humoral agonists and antagonists (21), is mediated in largest part by circulating amino acids. After the steak meal, however, plasma levels of each tested amino acid significantly increased. During the 0.025-M phenylalanine and 0.01-M tryptophan infusions, when gastric acid secretion was significantly greater than the saline control, the respective plasma amino acid concentrations were similar to, or less than, those after the steak meal. This would suggest that circulating levels of these amino acids could be considered physiologic stimuli of gastric acid secretion in man. The secretory response to 0.025 M glycine, although significant, was less than either phenylalanine or tryptophan, and requires further study.

It is possible that intravenous infusion of other individual amino acids may stimulate gastric acid secretion in man. However, if the response to intragastric amino acids (8) is a reflection of the response to intravenous amino acids, other amino acids may not be stimulatory. This can only be answered by systematic study.

Vagal stimulation to the stomach is a well recognized stimulus of gastric acid secretion (21, 23). Conversely, interruption of vagal innervation to the stomach by vagotomy decreases both basal and pentagastrin- or histamine-stimulated secretion (16). The results observed in subjects after vagotomy indicate that extrinsic vagal innervation is not necessary for the response to phenylalanine or tryptophan. Similar to the normal subjects, histidine did not alter secretion in subjects after vagotomy. Furthermore, in the subjects with vagotomy, acid secretion did not reach a plateau during infusion of the largest doses of phenylalanine or tryptophan as it did in the normal subjects. Whether this represents the effect of vagotomy, duodenal ulcer, or other factors requires further study. Also, the role of local cholinergic innervation needs to be examined.

During intravenous infusion of the five individual amino acids, total serum gastrin concentrations did not significantly change from basal concentrations or when compared to the saline control concentrations, except during the highest dose of phenylalanine when serum gastrin increased by 15.3 pg/ml. After an oral protein meal, ~40% of the increase in serum gastrin is due

to heptadecapeptide gastrin (G-17) and 60% is due to big gastrin (G-34) (28). Since the change in total serum gastrin were small, and since the sensitivity of the gastrin radioimmunoassay is ~10 pg/ml, gastrin fractions were not measured. However, if the increase in serum gastrin fractions after intravenous amino acids follows a similar pattern as it does after an intragastric protein meal, the increase in serum G-17 during the 0.1 M phenylalanine infusion would only be ~6 pg/ml or ~2.9 fmol/ml. Others (26, 27) have observed that an increase in serum G-17 of 3 fmol/ml increased gastric acid secretion by ~6 mmol/h. Therefore, the secretory response to the highest dose of phenylalanine may be due to the increase in serum gastrin concentrations. However, when gastric acid secretion was significantly increased during the 0.025 M dose of phenylalanine and the 0.01 M dose of tryptophan, total serum gastrin levels were only changed by 5.8, and −2.4 pg/ml, respectively. It is not known whether this slight change in serum gastrin levels: played a partial role in, totally explained, or had nothing to do with the secretory response. Further refinements to improve the sensitivity of the gastrin radioimmunoassay may provide an answer to this question. However, after intragastric instillation of amino acids or small peptides, significant positive correlations between changes in serum gastrin concentrations and acid secretion have been observed (8, 27, 28), indicating that gastrin release is an important factor in the secretory response to oral amino acids. In this study with intravenous amino acids there was no correlation between changes in serum gastrin levels and changes in acid secretion. This would tend to suggest that acid secretion and circulating serum gastrin were unrelated.

It is not possible to be certain of the mechanism(s) responsible for the amino acid-induced secretory effect. It is possible that phenylalanine and tryptophan stimulate gastric acid secretion by directly affecting the parietal cell to secrete acid, or by an indirect mechanism such as stimulating the release of histamine, gastrin, or other gastric secretory agonists. Another less likely possibility is that intravenous infusion of one of these amino acids produces their effect by inhibiting the level of circulating or local antagonists of acid secretion, e.g. secretin and somatostatin. To determine whether or not the effect on the parietal cell is direct, studies with in vitro human, isolated parietal cells (29) or isolated human gastric glands (30) are needed.

Many amino acids, including phenylalanine and tryptophan, cross the blood-brain barrier (31), and the mammalian brain contains many gastrointestinal hormones (32), some that are capable of altering gastric secretion e.g., somatostatin, cholecystokinin-8, secretin, vasoactive intestinal polypeptide, met-enkephalin). Therefore, it is possible that the stimulatory effect of phenylalanine and tryptophan could be due to a central, non-vagal-dependent, mechanism.

In summary, intravenous infusion of small quantities of phenylalanine and tryptophan stimulated gastric acid secretion in man without altering serum gastrin and produced their effects at plasma concentrations that were similar to those after a steak meal. In subjects with parietal cell vagotomy, the response to phenylalanine, tryptophan, and histidine were similar to those of normal subjects. These findings suggest that circulating levels of phenylalanine and tryptophan may have a physiologic role in the regulation of gastric acid secretion independent of both vagal innervation and gastrin release.

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