Relationship between amino acid dose and gastric secretory response

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SUMMARY Gastric secretory dose-response studies, using an 8.5% mixed L-amino acid solution as the agonist, were carried out in three dogs with Heidenhain pouches and gastric fistulae. Secretory responses of the Heidenhain pouches were measured during two hour infusions of amino acids given at rates of 0, 0.05, 0.1, 0.2, 0.4, 0.8, and 1.6 g/kg/h and plasma amino nitrogen was measured before and during the infusion. Three separate studies at each dose level were made in each dog. The maximum secretory response occurred at the dose of 0.4 g/kg/h and amounted to approximately 20% of the maximal histamine response. Larger doses produced no additional increase in secretion or an actual decrease in secretory rate. It is concluded that the solution of amino acids used acts as a modest gastric agonist and that increases in plasma amino nitrogen such as may be observed after a protein meal are capable of eliciting a slight, but definite, gastric secretory response.

The question whether amino acids would stimulate gastric secretion directly has been a long-standing one. Evidence, until recently, was equivocal, with most early work showing little or no stimulation^{1,2} and suggesting that the vagus nerves were essential for amino acid induced stimulation.^{3,4} Recent work⁵ has demonstrated conclusively that canine gastric secretion from a denervated pouch, as well as from the innervated stomach, is stimulated by the intravenous administration of a mixed solution of L-amino acids. This has been confirmed by Isenberg and Maxwell⁶ in the case of the innervated stomach of man.

Because relatively modest secretion was evoked by a purely arbitrary dose of amino acids in our earlier studies, it seemed important to determine the potency of amino acids as gastric secretagogues in relation to standard methods of stimulation of gastric secretion. Consequently, the current study was undertaken to measure the gastric secretory response to a range of doses of amino acids and to attempt to correlate this response with the level of amino nitrogen in the plasma.

Method

Three female mongrel dogs were each prepared with a Heidenhain pouch and gastric fistula. Operations

were performed aseptically with the dogs fully anaesthetised, and a recovery period of three to four weeks was allowed before secretory studies were undertaken. The studies were carried out after an 18 hour fast, during which water was allowed, and were repeated no more often than thrice weekly. With the dogs in modified Pavlov stands, an intravenous solution of 0.9% NaCl was begun. Secretion from the pouches was collected each 30 minutes and the H⁺ ion content was determined; secretion from the main stomach was allowed to drain externally and was discarded. After a basal collection period of 60 minutes the test solution was administered by a peristaltic pump at a constant infusion rate for two hours. The test solution consisted of an 8.5% solution of mixed L-amino acids (Freemine II, McGaw Laboratories) given at a dose of 0.05, 0.1, 0.2, 0.4, 0.8, or 1.6 g/kg/h or of a solution of 0.9% sodium chloride (control) given at 30 ml/h. Only one dose was given on each test day and the order in which the various doses was given was randomised. Three tests at each dose, as well as three control infusions, were made in each dog. Blood was taken during the basal period and at 30 and 90 minutes after start of the test infusion. After centrifugation, the plasma was frozen and stored at -20°C for subsequent amino nitrogen determinations by the method of Goodwin.⁷

When the dose which gave the maximum response had been determined, a second series of experiments was carried out to ensure that hyperosmolality of

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the test solution had not altered the secretory response. Tests were performed in the same way as those described above but with the single dose of 0.4 g/kg/h given either as the 8.5% solution (850 mOsm/l) or as a 3% solution (300 mOsm/l). Three tests with each solution were done in each of the three dogs with the gastric fistula open and also with the gastric fistula closed.

The mean of three maximal histamine responses (80 $\mu\text{g/kg/h}$ histamine) in each dog was taken as the dog's maximal response and gastric secretory responses to amino acids were expressed as percentage of maximal response. When differences between mean responses were compared, significance was assessed by using the *t* test for paired values.

Results

As can be seen in Fig. 1, the administration of larger doses of amino acids was associated with a greater gastric secretory response up to, and including, a dose of 0.4 g/kg/h. At this level, the gastric secretory response was approximately 20% of the maximal histamine response; the absolute mean secretory rate at this dose was $974 \pm 180 \mu\text{mol H}^+\text{ion/h}$. With the amino acid infusion at 0.8 g/kg/h, the acid secretory rate was essentially unchanged from that produced by 0.4 g/kg/h. With a further increase in infusion rate to 1.6 g/kg/h, there was a drop in secretory output to approximately 13% of the maximal histamine response. There was good correlation between the mean plasma amino nitrogen

Fig. 1 Mean gastric secretory responses and mean plasma amino nitrogen (SI: $\times 0.714$) during two-hour infusions of amino acids at various dose levels. Columns represent mean HCl secretion expressed as per cent maximal histamine response and vertical lines represent 1 SEM. Circles represent mean plasma amino nitrogen at 90 minutes.

Fig. 2 Mean secretory responses to the maximally effective dose of amino acids (0.4 g/kg/h) given as a 3% solution or as an 8.5% solution with gastric fistulae open or closed. Columns represent mean HCl secretion expressed as per cent maximal histamine response and vertical lines represent 1 SEM.

rise and acid secretion up to the dose which produced maximum secretion (correlation coefficient, $r=0.65$; $P<0.05$). Above this level, although there was a sharp increase in amino nitrogen, there was no further rise in acid output.

When the secretory response to 0.4 g/kg/h of amino acids given as a 3% solution was compared with that to the same dose given as an 8.5% solution, there was no significant difference ($P>0.45$), as seen in Fig. 2. With both solutions, significant inhibition of the secretory response to amino acids occurred when acid secretion from the main stomach was allowed to enter the duodenum by closure of the gastric fistula ($P<0.01$ in each case).

Discussion

It is apparent from these studies that a solution of mixed L-amino acids acts as a gastric secretagogue in a fashion not dissimilar from that of the more widely studied histamine and gastrin.^{8,9} These agents have in common the fact that larger doses are associated with greater secretory responses to a certain dose level, beyond which an increase in dose is associated either with no further rise or with an actual decrease in secretory response. Because the amino acid solution used is capable of stimulating gastric secretion to a level no greater than 20% of that seen with maximal histamine stimulation, it must be considered to be a relatively weak gastric agonist.

The hyperosmolarity of the solution apparently had no effect on gastric secretion, for identical

secretory responses were obtained at the maximally effective dose whether an isosmotic or hyperosmotic solution were given. Furthermore, the physiological inhibition of gastric secretion which takes place when acid from the stomach is allowed to flow into the duodenum (gastric fistula closed) was equally effective with both solutions.

Interest in amino acids as possible agonists for gastric secretion stems largely from the fact that they may be involved in the mediation of the intestinal phase of gastric secretion, which is activated by the presence of protein in the small bowel. Frame¹⁰ has shown that a 60 g protein meal in man is accompanied by mean rises of approximately 1.1 to 1.4 mmol/l (1.5 to 2.0 mg%) in plasma amino nitrogen. An increase in plasma amino nitrogen of this magnitude in our experiment evoked gastric secretion in the range of about 3 to 5% of the maximal histamine response. Thus, it seems likely that amino acids, absorbed into the gut, account for a significant proportion of intestinal phase secretion.

Whether or not amino acids contribute appreciably to the intestinal phase of gastric secretion, their current widespread use for the nutritional support of patients whose caloric needs cannot be supplied *via* the gastrointestinal tract makes their gastric secretory effect of interest to clinicians. At rates of administration generally used clinically in man, the secretory response of the dogs was no higher than 3% of the maximal histamine response, a level of secretion that is probably not high enough to be a cause for concern.

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