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STIMULATION OF SECRETION OF GASTRIC INHIBITORY POLYPEPTIDE AND INSULIN BY INTRADUODENAL AMINO ACID PERFUSION

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The effect of intraduodenal or intravenous administration of a 30-gm mixed amino acid solution on serum gastric inhibitory polypeptide (GIP), α-amino nitrogen (AAN), glucose, and insulin concentrations was studied in 10 normal subjects. Initially, an intraduodenal amino acid perfusion (15 ml per min $\times$ 60 min) was performed in each subject and was followed in 1 to 2 weeks by an intravenous infusion. Peak AAN concentrations occurred at 60 min after both routes of administration, but were greater with intravenous infusion, 145 $\pm$ 5.7 μg per ml vs. 89 $\pm$ 4.4 μg per ml ($P < 0.001$). Although serum AAN levels were significantly lower after intraduodenal administration, incremental insulin concentrations were greater after intraduodenal perfusion, 77.3 $\pm$ 8.8 μU per ml vs. 43.1 $\pm$ 5.6 μU per ml ($P < 0.005$). Total integrated insulin secretion was also greater after intraduodenal amino acids, 5000 vs. 2400 μU-min ml^{-1} ($P < 0.005$). With intravenous amino acid infusion, serum GIP concentrations remained below the assay detection limit. After intraduodenal perfusion, a mean maximum GIP increment of 468 pg per ml occurred at 15 min. In all subjects peak GIP concentrations occurred at 15 min and preceded the maximum insulin rise by 15 to 30 min. Total integrated GIP secretion was significantly greater after intraduodenal amino acid perfusion, 13,000 pg-min ml^{-1} vs. no measurable response with intravenous infusion. In separate studies performed in 12 subjects, no significant changes in serum GIP concentrations occurred after intraduodenal perfusion of 0.45% saline, 0.9% saline, or 10% mannitol. The results of this study demonstrate that intraduodenal amino acid administration stimulates the secretion of GIP and suggest that endogenously released GIP may be important in the enteric mediated release of insulin.

It is well established that orally administered glucose results in higher blood concentrations of immunoreactive insulin than those obtained after intravenous administration of comparable amounts of glucose.[1, 2] A similar pattern of insulin secretion also occurs after intraduodenal instillation of amino acids.[3] It is commonly held that this difference in insulin secretion is due to the release of an insulinotrophic intestinal hormone. Whereas several hormones, including gastrin, secretin, cholecystokinin (CCK), and enteroglucagon, have been implicated in this incretin effect,[4] the data available do not permit a firm conclusion as to the hormone, combination of hormones or other, as yet unidentified, insulin-releasing factors responsible for this effect.

Gastric inhibitory polypeptide (GIP) is a 43 amino acid straight chain polypeptide isolated during purification of CCK and subsequently detected by immunological methods in the proximal small intestinal mucosa and in human serum.[5-7] Physiological studies in animals have demonstrated that GIP is an effective inhibitor of gastric acid secretion stimulated by histamine, pentagastrin, or insulin hypoglycemia, and has inhibitory effects on gastric motility.[7] Previous studies in the authors' laboratory have shown that oral glucose ingestion results in elevations in serum GIP concentrations of greater than 700 pg per ml in man.[8] In contrast, intravenously administered glucose does not stimulate GIP release. Dupre et al., using intravenous purified porcine GIP in doses which raised serum GIP concentrations to those obtained in serum after alimentary glucose, have shown that GIP potentiates the pancreatic β-cell response to intravenous glucose and accelerates

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peripheral glucose disposal.[9] These observations demonstrate that GIP is insulinotropic and suggest that it may be a mediator of the enteroinsular axis. If GIP is an important factor in the eneric mediated release of insulin, one would anticipate that other nutrients known to augment insulin secretion, such as amino acids, would also stimulate the release of GIP. To test this hypothesis, we have studied serum GIP and insulin concentrations in response to intraduodenal and intravenous administration of a mixed amino acid solution in man. The observations obtained indicate that intraduodenal amino acid perfusion results in significant elevations of serum GIP concentrations in association with an augmentation of insulin secretion.

Methods

Ten healthy ambulatory volunteer subjects (6 males and 4 females) with an age range of 23 to 34 years were studied on the Clinical Research Unit of the Ohio State University Hospital after informed written consent was obtained. None of the subjects was receiving medication, including oral contraceptives, and all were within 10% of their ideal body weight. All had normal carbohydrate tolerance as determined by oral glucose tolerance testing. None had a family history of diabetes mellitus.

After a 12-hr overnight fast, a double lumen polyvinyl tube equipped with a proximal occluding balloon to diminish reflux orad was fluoroscopically positioned with the infusion port in the mid-duodenum. After a 30-min equilibration perfusion with isotonic saline, the amino acid test solution was infused for 60 min at a constant rate of 15 ml per min with a peristaltic infusion pump. The mixed amino acid solution was prepared from individual amino acids (table 1). The 30-gm mixed amino acid test solution was chosen for these studies since it has been shown to be a maximal protein stimulus for insulin secretion in man.[10] This solution (211.8 mM) was adjusted to 300 milliosmoles per kg by addition of sodium chloride; the *p*H was adjusted to 7.0 with 0.1 N sodium bicarbonate, and the solution was millipore filtered and warmed to 37°C. At intervals of 0, 5, 15, 30, 60, 120, and 180 min, venous blood samples were obtained for determination and α-amino nitrogen (AAN), glucose, and immunoreactive GIP and insulin concentrations. One to 2 weeks after the intraduodenal perfusion experiments, similar studies were carried out in the same subjects with intravenously infused amino acids. After a 30-min isotonic saline infusion, the identical mixed amino acid solution was infused into an antecubital vein at a constant rate of 15 ml per min. Blood samples were obtained from the opposite arm at intervals identical to those described above.

TABLE 1. *Composition of amino acid solution*

Amino acid	mM
Arginine	16.7
Histidine	9.5
Isoleucine	21.5
Leucine	36.0
Lysine	31.0
Methionine	19.1
Phenylalanine	23.6
Threonine	18.7
Tryptophan	4.9
Valine	30.8
Total	211.8 (30 g)

In addition to the amino acid perfusion studies, separate experiments were carried out in a second group of 12 normal subjects (age 20 to 31 years) to determine the effect of changes in the osmolality of the duodenal perfusate on serum GIP concentrations. Eight of these subjects served as volunteers for the amino acid experiments. For these studies the mid-duodenum was perfused with either 0.45% saline (154 milliosmoles per kg), 0.9% saline (308 milliosmoles per kg), or 10% mannitol (549 milliosmoles per kg) at a rate of 15 ml per min using an occluding balloon perfusion tube as described above. Blood samples were obtained before perfusion and at 5, 15, 30, and 60 min after the perfusion was begun.

Serum AAN concentrations were performed in duplicate by a modification of the method of Lacey and Crofford.[11] Serum glucose concentrations were measured in duplicate by the glucose oxidase method with a Beckman glucose analyzer. Serum insulin was determined by immunosorbent radioimmunoassay in which the antibody is coupled covalently to cross-linked dextran, Sephadex.[12] Immunoreactive GIP was determined by minor modifications of the method of Kuzio et al.[13] Highly purified porcine GIP was labeled with ^{125}I according to the technique of Hunter and Greenwood.[14] The reaction mixture was purified on a cellulose (CF 1) column (10 by 0.7 cm). The column was washed with 16 ml of 0.2 N acetic acid and labeled GIP eluted with 1.0-ml aliquots of 0.2 N acetic acid containing 10% hormone-free human serum. The fraction having the greatest immunoreactivity with excess anti-GIP serum (1:200) was used in the assay. Binding with excess anti-GIP serum ranged between 80 and 85%. The specific activity of ^{125}I-GIP so obtained was calculated to be 230 to 250 mc per mg. Although GIP shares certain homologies with glucagon, secretin, and vasoactive intestinal peptide, the guinea pig antiserum to porcine GIP had no immunological cross-reactivity with these hormones or with synthetic human gastrin I or with highly purified CCK. This same antibody has also been shown to have no cross-reactivity with motilin.[13] The composition of the incubation mixture for the standard curve was as follows: 100 μl guinea pig antiserum at an initial dilution of 1:3000 200 μl of charcoal-extracted hormone-free serum; 100 μl ^{125}I-GIP containing 5000 to 6000 counts per min; 100 μl of standard GIP in concentrations ranging from 25 to 600 pg per 100 μl; diluent buffer (0.05 M phosphate buffer, *p*H 6.5) containing 2% rabbit serum was added to a final incubation volume of 1.0 ml. For the assay of test sera 200 μl of serum was substituted for the GIP standard and an appropriate quantity of diluent buffer was added to a final incubation volume of 1.0 ml. Incubations were carried out at 4°C for 48 hr with ^{125}I-GIP being added after a 24-hr preincubation delay. Bound and free GIP were separated using polyethylene glycol according to the method of Desbuquois and Aurbach.[15] Nonspecific binding, i.e., precipitated radioactivity in the absence of antiserum, was 5.0 ± 1.2% SD. All assays were done in triplicate. In our laboratory, incubation times of up to 72 hr have resulted in no loss of immunoreactivity. However, incubations of 96 hr or more have resulted in a significant loss of immunological reactivity. The sensitivity of the assay in our laboratory is 25 pg, allowing the detection of 125 pg of GIP per ml of serum. The coefficient of variation was 8.0% for intra-assay and 14.8% interassay reproducibility. For statistical purposes, values below assay sensitivity were considered as zero.

Total integrated serum GIP and insulin were calculated from the areas curcumscribed by their respective curves and expressed as pg-minutes ml^{-1} and μU-minutes ml^{-1}, respectively.

Results were analyzed by standard methods using the paired *t* test and are expressed as mean ± SEM.

Results

Serum insulin concentrations after amino acid administration. Serum AAN concentrations increased after either route of amino acid administration. Maximum AAN levels were reached at 60 min after both the intraduodenal and intravenous routes of administration (fig. 1). There was a rather rapid rise in serum insulin concentrations at 5 min after either route of administration, with the peak insulin increment occurring at 30 min in both. Thereafter, serum insulin concentrations fell progressively and had returned to basal levels by 180 min. Although peak serum AAN concentrations after intraduodenal administration were lower than those after intravenous infusion (89 ± 4.4 vs. 145 ± 5.7 μg per ml, $P < 0.001$). The increments in serum insulin concentrations were significantly greater with intraduodenal administration at 30 min (77.3 ± 8.8 μU per ml vs. 43.1 ± 5.6 μU per ml, $P < 0.005$) and at 60 min (48.0 ± 4.7 μU per ml vs. 34.1 ± 3.8 μU per ml, $P < 0.05$).

Serum glucose tended to fall with both routes of administration, but the decreases were not significantly different from the fasting serum glucose concentrations. The failure of serum glucose concentrations to decrease significantly, in spite of an 80 μU per ml increment in serum insulin after intraduodenal amino acids, is probably attributable to simultaneous stimulation of pancreatic glucagon secretion, which in turn would tend to raise serum glucose.[16]

Serum GIP concentrations after amino acid administration. Before duodenal perfusion of amino acids, serum GIP concentrations were below the assay detection limit of 125 pg per ml in 7 of the 10 volunteer subjects. In the other 3 subjects preperfusion GIP concentrations were 290 pg per ml, 277 pg per ml, and 260 pg per ml. With intraduodenal amino acid perfusion, serum GIP concentrations increased significantly in all 10 subjects. The mean maximum GIP concentration occurred at 15 min (523 ± 42 pg per ml) and was significantly elevated over values obtained at 0 min ($P < 0.001$). This represents a mean incremental rise in serum GIP to 468 pg per ml. In all subjects peak serum GIP concentrations were obtained at 15 min and in all, the maximum rise in serum GIP concentration preceded the peak serum insulin level by 15 to 30 min. Although serum GIP concentrations began to fall at 30 min (334 ± 49 pg per ml), they remained significantly elevated above preperfusion values ($P < 0.01$).

Serum GIP concentrations were below assay sensitivity (125 pg per ml) in all 10 subjects before intravenous amino acid infusion. In contrast to intraduodenal amino acid perfusion, serum GIP concentrations did not increase after intravenous amino acid administration and remained below the assay detection limit during the entire 180-min study period.

Total integrated GIP and insulin secretion. Total integrated GIP and insulin secretion after intraduodenal and intravenous amino acids are shown in fig 2. Total GIP secretion was significantly greater ($P < 0.001$) after intraduodenal amino acids as compared to intravenous infusion, 13,000 pg-min ml^{-1} vs. no measurable secretory response. Total insulin secretion was also significantly greater ($P < 0.02$) after intraduodenal perfusion, as compared to intravenous infusion, 5000 μU-min ml^{-1} vs. 2400 μU-min ml^{-1}, respectively.

Effect of changes in osmolality of duodenal perfusate in serum GIP concentration. The effect of changes in the osmolality of the duodenal perfusate on peak incremental serum GIP concentrations is shown in fig. 3. Fasting serum GIP concentrations were below assay sensitivity in 4 of the 6 subjects having mannitol perfusions, 8 of the 10 subjects having 0.9% saline perfusions, and 4 of the 6 subjects having 0.45% saline perfusions. Thus, fasting GIP levels in these subjects were similar to those obtained in the subjects having amino acid perfusion. Compared to preperfusion concentrations there were no significant differences in the peak serum GIP values

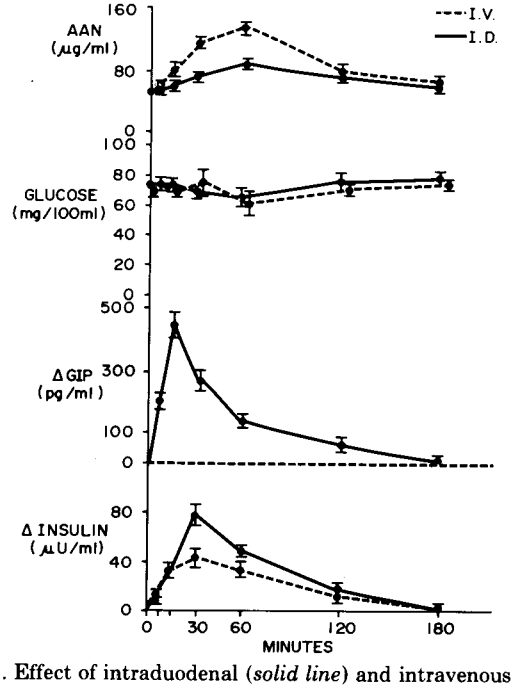

FIG. 1. Effect of intraduodenal (*solid line*) and intravenous (*broken line*) infusion of a mixed amino acid solution (15 ml per min) on serum AAN, glucose, incremental GIP, and incremental insulin concentrations. Shown are mean ± SEM of 10 experiments.

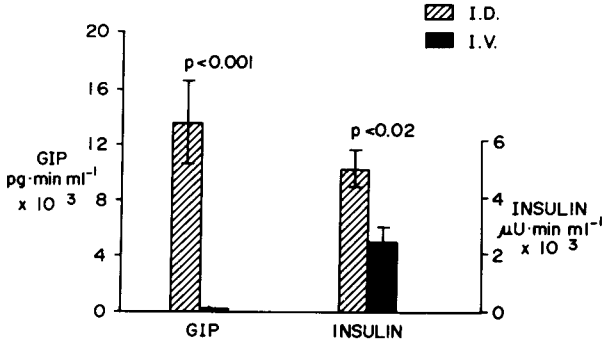

FIG. 2. Total integrated GIP and insulin secretion after intraduodenal (*ID*) and intravenous (*IV*) amino acids. Shown are mean ± SEM.

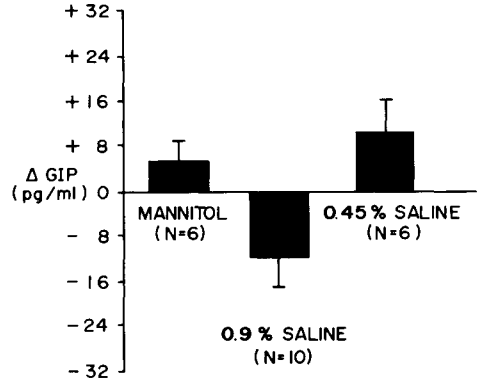

FIG. 3. Effect of intraduodenal perfusion of 0.45% saline, 0.9% saline, and 10% mannitol on peak incremental GIP concentrations. Shown are mean ± SEM. *Numbers in parentheses* represent number of subjects studied.

obtained after intraduodenal perfusion of hypotonic saline, isotonic saline, or 10% mannitol.

Discussion

Previous studies have demonstrated that the intraduodenal administration of amino acids results in a greater rise in serum insulin concentrations than that obtained after intravenous administration.[3] This augmented insulin secretion after intestinal instillation of amino acids was attributed to CCK. The data obtained in the present investigations confirm the differential pancreatic β-cell response to intraduodenal and intravenous amino acids, but suggest a possible role for GIP in mediating this effect.

We have demonstrated that intraduodenal amino acid perfusion causes the endogenous release of GIP in association with enhanced insulin secretion. Whereas maximum GIP concentrations are less than those previously reported after oral glucose,[8] the temporal relationship between the increases in serum GIP and insulin concentrations, together with the failure of intravenous amino acids to stimulate GIP secretion, suggests that endogenously released GIP is insulinotropic. In this connection, Dupre et al. have shown that administration of physiological quantities of purified porcine GIP to normal human subjects potentiates insulin secretion after intravenous glucose infusion and improves glucose tolerance.[9] However, neither exogenous nor endogenous GIP stimulated insulin secretion in the absence of simultaneous glucose administration.[9, 17] The results of the present study suggest that GIP may also augment insulin secretion in the presence of hyperaminoacidemia. Although we have not administered GIP to human volunteers, preliminary studies in animals have shown that administration of purified porcine GIP potentiates the increase in serum insulin concentration after intravenous amino acid infusion (F. B. Thomas et al. *unpublished observations*).

The precise mechanism responsible for the endogenous release of GIP remains incompletely answered by our studies. It is clear, however, that an intraluminally administered amino acid mixture does cause release of GIP. It is unlikely that GIP release is merely the result of an intestinal distention stimulus, since perfusion with comparable volumes of isotonic saline did not increase serum GIP levels. Likewise, the intraduodenal perfusion of solutions of varying osmolality had no significant stimulatory effect on GIP concentrations.

Although our studies suggest that GIP may be important in the alimentary stimulation of the endocrine pancreas, it is possible that other gut hormones may also be partially responsible for the augmented insulin secretion observed after the intraduodenal instillation of glucose or amino acids.

Participation of secretin in the enteroinsular axis has been suggested by studies demonstrating that secretin infusion potentiates insulin secretion induced by intravenous glucose.[18, 19] However, recent investigations with direct intraduodenal instillation of glucose or amino acids have failed to elicit any effect on either portal or peripheral immunoreactive secretin concentrations.[20] In addition, intraduodenal instillation of acid in quantities sufficient to produce significant elevations of portal and peripheral venous secretin concentrations does not result in an elevation of peripheral serum insulin levels.[21, 22] It is therefore unlikely that secretin was responsible for the enhanced insulin secretion elicited by intraduodenal amino acids in the present study.

CCK has also been implicated as a primary mediator of the enteroinsular axis. Previous investigations reporting an insulin-releasing effect of CCK were done with an impure CCK preparation known to be contaminated with GIP.[23] Although some studies have shown an insulin-releasing effect of the octapeptide of CCK in dogs,[24] when highly purified porcine CCK is administered to man, there is no rise in peripheral venous insulin concentrations, suggesting that insulin stimulation after crude CCK may have been due to GIP.[25] More important, the failure of intraduodenal glucose to stimulate pancreatic exocrine secretion argues against an incretin effect of CCK.[26, 27]

Intraduodenal instillation of amino acids, particularly phenylalanine, methionine, valine, and tryptophan, evoke CCK secretion in man,[28] and it is possible that CCK may have contributed to the increased insulin secretion observed in the present studies. In CCK bioassay investigations, removal of these four amino acids from the duodenal perfusate has been shown to reduce or abolish CCK secretion. In an attempt to eliminate any contribution of CCK to the augmentation of insulin secretion, we have perfused comparable concentrations and volumes of a mixed amino acid solution containing none of these four amino acids. In preliminary studies the results are similar to those obtained with the original amino acid test solution, i.e., elevations in serum GIP concentrations and augmentation of insulin secretion (F. B. Thomas et al., *unpublished observations*). In addition, no significant increase in pancreatic trypsin output was observed, confirming the absence of CCK stimulation.

The effect of gastrin on insulin release is also controversial. Gastrin increases only slightly in normal subjects after oral glucose ingestion.[29] Intravenous adminis-

tration of gastrin in amounts approximating serum levels obtained after oral glucose loading fail to stimulate insulin secretion. However, Rehfeld and Stadil have demonstrated that physiological doses of gastrin do potentiate insulin secretion when simultaneously administered with intravenous glucose injections.[29] With more potent stimulators of gastrin secretion such as amino acids, it is possible that this hormone may contribute to the gastrointestinal augmentation of insulin secretion.

Gut glucagon-like immunoreactivity (GLI) released by glucose ingestion and a variety of other intraduodenal stimuli has been suggested as the enteric factor augmenting the β-cell response to ingested glucose.[30] However, when GLI is released by non-glucose stimuli, it is not accompanied by a rise in plasma insulin, even when blood glucose levels are maintained well above normal by the simultaneous intravenous infusion of glucose.[31] Additionally, Ohneda et al. failed to observe a release of GLI in response to intraduodenally administered amino acids.[16] These observations cast doubt upon the role of GLI as an enteric mediator of insulin release.

In summary, our results demonstrate that (1) intraduodenal, but not intravenous, infusion of an amino acid mixture stimulates GIP secretion; (2) insulin secretion is greater after intraduodenal amino acid perfusion, as compared to intravenous infusion. Although these and other observations suggest that GIP may be an important enteric augmenter of insulin secretion, it is not certain that GIP alone is responsible for the increased secretion observed after intraduodenal amino acid administration.

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