Gastric Inhibitory Polypeptide Secretion After Radical Pancreatoduodenectomy

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To elucidate the role of gastric inhibitory polypeptide (GIP) in the alteration of insulin secretion following pancreatoduodenal resection, in which the main sources of GIP are removed, plasma levels of GIP were measured for 180 minutes after oral glucose administration, both before and after radical pancreatoduodenectomy in nine patients with periampullary cancer. Fasting plasma levels of GIP remained much the same before and after surgery, and were not different from those in normal controls. The levels of GIP after glucose ingestion were significantly greater in the preoperative patients than in normal controls throughout 180 minutes. After pancreatoduodenectomy, the postglucose levels significantly diminished but remained within normal limits. Changes in plasma levels of insulin early after glucose ingestion in these patients, however, were significantly less both before and after surgery than in normal controls, and were not concomitant with the initial increase in plasma GIP. On the other hand, plasma levels of insulin greatly increased immediately after glucose ingestion in accordance with a rapid elevation of plasma GIP in 11 gastrectomized patients in whom the duodenum and the pancreas were preserved intact and who served as the control group. Thus, the diminution in GIP secretion following pancreatoduodenectomy may relate to the lack of main sources of this gut hormone and not to factors involved in the reconstruction of the alimentary tract. We conclude that the impaired insulin secretion following oral glucose ingestion in patients before and after pancreatoduodenectomy does not relate to the secretion of GIP.

GASTRIC INHIBITORY POLYPEPTIDE (GIP), located in K-cells[1] mainly distributed in the mucosa of the duodenum and the upper small intestine in man,[2] is secreted into the blood with various postcibal luminal stimuli. Interestingly, this polypeptide is the only validated substance of gastrointestinal origin with the ability to stimulate insulin secretion.[3] Therefore, this gut hormone is considered to play an important role in producing specific responses of insulin to food ingestion in patients undergoing gastrointestinal reconstructions; for instance, a rapid enhanced insulin secretion in gastrectomized patients,[4–6] impaired insulin secretion in patients following pancreatoduodenectomy,[6,7] or massive resection of the small intestine.[8]

As there is a paucity of data concerning secretion of GIP in such patients, we measured plasma levels of GIP during oral glucose administration both before and after radical pancreatoduodenectomy, in an attempt to elucidate changes in secretion of this gut hormone following removal of its main sources. In comparison with pancreatoduodenectomized patients, we also clarified the changes in response of GIP after gastrectomy, conditions under which the main sources of GIP are preserved intact.

Materials and Methods

Nine patients (seven men and two women) with periampullary cancer, ranging in age from 46 to 66 (average 61.6) years, were investigated. Included were four with cancer of papilla of Vater, four with cancer of the head of the pancreas, and one with cancer of the intrapancreatic common bile duct, respectively. In eight patients, a catheter for percutaneous transhepatic bile drainage was placed, and bile was entirely excluded externally. Preoperative investigation was carried out within 1 week prior to the day of surgery. There was no remarkable abnormality in the liver functions on routine laboratory tests, except for serum bilirubin levels of 0.7 to 6.1 (mean 2.4) mg/dl. In these nine patients, radical pancreatoduodenectomy was carried out. Division of the pancreas was made at the junction of the head and body. Resection of the head of the pancreas was performed together with the distal half of the stomach, entire duodenum, and 20 cm of the upper jejunum, *en bloc*. Cholecystectomy was also done. Reconstruction of the alimentary tract was made after the fashion of Child.[9] Postoperative courses in these patients were uneventful. From 4 to 14 (mean

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8.9) weeks after the surgery, postoperative investigations were initiated, and at this time, these patients required no particular treatment.

Eleven patients undergoing gastrectomy (nine men and two women), ranging in age from 36 to 66 (average 51.7) years, were investigated as a control group. Included were nine with early cancer of the stomach, one with duodenal ulcer, and one with gastric ulcer, respectively. Gastrointestinal stenosis was nil in these patients. The examination was done within 1 week prior to the surgery. In six, distal gastrectomy was done, followed by a gastroduodenostomy. In five, total gastrectomy was done and reconstruction of the alimentary tract involved a retrocolic end-to-side esophagojejunostomy with Braun's anastomosis. Postoperative courses were uneventful and in these patients investigation was carried out from 4 to 14 (mean 8.6) weeks after the surgery.

Ten healthy volunteers (eight men and two women), ranging in age from 26 to 49 (average 39.2) years, served as normal controls.

In the present series, no individual had a family history of metabolic or endocrine disorders. Body weight at the time of investigation was within ±10% of the ideal value of each instance.

In the early morning, after an overnight fast, 50 g of glucose was orally administered as the stimulus for secretion of GIP. Blood samples were obtained from an antecubital vein through an indwelling catheter 15 minutes before and just before glucose was ingested, as the control. Samples were obtained serially until 180 minutes thereafter. Blood was transferred immediately into a chilled test tube containing Trasylol®, kallikrein inactivator (500 KIU/ml of whole blood, Bayer, Germany), and EDTA [2Na] (1 mg/ml of whole blood). The blood was centrifuged at 4 C and the plasma stored at −20 C until the time of assay.

Plasma levels of glucose were determined by a modification of the glucose oxidase method,[10] adopted to an autoanalyser (Boehringer-mannheim, USA). Plasma levels of insulin were measured by double antibody radioimmunoassay.[11] Assay kits for insulin were obtained from CIS-SORIN Association, France. Plasma levels of GIP were measured by single antibody radioimmunoassay, according to the method of Kuzio et al.[12] Specific antibody against GIP (GP01) was obtained from the laboratory of Dr. JC Brown (Canada). Purified natural porcine GIP was also obtained from the same laboratory, and was utilized both for standards and for iodination in the assay. The limit of sensitivity of our assay of GIP varied from 50 to 100 pg/ml, on each occasion. The intra-assay variance was 6.9%, and the interassay variance was 13.8%, respectively. The series of samples obtained from the same individuals were measured using the same assay system to avoid interassay variation.

Based on the results of plasma levels of GIP, maximum response value during the test (MaxΔGIP: peak level minus basal level) and integrated incremental value ($\sum_{0}^{180}$ ΔGIP: the sum of products of the value of the level above basal level during each time period multiplied by the number of the corresponding time period, from 0 to 180 min) were calculated in each individual as parameters for evaluating the response of GIP.

Data are expressed as the mean plus and minus one SEM. Statistical analysis was made by Student's t-test for paired and unpaired data. Probability values of less than 0.05 were considered to be significant.

Results

Plasma Levels of Glucose

Mean fasting plasma levels of glucose were not significantly different among normal controls, two preoperative groups, and two postoperative groups of patients (Fig. 1, top graphs).

After an initial elevation of the plasma glucose levels following glucose ingestion, the levels rapidly decreased in the normal control group. In the patients with periampullary cancer, the levels remained elevated up to 180 minutes. A similar pattern of the curve of mean plasma levels of glucose was noted in the patients after pancreatoduodenectomy. In gastrectomized patients, the mean blood sugar levels rapidly increased following glucose ingestion and then rapidly decreased, while the levels gradually increased and decreased in the same patients before surgery. The level in gastrectomized patients at 30 minutes was significantly greater than in pancreatoduodenectomized patients. The level at 180 minutes was significantly less in the former than in the latter.

Plasma Levels of Insulin

Mean fasting plasma levels of insulin were not significantly different among these five groups (Fig. 1, middle graphs). After glucose ingestion, mean plasma levels of insulin rapidly increased and then decreased gradually in normal controls. In patients prior to pancreatoduodenectomy, the levels increased gradually and remained elevated up to 180 minutes. After pancreatoduodenectomy the levels increased gradually and then decreased. On the other hand, mean plasma levels of insulin in the patients before gastrectomy increased gradually and then decreased rapidly. In the same patients after gastrectomy, the levels rapidly increased up to the peak value of 127.2 ± 19.5 μU/ml at 30 minutes, and then soon decreased.

Plasma Levels of GIP

Mean fasting plasma levels of GIP did not differ among these five groups (Fig. 1, bottom graphs). After glucose ingestion, plasma levels of GIP rapidly increased and remained elevated up to 150 minutes in normal controls.

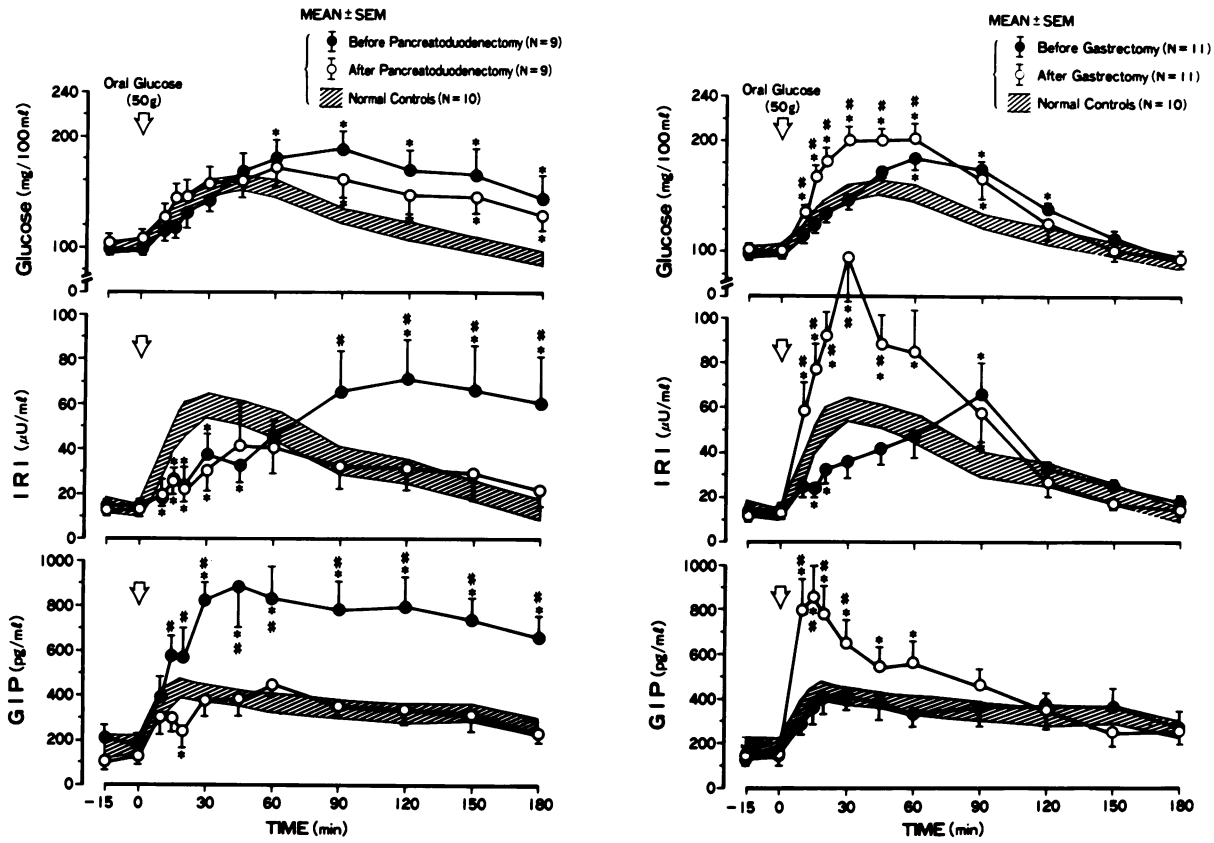

FIG. 1. Plasma levels of glucose, insulin (IRI), and gastric inhibitory polypeptide (GIP) throughout oral glucose loading in pancreatoduodenectomized patients (on left panel) and gastrectomized patients (on right panel). *Indicates significant difference ($p < 0.05$) compared with normal controls. # Indicates significant difference ($p < 0.05$) between pre- and postsurgery, in the same patients.

In patients with periampullary cancer, the levels increased to values much higher than in normal controls and then remained elevated up to 180 minutes. After pancreatoduodenectomy in the same patients, the levels also increased but were significantly less than the preoperative levels. On the other hand, changes in plasma levels of GIP in patients before gastrectomy did not significantly differ from those in normal controls. Following gastrectomy, the levels sharply increased after glucose ingestion and then decreased rapidly. The levels during the first 90 minutes in gastrectomized patients were significantly greater than in pancreatoduodenectomized patients.

Changes in Basal Plasma GIP

Following pancreatoduodenectomy, mean basal plasma levels of GIP decreased in all but one instance (Fig. 2). There was, however, no statistical difference in the level between before and after the surgery. No significant difference was noted in the basal levels between before and after gastrectomy.

Changes in MaxΔGIP

The values in the preoperative patients with periampullary cancer were significantly greater ($p < 0.02$) than in normal controls (Fig. 3). After pancreatoduodenectomy, the values decreased in all instances, to levels much the same as in the normal controls.

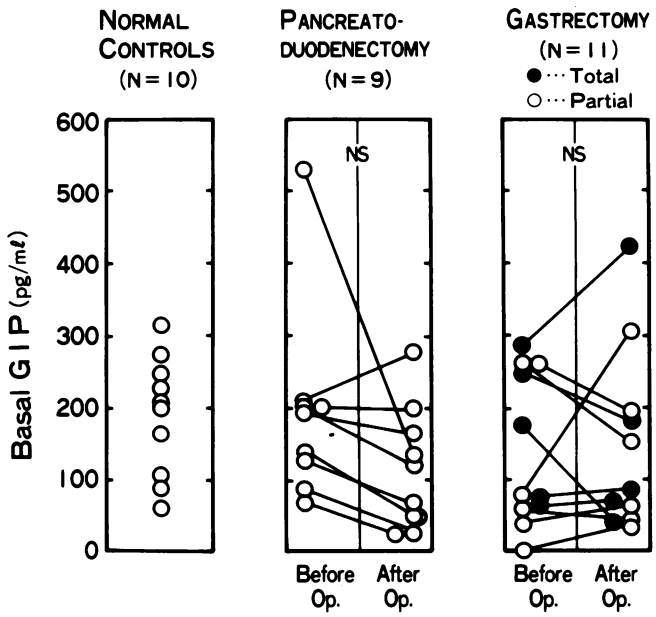

FIG. 2. Changes in basal plasma levels of gastric inhibitory polypeptide (GIP) after pancreatoduodenectomy or gastrectomy.

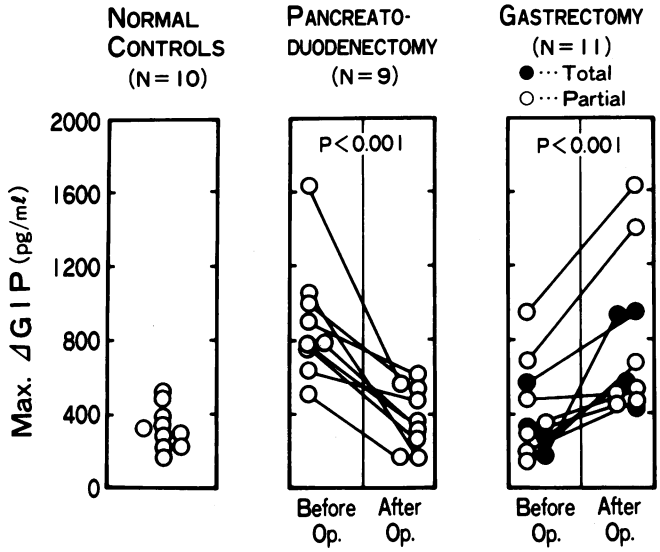

FIG. 3. Changes in maximum response values of plasma gastric inhibitory polypeptide (MaxΔGIP) following glucose ingestion after pancreatoduodenectomy or gastrectomy.

The values in the patients before gastrectomy, which were much the same as in the normal control, increased in all instances after gastrectomy. The values in gastrectomized patients were significantly greater than in pancreatoduodenectomized patients ($p < 0.025$).

$$\textit{Changes in } \sum_{0}^{180} \Delta GIP$$

The values in the preoperative patients with periampullary cancer, which were significantly greater ($p < 0.005$) than in normal controls, decreased in all instances after pancreatoduodenectomy (Fig. 4). There was no difference in the value between the pancreatoduodenectomized patients and normal controls. Prior to gastrectomy, the values were not significantly different from those in normal controls. After gastrectomy, the values increased in nine of 11 cases and these were significantly greater ($p < 0.05$) than in normal controls but not in the pancreatoduodenectomized patients.

There is no significant difference in values between patients undergoing partial and total gastrectomy.

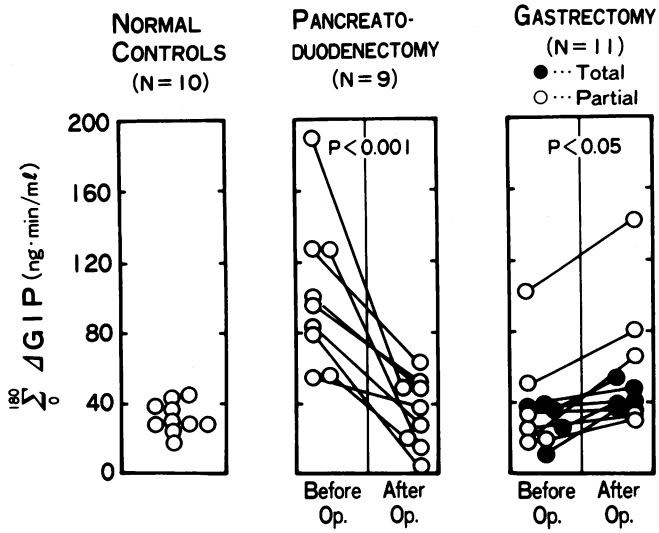

FIG. 4. Changes in integrated incremental values of plasma gastric inhibitory polypeptide for 180 min ($\sum_{0}^{180}$ ΔGIP) following glucose ingestion after pancreatoduodenectomy or gastrectomy.

Discussion

The release of GIP in response to oral glucose loading diminished in all instances following pancreatoduodenectomy, as compared with each preoperative response. In these patients, there was no remarkable difference in plasma levels of glucose following ingestion of the same amount of glucose, before and after surgery. Therefore, it is unlikely that poor luminal stimulation of glucose and/or disturbance of glucose absorption are related to the diminution of GIP response after pancreatoduodenectomy. On the other hand, increase in the GIP response was noted postoperatively in the gastrectomized patients who served as the control group and in whom the duodenum and the entire small intestine were left intact. This observation is compatible with reports of Bröger et al.[13] and Jorde et al.[14] that the postcibal release of GIP in gastrectomized patients was significantly greater than in normal controls. Consequently, reconstruction of the alimentary tract in cases of pancreatoduodenectomy probably does not play a causative role in decreasing the GIP response. Vagotomy that was done partially or truncally to completely dissect lymphnodes during radical pancreatoduodenectomy may lead to a diminution in the GIP response, since atropine-induced vagotomy reduced the response of plasma GIP to intraduodenal perfusion of glucose in man.[16] The direct effect of vagotomy on the response of GIP has not been clarified. An enhanced response of plasma GIP to oral glucose, however, was noted in patients who had undergone truncal vagotomy and pyloroplasty,[17] an observation compatible with our results in total gastrectomized patients in whom truncal vagotomy was routinely done. These enhanced responses seem to relate to the rapid emptying of glucose in these patients. Therefore, the role of vagotomy in decreasing the GIP response after radical pancreatoduodenectomy is probably trivial. Becker et al.[15] reported a significant decrease in GIP response to test meal in dogs following massive resection of the small intestine, a source of GIP. As the major locations of K-cells, the entire duodenum and a part of the upper jejunum, are removed by pancreatoduodenectomy, we conclude that the GIP response diminished following pancreatoduodenectomy due to decrease in the sources of GIP.

In our pancreatoduodenectomized patients, however,

the response of GIP to oral glucose was not significantly different from that in normal controls. This evidence is not compatible with the observation of Creutzfeldt et al.[18] that the response of plasma GIP to the standard test meal was increased significantly in patients undergoing Whipple's procedure, as compared with normal controls. This discrepancy is probably related to differences in 1) stimulation for GIP secretion: test meal *versus* oral glucose; 2) primary lesion: chronic pancreatitis *versus* periampullary cancer; 3) postoperative period: at least 3 months *versus* average 8.9 weeks; and 4) individual variations. At any rate, secretion of GIP is apparently not impaired in patients lacking the duodenum. This finding may reflect a compensatory increase in the rate of secretion of the remaining K-cells.

We found that the response of GIP to oral glucose loading is remarkably increased in patients with periampullary cancer. Several common abnormalities observed among these patients may be causative factors, *i.e.*, glucose intolerance, chronic pancreatitis associated with periampullary cancer, lack of the bile in the alimentary tract due to obstruction of the duct system, and hyperbilirubinemia. This hypersecretion of GIP may relate to the delayed hypersecretion of insulin in these patients. Although simultaneous high plasma levels of GIP and glucose were present after glucose ingestion in these patients, the early insulin secretion (10–45 minutes) was significantly less than in normal controls. There was also such a diminution of insulin secretion despite a concomitant hyperglycemia and normal response of plasma GIP following pancreatoduodenectomy. On the other hand, the early hypersecretion of insulin was present in accordance with simultaneous oxyhyperglycemia and an enhancement in plasma GIP levels in gastrectomized patients in whom the pancreas was intact. Therefore, we speculate that the pancreas in these pancreatoduodenectomized patients does not respond adequately to the stimulation required to secrete insulin (that is, elevation of plasma GIP and glucose) even before pancreatoduodenal resection.

In conclusion, hypersecretion of plasma GIP in patients with periampullary cancer diminishes after radical pancreatoduodenectomy, due to removal of the major source of this gastrointestinal hormone; the postoperative secretion of GIP remains normal. It is unlikely that the response of GIP plays a causative role in producing an inadequate secretion of insulin after pancreatoduodenectomy.

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