Plasma Cholecystokinin and Pancreatic Polypeptide Response after Radical Pancreatoduodenectomy with Billroth I and Billroth II Type of Reconstruction

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This study was conducted to elucidate plasma cholecystokinin (CCK) and pancreatic polypeptide (PP) response after pancreatoduodenectomy and to compare response of CCK and PP in patients who had pancreatoduodenectomy with Billroth I and Billroth II type of reconstruction. Basal levels of plasma CCK were significantly lower in patients who had pancreatoduodenectomy (9.6 ± 0.8 pmol/L) than in the control (preoperative patients: 14.6 ± 2.0 pmol/L) probably because of the removal of the entire duodenum due to pancreatoduodenectomy, since vagotomy, which is concomitantly brought about by pancreatoduodenectomy, does not appear to interfere with release of CCK. Significant amounts of CCK (integrated CCK: 497 ± 111 pmol–120 min/L), although less amounts than in the preoperative patients (integrated CCK: 901 ± 167 pmol–120 min/L), were still released in response to oral fatty meal after pancreatoduodenectomy. Plasma CCK response to oral fatty meal was significantly greater in patients who had pancreatoduodenectomy with Billroth I type of reconstruction (integrated CCK: 705 ± 153 pmol–120 min/L) than in patients who had pancreatoduodenectomy with Billroth II type of reconstruction (248 ± 63 pmol–120 min/L). Simultaneous measurement of plasma levels of PP revealed complete abolishment of PP response by pancreatoduodenectomy. Since PP secretion can be produced by vagal stimulation, it is most likely that the decreased PP secretion is due to vagotomy rather than removal of the duodenum and pancreas. Significant amounts of CCK released after pancreatoduodenectomy, in which the main sources of release of CCK are removed, may suggest the compensatory mechanism of the remnant upper small intestine. This study also suggests the necessity of re-evaluating Billroth I type of anastomosis as a physiologic reconstruction procedure for the remnant alimentary tract after pancreatoduodenectomy.

Supported by a grant from the Ministry of Education, Japan (#A59440057).

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Submitted for publication: October 28, 1986.

ALTHOUGH SURVIVAL RATES after pancreatoduodenectomy for patients with cancer of the head of the pancreas still remain at low levels, the recent remarkable progress in the diagnostic screening tests, such as computed tomography, ultrasonography, and measurements of serum CA19-9 levels, have made it possible, to a certain extent, to detect a relatively early stage of pancreatic cancer,[1] resulting in the slight but gradual increase of the long-term survival rate after pancreatoduodenectomy. Cholecystokinin (CCK) is a well-known gastrointestinal hormone that plays a physiologic role not only in stimulating pancreatic enzyme secretion[2–4] and insulin release[5] but also in exerting a trophic effect on the pancreas.[6] It is, therefore, of great significance to investigate the plasma CCK response in patients with pancreatoduodenal resection to assess the exocrine and endocrine function of the remnant pancreas and to compare plasma CCK responses after different reconstructive procedures in pursuit of the most physiologically pertinent reconstruction of the alimentary tract after pancreatoduodenectomy.

Assumedly, CCK could exert an important role for the modulation of the function of the remnant pancreas even after pancreatoduodenal resection, but no information is available as to whether CCK is released into circulation after pancreatoduodenectomy, which removes the main sources[7] of release of CCK.

The current study was done to clarify changes in plasma CCK levels after pancreatoduodenectomy with special reference to the comparison of plasma CCK response after reconstruction of the alimentary tract with

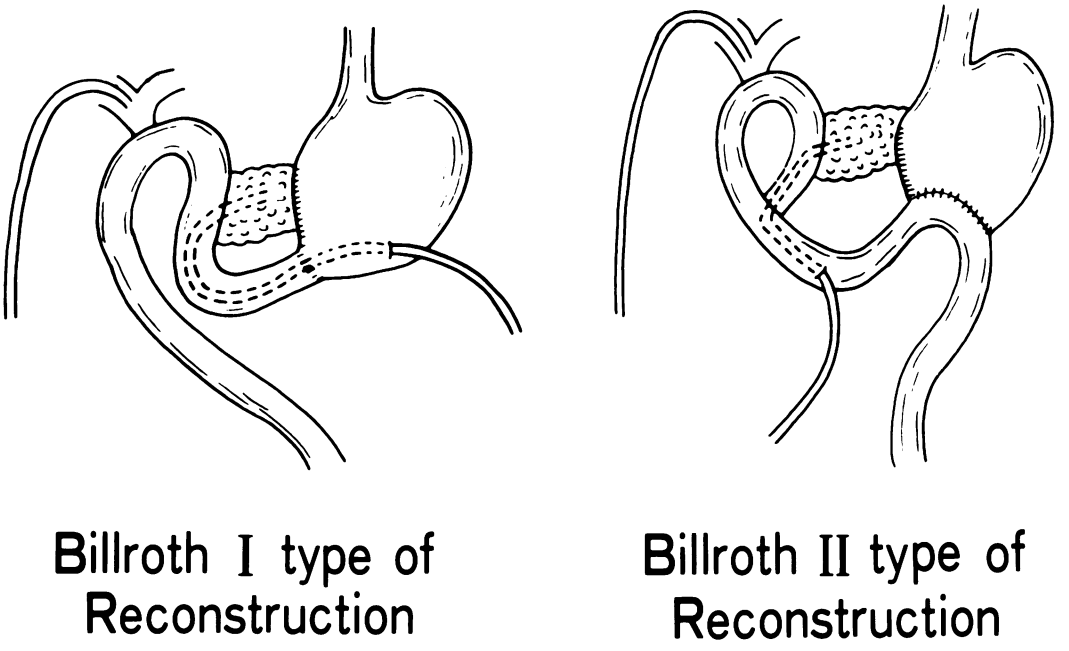

FIG. 1. Two types of reconstruction method for the alimentary tract after radical pancreatoduodenectomy in our department.

Billroth I and Billroth II type of anastomosis, both of which have been performed in our department (Fig. 1).

Simultaneous measurement of plasma levels of pancreatic polypeptide (PP), which plays a physiologic role for inhibition of exocrine pancreatic secretion,[8] was also done.

Materials and Methods

Eleven patients (8 men and 3 women) who had had pancreatoduodenectomy, ranging in age from 35 to 72 years with a median age of 56 years, were investigated. Included were seven patients with cancer of the head of the pancreas, two patients with cancer of the intrapancreatic common bile duct, one patient with cancer of papilla of Vater, and one patient with cancer of the duodenum, respectively. Radical pancreatoduodenectomy had been performed on these patients with *en bloc* resection of the head of the pancreas, entire duodenum, 5 cm of the upper jejunum, and distal half of the stomach, followed by cholecystectomy. The alimentary tract had been reconstructed either with Billroth I type of anastomosis (6 patients) or with Billroth II type of anastomosis (5 patients) (Fig. 1). Postoperative periods of these patients were 1 month (1 patient), 2 months (1 patient), 3 months (1 patient), and 12 months (3 patients) among patients with Billroth I type of reconstruction, and 1 month (1 patient), 2 months (1 patient), 3 months (1 patient), 6 years and 9 months (1 patient), and 6 years and 11 months (1 patient) among patients with Billroth II type of reconstruction, respectively. Postoperative courses in these 11 patients had been uneventful. Seven preoperative patients with early gastric cancer (2 men and 5 women), ranging in age from 51 to 71 years (mean: 62 years), were also studied as a control group for comparison with patients who had pancreatoduodenectomy. There was no pyloric stenosis in these preoperative patients.

After a 14-hour fast, patients who had pancreatoduodenectomy and preoperative patients were ingested with 200 mL of a fatty meal (chemically defined diet containing 14 g of fat; Clinimeal, Eisai Company, Japan). Peripheral blood samples were drawn before and serially at 10-minute intervals for 120 minutes after Clinimeal. Samples of blood were collected in tubes containing 50 KIU of Trasylol and 10 U of heparin per milliliter of blood and centrifuged at 3000 rpm with the constant temperature at 4 C for 15 minutes. The plasma was separated and stored at −20 C for future measurement of CCK and PP by specific radioimmunoassays.

Radioimmunoassay of CCK

Plasma levels of CCK was measured by means of a sensitive and specific radioimmunoassay for CCK-33 and CCK-39 that was developed by Thompson and Rayford,[3,9–12] using the CCK antibody (UT132), generously provided by Professor Phillip L. Rayford (Department of Physiology, University of Arkansas Medical Sciences, Little Rock, AR). The validation and details of

CCK radioimmunoassay conducted in our laboratory[13] are as follows.

CCK variant (CCK-39), supplied by Professor V. Mutt (Karolinska Institute, Sweden), was labeled (2.5 μg) with ^{125}iodine (1 mCi) by the chloramine-T method (25 μg/10 μL of chloramine T in 0.5 M potassium phosphate [PB] pH 6.0) for 60 seconds, followed by 62.5 μg/25 μL of sodium metabisulfite in 0.15 M PB. Labeled hormone was separated from other contaminants on an 11 × 0.9-cm Sephadex G-25 fine column (Pharmacia Fine Chemicals, Piscataway, NJ) eluted with 0.15 M PB containing 1 M NaCl (pH 6.0). ^{125}I-CCK-39 was further purified on a 4-cm column (Pasteur pipette) containing cellulose CF-11 (Whatman, Clifton, NJ) immediately before being used as a labeled tracer. Assay tubes were prepared with 200 μL of standards or plasma samples, 300 μL of phosphate buffer (0.02 M sodium phosphate, 0.15 M NaCl, 0.1% sodium azide, 0.5% normal rabbit serum, pH 6.8), 100 μL of antibody solution (final dilution 1:75,000), 100 μL of 0.1 M ethylenediaminetetraacetic acid (EDTA), and 100 μL of Trasylol (250 KIE/tube). The assay tube was then incubated for 24 hours at 4 C. Labeled CCK-39 (200 μL, 8000 cpm) was added to each tube and incubated for another 48 hours. The assay was terminated by an overnight incubation with goat antirabbit-γ globulin serum (Organon Teknika N.V., Malvern, PA).

The antibody bound 25–30%, 30–35%, and more than 75% of labeled CCK-39 at the final dilution of 75,000, 50,000, and 500, respectively, and nonspecific binding was less than 2%. Ten per cent inhibition of maximum binding (detection limit) was 1.6 ± 0.2 fmol/tube of standard CCK-33 and 50% inhibition (ID_{50}) was 13.4 ± 0.9 fmol/tube in five different assays. The intra-assay variance was 8% and interassay variance was 10%. In this study, all samples were measured in duplicate in the same assay, and plasma CCK-33 levels were determined using standards containing 200 μL of hormone-free human plasma. When graded doses of CCK-33, CCK-39 (Professor V. Mutt), CCK-op (Dr. N. Yanaihara, Shizuoka, Japan), and synthetic human gastrin (G-17, Sigma, St. Louis, MO) were measured in the assay system, the slopes of the dose-response curve generated by CCK-33 and CCK-39 were −2.3 and −2.0, respectively. Estimation of ID_{50} revealed that CCK-33 and CCK-39 were almost equally potent. In contrast, the slopes of the dose-response curve for G-17 and CCK-op were −0.58 and −0.46, respectively, and the potency of both peptides was less than 0.5% when compared with that of CCK-33 at ID_{50}. No cross-reactivity was observed with structurally unrelated gastrointestinal peptides such as secretin, GIP, VIP, substance p, PYY, neuromedin C, or GRP. Serial dilutions of dog postprandial plasma (25–200 μL) and duodenal extracts (1:200–1:3200) produced parallel dose-response curve compared with that of standard CCK-33.

The comparison of dose-response curves generated by CCK standard diluted with or without 200 μL of hormone-free plasma clarified that the slopes and ID_{50} of CCK standard diluted with hormone-free dog plasma, with hormone-free human plasma, and with buffer (without hormone-free plasma) are −2.0 and 11.1 fmol/tube, −1.8 and 15.1 fmol/tube, and −1.8 and 9.9 fmol/tube, respectively, demonstrating that this assay system is free from the influence of interference substances in the plasma.

Radioimmunoassay of PP

Plasma PP levels were measured by specific radioimmunoassay[14] using rabbit anti-h PP serum, kindly donated by Dr. R. E. Chance (Lilly Research Laboratories, Eli Lilly Co., Indianapolis, IN).

The results of this study are expressed as mean ± SEM. Student's paired or unpaired t-test was used to analyze the data for statistical differences. Differences with a p value of less than 0.05 were considered significant.

Results

Basal Plasma Levels of CCK

Mean basal plasma levels of CCK in the pancreatoduodenectomy group (11 patients) (9.6 ± 0.8 pmol/L) were significantly lower than those observed in the control group (7 preoperative patients) (14.6 ± 2.0 pmol/L). No significant difference was noted between mean basal plasma CCK levels in the pancreatoduodenectomy group reconstructed with Billroth I type of anastomosis (6 patients) (8.9 ± 0.6 pmol/L) and Billroth II type of anastomosis (5 patients) (10.4 ± 1.0 pmol/L).

Plasma CCK Response

In the control group (preoperative patients), in response to oral fatty meal, incremental values of CCK (ΔCCK) were significantly increased to 3.7 ± 1.3 pmol/L at 5 minutes, attained the peak of 11.7 ± 3.3 pmol/L at 20 minutes, and then remained significantly elevated up to 120 minutes. In the pancreatoduodenectomy group, ΔCCK values were also significantly elevated after oral fatty meal, showing the peak value of 7.2 ± 1.5 pmol/L at 20 minutes. Although ΔCCK values remained significantly elevated throughout the study, plasma CCK response in the pancreatoduodenectomy group was lower than that observed in the preoperative group (Fig. 2). The integrated CCK in the pancreatoduodenectomy group (497 ± 111 pmol–120 min/L) was significantly less than that noted in the control group (901 ± 167 pmol–120 min/L) (Fig. 3).

Plasma CCK response to oral fatty meal was com-

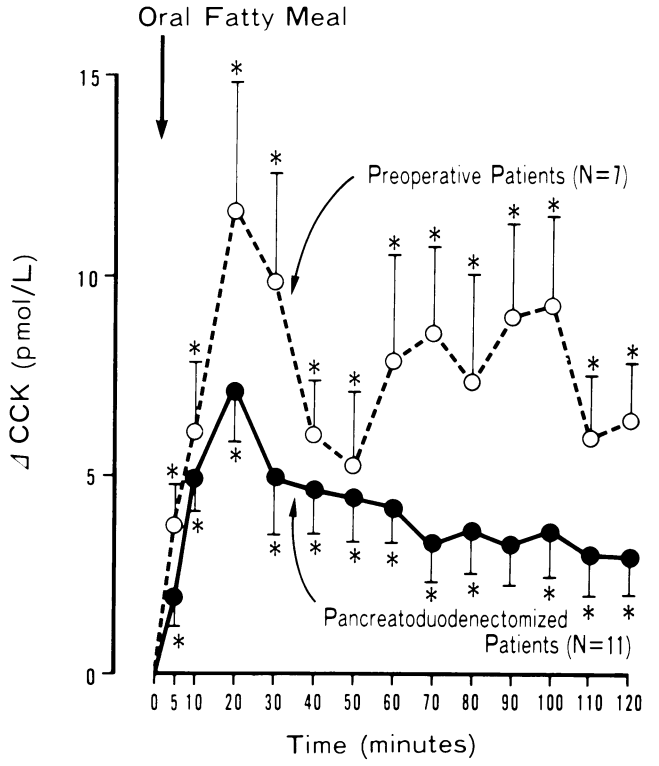

FIG. 2. Comparison of the plasma CCK response to oral fatty meal in preoperative patients and patients who had pancreatoduodenectomy. Asterisks indicate significant elevation above basal.

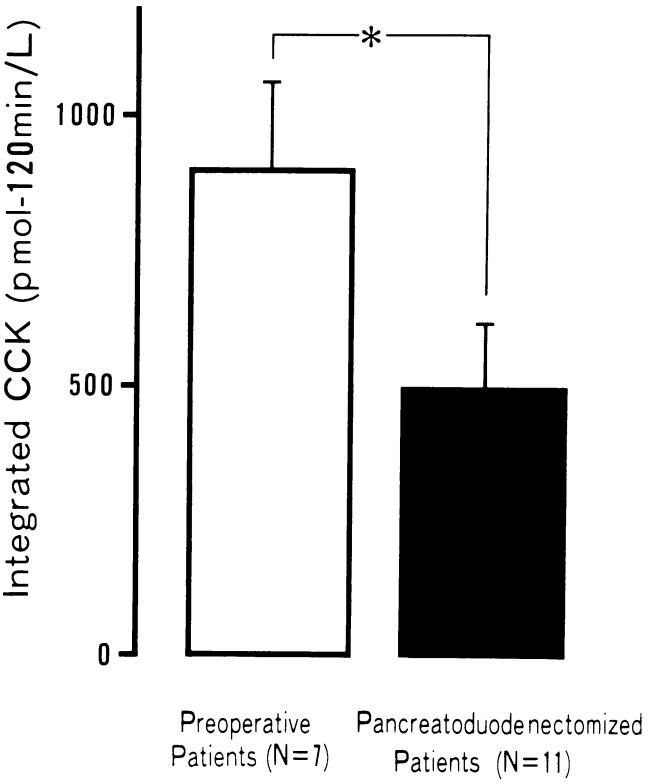

FIG. 3. Integrated CCK in preoperative patients and patients who had pancreatoduodenectomy. Asterisk indicates significant difference in integrated CCK between preoperative patients and patients who had pancreatoduodenectomy.

pared among patients who had pancreatoduodenectomy with Billroth I and Billroth II type of anastomosis (Fig. 4). Patients with Billroth I type of anastomosis showed a rapid and greater plasma CCK response when compared with plasma CCK response in patients with Billroth II type of anastomosis. In patients with Billroth I type of reconstruction, ΔCCK values rose significantly to the maximum of 10.8 ± 1.7 pmol/L at 20 minutes and then gradually began to fall, however, remaining elevated up to 100 minutes. On the other hand, patients with Billroth II type of reconstruction showed a delayed and lower plasma CCK response compared with that noted in patients with Billroth I type of reconstruction; significant increase in ΔCCK values was achieved at 30, 40, 50, 60, 110, and 120 minutes after oral fatty meal (Fig. 4). The integrated CCK was significantly greater in patients who had pancreatoduodenectomy with Billroth I type of reconstruction (705 ± 153 pmol–120 min/L) than in patients who had pancreatoduodenectomy with Billroth II type of reconstruction (248 ± 63 pmol–120 min/L) (Fig. 5).

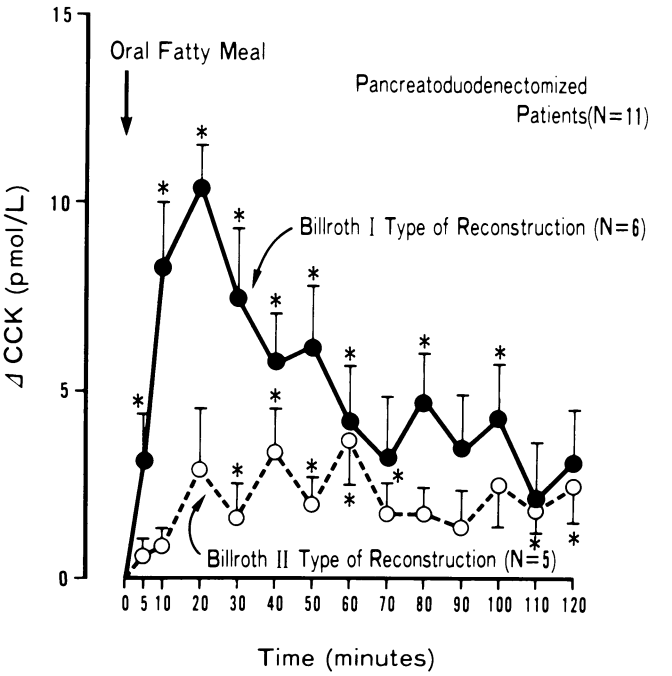

FIG. 4. Comparison of the plasma CCK response to oral fatty meal in patients who had pancreatoduodenectomy with Billroth I and Billroth II type of reconstruction. Asterisks indicate significant elevation above basal.

Basal Plasma Levels of PP

The mean basal plasma level of PP in the control group was 35 ± 8 pmol/L. In contrast, basal plasma levels of PP were undetectable (below detection limit) in

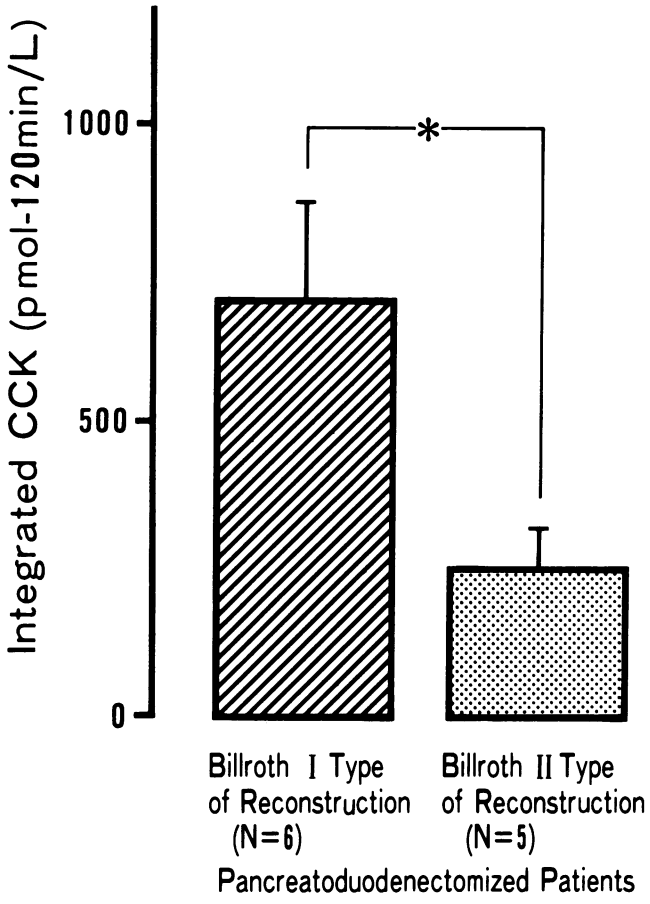

FIG. 5. Integrated CCK in patients who had pancreatoduodenectomy with Billroth I and Billroth II type of reconstruction. Asterisk indicates significant difference in integrated CCK between Billroth I and Billroth II type of reconstruction.

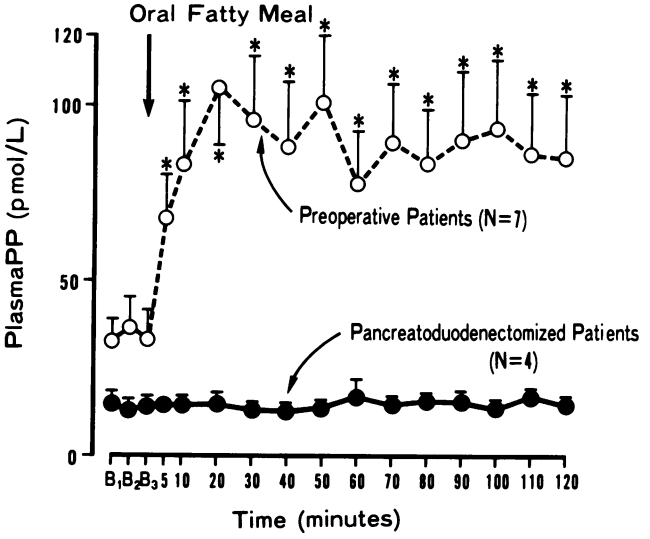

FIG. 6. Comparison of the plasma PP response to oral fatty meal in preoperative patients and patients who had pancreatoduodenectomy. Asterisks indicate significant elevation above basal.

seven of 11 patients with pancreatoduodenal resection. The mean basal plasma level of PP in four patients in whom PP levels were detectable (16 ± 1 pmol/L) was significantly less than that found in the control group (Fig. 6).

Plasma PP Response

Plasma PP in preoperative patients showed a rapid and significant increase in response to oral fatty meal; significant elevation was achieved at 5 minutes (68 ± 14 pmol/L) and remained significantly elevated up to 120 minutes. On the contrary, patients with pancreatoduodenal resection did not show any increase in plasma PP levels after ingestion of a fatty meal (Fig. 6).

Discussion

The role of hormonal factors, especially that of CCK, is supposedly of great importance in modulating the exocrine and endocrine function[2-6] of the remnant pancreas after pancreatoduodenal resection that is performed on patients with periampullary cancer, since radical pancreatoduodenectomy is inevitably accompanied by vagotomy. The effect of vagotomy on gastrointestinal hormones has been widely documented.[15-21] To evaluate whether CCK release is under vagal control, Guzman and colleagues[17] electrically stimulated the vagus nerves of anesthetized dogs and found increased pancreatic protein secretion, but no increase in plasma levels of CCK, indicating that CCK release is not under vagal control and that vagal stimulation of pancreatic secretion occurs through a mechanism independent of CCK. They have also demonstrated that vagotomy has no effect on the release of CCK.[18] This observation is inconsistent with reports by Fried and colleagues who have shown that CCK secretion in response to intraduodenal oleate[19,20] or to exogenous bombesin[20] or CCK[20] was not significantly affected by vagotomy. On the other hand, PP secretion is predominantly mediated through the vagal cholinergic pathways. Modlin and colleagues[21] have demonstrated that the release of PP is inhibited to a significantly greater extent by vagotomy than by atropine. Prominent decrease of PP secretion by vagotomy has been also confirmed by Guzman and colleagues[18] and by Fried and colleagues.[20] However, to our knowledge, radioimmunoassay measurement of plasma levels of CCK and PP after pancreatoduodenectomy has not been performed. The current study revealed that basal concentrations of plasma CCK were significantly lower in patients who had pancreatoduodenectomy than in the preoperative patients. This relatively low basal level of plasma CCK after pancreatoduodenal resection could be possibly attributed to the elimination of the entire duodenum in which CCK producing cells are most numerously distributed,[7] since vagotomy does not

appear to interfere with release of CCK. Despite the low fasting secretion of CCK in patients who had pancreatoduodenectomy, this study demonstrates that significant amounts of CCK, although less amounts than in the preoperative patients, are still released postprandially even after pancreatoduodenectomy, which removes the main sources of release of CCK, suggesting that this phenomenon may reflect the compensatory mechanism of the remnant upper small intestine. Plasma responses of other hormonal factors, such as secretin, gastrin, and gastric inhibitory polypeptide, in patients who had pancreatoduodenectomy have also been documented; diminished secretin response to the ingestion of hydrochloride solution,[22] food,[23] no response of gastrin to intravenous infusion of arginine,[22] and almost the same response of gastric inhibitory polypeptide to oral glucose as observed in the control group.[24] In these reports, however, reconstruction of the alimentary tract after pancreatoduodenectomy has been performed with Billroth II type of anastomosis (modified Child method).

There have been two types of reconstruction procedure for the remnant alimentary tract after pancreatoduodenectomy; Billroth I type (Cattell[25] and Imanaga[26]) and Billroth II type (Whipple[27] and Child[28]).

In our department, we have been performing Billroth I type of anastomosis as well as Billroth II type of anastomosis after pancreatoduodenal resection as represented on Figure 1. One of the original aspects of Billroth I type of reconstruction procedure in our department lies in the retrocolic approach for the anastomosis of the remnant alimentary tract after pancreatoduodenectomy. The unique Billroth I type of reconstruction procedure after pancreatoduodenectomy was started about 7 years ago in our department, since it was conceivable that the passage of food through the entire remnant upper small intestine was more physiologic than food bypassing the upper portion of the remnant small intestine in view of the release of gastrointestinal hormones, which presumably play a significant role in the modulation of the function of the remnant alimentary tract.

The current study first did a comparative study on the plasma response of gastrointestinal hormones in patients who had pancreatoduodenectomy with Billroth I type and II type of anastomosis. The interesting phenomenon that plasma CCK response was significantly greater in patients who had pancreatoduodenectomy with Billroth I type of anastomosis than in patients with Billroth II type of anastomosis may support the hypothesis that after pancreatoduodenectomy, Billroth I type of reconstruction method is a more physiologic procedure than Billroth II type of reconstruction because CCK could exert a trophic effect[6] on the remnant pancreas as well as play an important role in the regulation of exocrine[2-4] and endocrine[5] function. Approximately 100 pancreatoduodenal resections have been performed in our department over the last 7 years from 1979 to 1985. Comparative studies on surgical complications after pancreatoduodenectomy in our department revealed that there was no significant difference between Billroth I and Billroth II type of reconstruction in both morbidity and mortality after pancreatoduodenectomy, except that intermittent fever due to the late stage of biliary infection was more frequently observed after Billroth II type of reconstruction.

It has been controversial relating to the molecular forms of CCK in the circulation and physiologic importance of CCK-33 and CCK-8. Recent studies by Solomon et al.[29] and Konturek et al.[4] have clarified that larger molecular forms of CCK is quantitatively the most important mediators of CCK action on the pancreas. The antibody used in this study has its greatest affinity for larger forms of CCK (CCK-33 and CCK-39) and has little or no affinity for the smaller forms of this peptide.[3,9-13] The same CCK antibody that was used in the current study has been proved to inhibit not only the stimulatory effects of pure CCK and extracts of the duodenum on gallbladder contraction[11] but also the bioactivity of both exogenously administered and endogenously released CCK on the pancreas,[3] supporting the concept that larger forms of CCK are mediators of the two major biologic actions of CCK.

In contrast to plasma CCK response, pancreatoduodenectomy completely abolished plasma PP response. Basal plasma levels of PP were even undetectable in seven of 11 patients who had pancreatoduodenectomy. Since PP secretion is to a great extent mediated through the vagal cholinergic pathways,[18,20,21] it is most likely that the decreased PP secretion is due to vagotomy rather than removal of the duodenum and pancreas. PP originates from cells localized almost exclusively in the pancreas.[30] Regional differences in PP distribution exist, with PP found predominantly in the uncinate process and head of the pancreas.[31] Total pancreatectomy has been reported to abolish the increase in circulating PP seen after a meal, which led to the suggestion that the pancreas is the only site of PP release.[32] The complete abolishment of PP release even after pancreatoduodenectomy, which preserves most of the left lobe (body and tail) of the pancreas, might be partly attributed to the predominant distribution of PP cells in the right lobe of the pancreas.

In conclusion, this study demonstrates that significant amounts of CCK, but not PP, are released even after pancreatoduodenectomy, which removes the main sources of release of CCK, suggesting the compensatory mechanism of the remnant upper small intestine. Significantly greater CCK response in patients who had pan-

creatoduodenectomy with Billroth I type of reconstruction than in patients with Billroth II type of reconstruction might prompt us to re-evaluate Billroth I type of anastomosis as a more physiologic reconstruction procedure for the alimentary tract after pancreatoduodenectomy.

Acknowledgments

We are grateful to Professor Viktor Mutt (Karolinska Institute, Sweden) and Dr. Kazuhiko Tatemoto (Stanford University School of Medicine, Stanford, CA) for supplying us with the pure CCK-33 and CCK-39. We are also grateful to Professor Phillip L. Rayford (University of Arkansas Medical Sciences, Little Rock, AR) for his generous gift of the CCK antibody (UT 132).

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