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Role of Endogenous Hypergastrinemia in Regenerating Endocrine Pancreas After Partial Pancreatectomy

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We studied the possible role of endogenous gastrin in the regenerating pancreas. Male Wistar rats underwent sham operation or 90% partial pancreatectomy (Px). Lansoprazole (30 mg/kg body wt), a proton pump inhibitor (PPI), was given p.o. for 3 weeks after surgery. Plasma glucose levels were higher in Px rats than in shams. Lansoprazole lowered plasma glucose levels in the Px rats. In addition, integrated insulin secretion during an oral glucose tolerance test (2 g/kg body wt) was significantly ($p < 0.01$) higher in lansoprazole-treated Px rats than in control Px rats, while lansoprazole did not affect insulin secretion in shams. Fasting serum gastrin levels were higher ($p < 0.01$) in lansoprazole-treated animals than in controls both in sham rats and in Px rats. Furthermore, lansoprazole increased the pancreas weight per body weight and elevated the insulin content of the pancreas in Px rats. These results suggest that endogenous hypergastrinemia has a trophic effect on endocrine pancreas during regenerating processes and that administration of PPI may be clinically beneficial to the remnant pancreas after pancreatectomy if the whole stomach is preserved.

KEY WORDS: pancreatectomy; endogenous gastrin; regeneration; insulin secretion.

Pylorus-preserving pancreatoduodenectomy (PPPD) is a surgical procedure of reconstruction that preserves the gastrointestinal function after pancreatoduodenectomy (1). Gastric acid release, gastric emptying, and marginal ulcer formation have been reported after PPPD (2–4). Antacid drugs are widely used to prevent the hyperacid state, though these drugs evoke hypergastrinemia in different species (5–9). In spite of several published studies on the effects of gastrin on pancreatic growth, the role of gastrin in regulating endocrine pancreatic growth is not well defined. Furthermore, even though many interventions have been used, such as antrectomy (10, 11), total parenteral nutrition (12), administration of pentagastrin (10, 11, 13), antral transposition to the colon (14), and intestine resection (15), the targets were always the intact pancreas.

Partial pancreatectomy (Px) has been used as an experimental model of regenerating pancreas in rats (16–19). Smith *et al.* (20) demonstrated that the levels of insulin-like growth factor I mRNA of the pancreatic remnant were increased 3 days after Px, but thereafter gradually decreased, suggesting that the regeneration occurs in the early period after pancreatectomy.

We investigated the possible role of endogenous hypergastrinemia induced by lansoprazole (AG-1749) (21, 22), a proton pump (H^+-K^+-ATPase) inhibitor, on regenerating pancreas with a 90% pancreatecto-

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mized rat model which is similar to PPPD in view of preserving the pylorus (stomach).

MATERIALS AND METHODS

Animals. Male Wistar rats were purchased from Crea Laboratories (Atsugi, Japan) and delivered to our laboratory at 7 weeks of age. The animals were housed in air-conditioned quarters at 24°C under artificial lighting (lights on, 0800–2000). Tap water and chow pellets were given ad libitum. At 9 weeks of age, animals (weighing 300–310 g) underwent either sham operation or 90% partial pancreatectomy. The rats were anesthetized with pentobarbital (50 mg/kg body wt, i.p.) and a midline abdominal incision was made. All pancreatic tissue except the parabiliary segment was removed as described by Bonner-Weir *et al.* (17). The sham-operated rats were laparotomized, and their pancreas was ablated from the mesentery and gently rubbed between the fingertips.

Treatments. The animals were divided into the following treatment groups: group 1 (n = 8), sham-operated rats (sham-control); group 2 (n = 8), shams treated with lansoprazole (sham-PPI); group 3 (n = 6), 90% partial pancreatectomized rats (Px-control); and group 4 (n = 6), Px rats treated with lansoprazole (Px-PPI). Lansoprazole (Takeda Chemical Industries Ltd., Osaka, Japan; 30 mg/kg body wt) suspended in 0.5% methyl cellulose was administered daily from the day of the operation for 3 weeks by stomach gavage through a metal catheter attached to a syringe. The dose employed in the present study is a maximal one which potently inhibits gastric acid secretion with hypergastrinemia (21) and accelerates healing of acetic acid-induced gastric and duodenal ulcer in rats (22).

***In Vivo* Study.** Blood was collected into heparinized hematocrit tubes after cutting the tip of the tail in the fed state once a week. On day 21 of treatment, an oral glucose tolerance test (OGTT) was performed in the conscious state after 16 hr of fasting. Glucose was administered as an 80 g/dl solution at a dose of 200 mg/0.25 ml solution/100 g body weight by stomach gavage. The blood was collected into heparinized hematocrit tubes after cutting the tail vein. Insulinogenesis was calculated as the integrated insulin response during 120 min after the glucose load.

Extraction of Insulin and Assays. Eight hours after glucose challenge, the animals were sacrificed, and a blood sample was obtained from the heart to determine fasting serum gastrin levels. The pancreas and stomach were removed, weighed, and stored at −70°C until further examination.

Pancreas from sham rats were divided into the remnant equivalent (parabiliary segment) and the rest. The pancreatic tissue specimens from shams and Px remnant were divided into two parts. One of them was homogenized in 3 ml of cold acid–ethanol (0.18 *M* HCl in 75%, v/v, ethanol) and kept for 24 hr at 4°C. After centrifugation at 1800*g* for 20 min at 4°C, the supernatant was collected, then stored at −70°C until assayed for insulin. Another part of each pancreatic tissue specimen was mechanically homogenized in ice-cold 0.9% NaCl solution, then the supernatant was collected and stored at −70°C until assayed for protein.

Plasma glucose was measured by the glucose oxidase method using a glucose analyzer (Fuji Film Co., Tokyo). Protein content was determined by the method of Bradford with human serum albumin as the standard. Immunoreactive insulin was measured by specific radioimmunoassay (23) using rat insulin (Novo, Bagsvaerd, Denmark) as the standard. The sensitivity of this assay was 6 μU/ml, and the interassay coefficient of variation was 10%. Serum gastrin was also determined by specific radioimmunoassay.

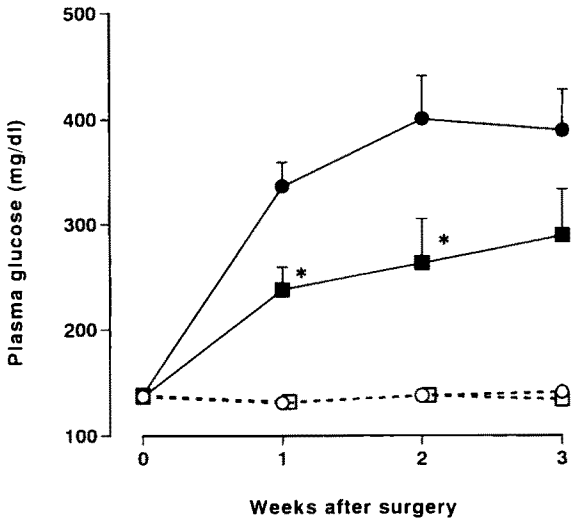

Fig 1. Effect of PPI on plasma glucose levels in the fed state. Sham-control, open circles; sham-PPI, open squares; Px-control, filled circles; Px-PPI, filled squares. Each error bar shows the SE. Plasma glucose concentrations were significantly higher in the Px groups than in the sham groups from 1 week after the surgery. PPI significantly lowered plasma glucose levels at the first and second weeks compared with Px-control. $^*p < 0.05$ vs Px-control.

Statistical Analysis. Gastric weight and pancreatic weight were normalized by body weight. Values are expressed as the mean ± SEM and analyzed using ANOVA followed by the multiple comparison of Fisher. A p value of less than 0.05 was considered significant.

RESULTS

There was no difference in food consumption, as measured daily during the study period, either between shams or between Px rats. The effect of PPI administration on plasma glucose levels is shown in Figure 1. The plasma glucose concentration was significantly higher in the Px rats than in the sham rats from 1 week after surgery. PPI significantly lowered plasma glucose levels at the first and second weeks after treatment compared with those of the Px-control rats.

Figure 2 shows plasma glucose and insulin concentrations during the OGTT. There was no difference in glucose or insulin concentration between the sham groups. Plasma glucose was lower while insulin was higher in Px-PPI than Px-control at 60 min. The

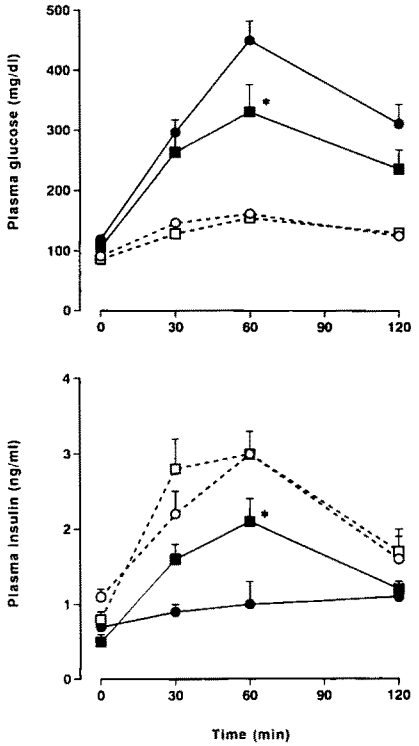

Fig 2. Plasma glucose (top) and insulin (bottom) concentrations in the OGTT. Sham-control, open circles; sham-PPI, open squares; Px-control, filled circles; Px-PPI, filled squares. Each error bar shows SE. There was no difference between sham groups in either glucose or insulin concentration. Plasma glucose was lower, while insulin was higher, in Px-PPI than in Px-control at 60 min. $*p < 0.01$ vs Px-control.

integrated insulin response for the 120 min after glucose challenge was greater in Px-PPI than in Px-control (Figure 3).

The effect of PPI administration on serum gastrin concentration is shown in Figure 4. After 24 hr of fasting, except for glucose challenge 8 hr before sampling, the serum gastrin concentration was significantly increased in the PPI-treated animals compared with the control groups both in the sham rats (357.4 ± 38.1 vs 156.8 ± 24.1 pg/ml; $P < 0.01$) and in the Px rats (338.6 ± 54.7 vs 148.3 ± 12.8 pg/ml; $P < 0.01$).

The organ weights in the experimental animals are shown in Table 1. No significant difference in mean body weight was observed either between sham groups or between Px groups. Pancreas weight per body weight was significantly greater in Px-PPI than in Px-control and also greater in both Px groups than in sham groups. However, no significant difference was observed between sham groups. Wet weight of the stomach was greater in Px-PPI, Px-control, and sham-PPI than in sham-control, whereas there was no difference between Px groups (Table 1).

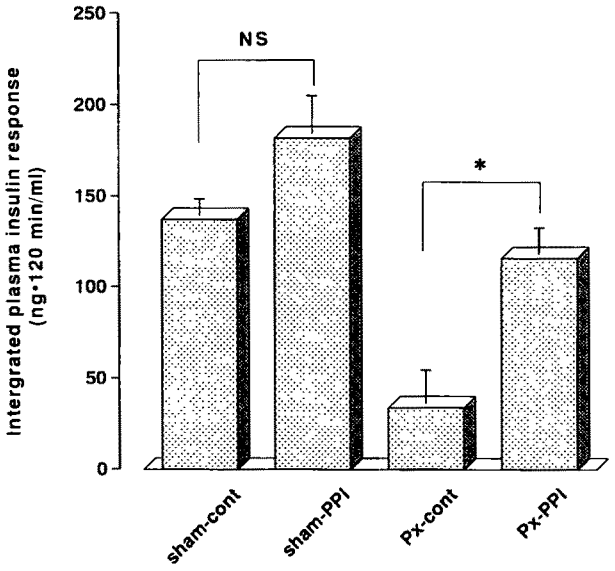

Fig 3. Integrated insulin response for 120 min in the OGTT. The integrated insulin response was greater in Px-PPI than in Px-control. $*p < 0.01$. Each error bar shows the SE. NS, not significant.

The effect of PPI administration on pancreatic protein and insulin content is shown in Table 2. Pancreatectomy led to an increase in protein content compared with the remnant equivalent of sham-operated groups. No significant difference in pancreatic protein content was noted between sham groups or between Px groups. There was no difference in insulin content between Px control and sham groups, whereas PPI administration in Px rats raised the insulin content to reach statistical significance compared with sham groups (Table 2).

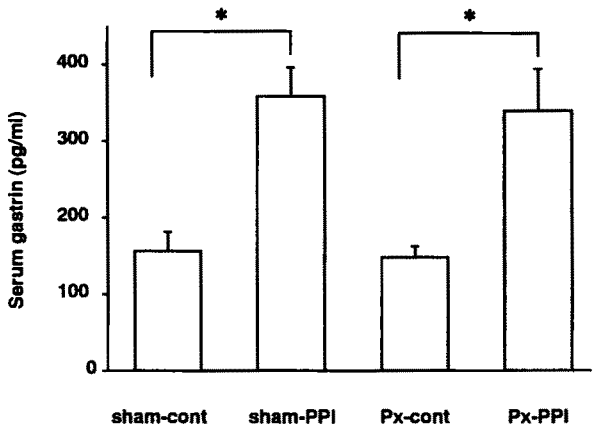

Fig 4. Effect of PPI administration on serum gastrin concentrations. After 24 hr of fasting, serum gastrin concentration was significantly increased in the PPI-treated groups compared with the control groups both in sham and in Px rats. $*p < 0.01$. Each error bar shows the SE.

TABLE 1. BODY WEIGHT AND WET WEIGHT OF THE PANCREAS AND THE STOMACH 3 WEEKS AFTER SURGERY*

Group	n	Body weight (g)	Pancreas weight (mg) / Body weight (g)	Stomach weight (mg) / Body weight (g)
Sham-control	8	364.8 ± 5.2	0.314 ± 0.024 (3.21 ± 0.08)	2.69 ± 0.05
Sham-PPI	8	350.9 ± 5.7	0.317 ± 0.200 (3.33 ± 0.16)	3.33 ± 0.05[b,†]
Px-control	6	334.0 ± 9.2[b]	0.578 ± 0.002[b,c]	3.33 ± 0.11[b]
Px-PPI	6	321.5 ± 5.9[b,c]	0.650 ± 0.028[a,b,c]	3.51 ± 0.04[b]

* Values are given as mean ± SE. Pancreatic weight indicates remnant equivalent in sham-operated rats or remnant in Px rats. Values in parentheses indicate whole pancreas.
† Superscript a, $p < 0.05$ vs Px-control; b, $p < 0.001$ vs sham control; c, $p < 0.001$ vs sham-PPI.

DISCUSSION

Traverso and Longmire, who developed PPPD, suggested that PPPD with Billroth-II type reconstruction could prevent dumping and other postoperative symptoms as well as maintain weight gain (1). Hyperacid state and marginal ulcer formation have been reported after PPPD (2–4). Antacid drugs can prevent the postoperative symptoms induced by this hyperacid state (3, 4) but evoke hypergastrinemia. Although the mechanism of the exaggerated gastrin secretion is not fully understood, high gastrin levels after antacid administration have been reported in many species (5–9). We confirmed an exaggerated increase in serum gastrin levels (endogenous hypergastrinemia) by lansoprazole administration in both Px and sham rats.

Previous studies showed the growth-promoting effect of gastrin analogues, such as pentagastrin, tetragastrin, and gastrin, on rodent pancreas (10–13), whereas the effects of alterations in endogenous gastrin are far less clear. Antrectomy, which induces hypogastrinemia, did not decrease pancreatic weight in some studies (14, 24) but did so in another study (10), in which the decrease could be reversed by pentagastrin. Endogenous hypergastrinemia induced by transplantation of the antrum to the colon (14) and by split gastrojejunostomy (25) has been shown to lead to an increase in pancreatic weight, while other models of endogenous hypergastrinemia (10, 26–28) have not definitely shown a trophic effect on the pancreas. However, none of these studies assessed the proliferation of endocrine pancreas, because it is impossible to estimate to what extent B cells are regenerated by using the intact pancreas. In the present study, 90% pancreatectomized rats were used to clarify the roles of endogenous gastrin induced by PPI administration on the regenerating pancreas.

TABLE 2. PROTEIN AND INSULIN CONTENT OF THE REMNANT EQUIVALENT IN SHAM-OPERATED RATS OR REMNANT PANCREAS IN PX RATS 3 WEEKS AFTER SURGERY*

Group	n	Protein (mg)	Insulin content (μg)
Sham-control	8	10.2 ± 1.2	7.9 ± 0.6
Sham-PPI	8	12.1 ± 0.8	8.7 ± 1.2
Px-control	6	23.9 ± 2.6†	14.7 ± 1.8
Px-PPI	6	27.4 ± 2.2†	19.2 ± 2.7†

* Values are given as mean ± SE.
† $p < 0.01$ vs both sham-control and sham-PPI.

The main findings of this study were that PPI had an ameliorating effect on the endocrine pancreas. There are two possibilities regarding the mechanism of improvement of endocrine pancreas after pancreatectomy with oral administration of the proton pump inhibitor. The first is that endogenous hypergastrinemia evoked by PPI administration has an insulin-releasing effect on the remnant pancreas, thereby improving the pancreatic endocrine function in Px rats. Rehfeld and Stadil (29) have reported that gastrin potentiates the glucose-stimulated insulin secretion without having an effect on basal insulin secretion. Jensen *et al.* (30) found that gastrin may influence the endocrine secretion in diseases with endogenous hypergastrinemia. Our data showed that insulin release was ameliorated in Px-PPI but not in sham-PPI. Portha and Picon (31) revealed a long-term ameliorating effect of insulin treatment on the development of diabetes, when insulin was administered for only 4 days after streptozotocin injection into neonatal rats. Thus, it is possible that early therapy may be very effective in protecting B-cell mass and function. Brockenbrough *et al.* (32) reported that the insulin content of remnant pancreas is reduced compared with that of the remnant equivalent until 21 days after 90% pancreatectomy. The lower insulin content during the first 2 weeks may be a reflection of the degranulation of B cells that occurs

with sustained moderate hyperglycemia. In the present study, no difference in insulin content between remnant of Px-control and remnant equivalent of the sham groups was observed, whereas the insulin content was significantly higher in the Px-PPI group than in the sham groups, indicating B-cell compensation earlier in Px-PPI than in Px-control due to the PPI administration. It is therefore likely that elevated gastrin levels stimulated insulin release from the early period of the diabetic state in Px rats, which resulted in an ameliorated B-cell function.

Another possibility for the ameliorating effect of gastrin could be the trophic effect of gastrin on endocrine pancreas. Solomon *et al.* (13) have reported that the pancreas is more sensitive than other organs to the trophic effects of pentagastrin. We speculate that the regenerating pancreas would be more sensitive to the trophic effects of gastrin. Partial pancreatectomy has been used as an experimental model of regenerating pancreas in rats (16–19). Pearson *et al.* reported that the residual pancreas regenerated B-cell mass to 42% of the whole pancreas of the control. Smith *et al.* (20) demonstrated that the levels of insulin-like growth factor I mRNA of the pancreatic remnant were increased 3 days after Px, but thereafter gradually decreased, suggesting that the regeneration occurs mainly in the early period after pancreatectomy. Since hypergastrinemia was induced by lansoprazole administration, regeneration of islets might be enhanced by the elevated levels of endogenous gastrin. This assumption is supported by the recent finding that the replication of pancreatic islet was markedly stimulated by gastrin. Wang *et al.* (33) reported that islet neogenesis can be reactivated in the ductular epithelium of the adult pancreas by high levels of gastrin in the TGFα-induced metaplastic ducts and suggested that gastrin is the growth factor that stimulates islet growth. Indeed, in the present study, there was no difference between sham-control and sham-PPI in OGTT and the insulin content, indicating that the stimulating effect works mainly on regenerating cells after pancreatectomy.

The results of pancreatic weight which reflects exocrine pancreas showed an evident difference between sham and Px groups and a less evident but still significant difference between Px-control and Px-PPI, although no difference was observed between sham-operated pancreata. The generally accepted criteria for demonstrating a physiological role for any hormone seem to be fulfilled by cholecystokinin (CCK) in pancreatic regeneration (34). It would be reasonable to assume that the differences in pancreatic weight, as well as pancreatic protein content, between sham and Px groups were caused by the hyperCCKemia (34) and other growth factors (20, 35) after pancreatectomy. On the other hand, the difference between Px-control and Px-PPI suggests that gastrin has a trophic effect not only on endocrine but also on exocrine pancreas during regeneration. Reportedly, CCK-B receptors, which equally bind to CCK and gastrin, are not detected in normal rat pancreas, but they seem to be expressed in damaged pancreas (36–38). However, expression of the gastrin (CCK-B) receptors in proliferating cells remains to be investigated. Further studies are necessary to determine and localize the receptors in both acinar and islet during the pancreatic regenerating process.

One of the interesting findings of the present study is that the stomach weight of Px-control was significantly greater than that of sham-control. Since gastrin has a trophic effect on the stomach (39), PPI-induced hypergastrinemia could increase gastric weight as observed in sham-PPI. However, plasma gastrin levels were equivalent between Px-control and sham-control. These results suggest that Px alone has a growth promoting effect on the stomach. CCK shares the receptor with gastrin in rat stomach (40) and CCK or its analogue stimulates proliferation in gastric zymogenic cells (41) and the antral epithelium (42). It was likely that Px-induced hyperCCKemia might have stimulated gastric proliferation to some extent, although Johnson and Guthrie (43) reported earlier that CCK is not as potent a trophic hormone as gastrin in the stomach. The mechanism by which Px induces an increase in gastric weight awaits further elucidation.

Omeprazole, another PPI, is reported to reduce postprandial pancreatic bicarbonate secretion in dogs (44) and to lower plasma secretin levels in fasting and immediate postprandial periods in humans (45). In addition, perfusion of the duodenum with hydrochloride, which stimulates secretin release, is shown to increase pancreatic weight (46). These reports lead to the possibility that inhibited gastric acid secretion by PPI impairs the function and/or growth of the pancreas by reducing plasma secretin levels. Secretin physiologically stimulates pancreatic exocrine secretion (47, 48). On the contrary, the effects on endocrine secretion (49) and growth (47) of the pancreas seem pharmacologic. Therefore, it is unlikely that the possibly suppressed plasma levels of secretin could inhibit endocrine function or growth of the pancreas in the present study. However, if we use PPI after pylorus-preserving pancreatectomy for humans, it is

worth noting that PPI can reduce exocrine secretion to some extent.

In summary, the present results indicate that lansoprazole-induced endogenous hypergastrinemia leads to amelioration of hyperglycemia and B-cell function after 90% partial pancreatectomy. This indicates that endogenous hypergastrinemia has trophic effects on the endocrine pancreas during regenerating processes and that administration of PPI may be clinically beneficial to the remnant pancreas after pylorus-preserving pancreatoduodenectomy.

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