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ABOUT COVER

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ORIGINAL ARTICLE

Basic Study

Impacts of different pancreatic resection ranges on endocrine function in *Suncus murinus*

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Abstract

BACKGROUND

Surgical intervention involving the pancreas can lead to impaired glucose tolerance and other types of endocrine dysfunction. The scope of pancreatectomy and whether it includes the ventral pancreas are the key factors in the development of postoperative diabetes. The ventral and dorsal pancreases are almost separated in *Suncus murinus* (*S. murinus*).

AIM

To investigate the effects of different extents of pancreatic resection on endocrine function in *S. murinus*.

METHODS

Eight-week-old male *S. murinus* shrews were randomly divided into three experimental groups according to different pancreatic resection ranges as follows: ventral pancreatectomy (VPx) group; partial pancreatectomy (PPx) group; subtotal pancreatectomy (SPx) group; and a sham-operated group. Postprandial serum insulin, glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PP), and somatostatin (SST) levels, as well as food intake, weight, blood glucose, and glucose tolerance were regularly measured for each animal.

RESULTS

S. murinus treated with PPx and SPx suffered from varying degrees of impaired glucose tolerance, but only a small proportion of the SPx group developed diabetes. Only *S. murinus* in the SPx group showed a significant decrease in food intake accompanied by severe weight loss, as well as a significant increase in postprandial serum GLP-1 levels. Postprandial serum PP levels decreased in both the VPx and PPx groups, but not in the SPx group. Postprandial serum SST levels decreased in both VPx and PPx groups, but the decrease was marginal.

CONCLUSION

Severe weight loss after pancreatectomy may be related to loss of appetite caused by compensatory elevation of GLP-1. PP and GLP-1 may play a role in resisting blood glucose imbalance.

Key Words: Pancreatectomy; Glucose homeostasis; Endocrine dysfunction; Glucagon-like peptide-1; Pancreatic polypeptide

Core Tip: Surgical intervention involving the pancreas can lead to impaired glucose tolerance and other types of endocrine dysfunction. The scope of pancreatectomy and whether it includes the ventral pancreas are the key factors in development of postoperative diabetes. Here, we investigated the impacts of three different pancreatic resection ranges (all containing ventral pancreas resection) on endocrine function in *Suncus murinus* and found that severe weight loss after pancreatectomy may be related to loss of appetite caused by compensatory elevation of glucagon-like peptide-1 (GLP-1) and that pancreatic polypeptide and GLP-1 may play a non-negligible role in resisting blood glucose imbalance after pancreatectomy.

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INTRODUCTION

The pancreas is an important exocrine and endocrine organ, and there are complex interactions between the endocrine and exocrine functions of the pancreas and gut hormones. Surgical interventions involving the pancreas can lead to impaired glucose tolerance and other endocrine dysfunction. Gall *et al*[1] reported 49 partial pancreaticoduodenectomy and 68 total pancreaticoduodenectomy procedures performed for chronic pancreatitis. In the partial pancreatectomy group, 16% of patients had diabetes before surgery. This increased to 22% thereafter. Miyata *et al*[2] found no significant difference in fasting blood glucose levels compared to the normal control group in their study of insulin secretion after partial pancreaticoduodenectomy in 10 patients; however, in the resection group, hyperglycemia persisted for 3 h after oral glucose administration. Izbicki *et al*[3] studied the endocrine function of 30 patients who underwent pylorus-preserving pancreaticoduodenectomy and found that their glucose tolerance further deteriorated, requiring insulin to control blood glucose levels; 3 patients with normal preoperative glucose metabolism developed impaired glucose tolerance after surgery. Eddes *et al*[4] also reported that, in patients after pancreatic surgery that included pancreatic head resection, basal and stimulated pancreatic polypeptide (PP) secretions were significantly reduced. Therefore, the effect of pancreatectomy on glucose tolerance and other endocrine functions cannot be ignored.

Further research shows that preservation of the ventral pancreas is key to preventing postoperative diabetes after pancreatectomy. Büchler *et al*[5] indicated that preservation of the duodenum (or the PP and the ventral pancreas) was the main reason for improving postoperative glucose tolerance in their study of endocrine function after pylorus-preserving partial pancreaticoduodenectomy or duodenum-preserving pancreatic head resection. Central pancreatectomy is a parenchyma-sparing surgical procedure that enables the removal of benign or low-grade malignant lesions from the neck and proximal body of the pancreas. A systematic review indicated that central pancreatectomy is associated with a lower risk of endocrine insufficiency in comparison to distal pancreatectomy[6].

The liver is crucial for glucose homeostasis, and its impact on glucose metabolism largely depends on insulin, glucagon, and PP, which are all circulating hormones secreted by the pancreas[7]. Alpha cells (producing glucagon) and PP cells (producing PP) are respectively distributed in the tail and head of the pancreas, while β cells (producing glucagon) are evenly distributed throughout the pancreas[8,9]. Therefore, postoperative pancreatic endocrine dysfunction depends on the specific scope and area of pancreatic resection. Based on our previous studies[10] on the anatomy of the hepatobiliary pancreatic system of *Suncus murinus* (*S. murinus*), we found that the ventral and dorsal pancreases were almost separated, making ventral pancreatic resection easier. For this reason, *S. murinus* was chosen as the experimental animal in this study.

Glucagon-like peptide-1 (GLP-1) stimulates insulin secretion and reduces food intake. GLP-1 promotes insulin secretion in mice[11], rats[12], and pigs[13]. The insulinotropic effect of GLP-1 is based on a permissive degree of hyperglycemia[14]. The stimulation of adenylate cyclase and intracellular production of cAMP due to the binding of GLP-1

receptors to G-proteins activates protein kinase A and triggers biological effects[15]. The food intake in rodents decreases even by administering intracerebroventricular microgram amounts of GLP-1[16]. Peripherally administered GLP-1 can reach certain areas of the central nervous system[17], and decrease food intake and appetite[18].

The pancreas secretes somatostatin (SST), which can inhibit pancreatic exocrine function. SST and its receptors are widely distributed in the digestive system. Enteric endocrine cells, D cells in the stomach, and δ cells in the pancreas secrete SST[19,20]. The digestive and absorption functions of the gastrointestinal (GI) system can be suppressed by SST and its receptors[21,22]. The use of perioperative SST or its analogs, which suppress pancreatic exocrine secretion, may contribute to reducing the incidence of postoperative complications in pancreatic surgery. Although many surgeons have accepted this viewpoint, it remains controversial[23].

In this study, we hypothesized that pancreatectomy involving the ventral pancreas could provide a stable model of impaired glucose tolerance/diabetes and endocrine dysfunction after surgery in *S. murinus*. The animals were randomly divided into three experimental groups and a control group according to different pancreatic resection ranges. Postprandial serum insulin, GLP-1, PP, and SST levels, as well as food intake, weight, blood glucose, and glucose tolerance were regularly measured in each experimental animal.

MATERIALS AND METHODS

Experimental animals

Male house musk shrews [*S. murinus* (n = 27; age of 8 wk; body weight of 80-105 g)] were used. *S. murinus* were maintained in a closed breeding colony (JIc: KAT-c, at our laboratory), which was kept in an experimental animal facility at a room temperature (RT) of 25-28 °C, under a 12-h light and dark cycle, with *ad libitum* access to trout chow and water [10]. The food pellets consisted of 45.0% protein, 4.0% fat, 3.0% fiber, 15.0% ash, and 26.2% complex carbohydrates (Oriental Yeast Co. Ltd. Bioindustry Division, Chiba, Japan). The metabolizable energy content was 357 kcal/100 g.

All animal experiments were approved by the Institutional Animal Care and Use Committee of the Tokyo Metropolitan University (Permit Numbers: A4-26 and A5-17). All experimental procedures were performed in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals.

Experimental design for pancreatectomy

All surgeries were performed under isoflurane anesthesia to alleviate pain, and all efforts were made to minimize suffering. Animals were monitored continuously after surgery until they were able to maintain sternal recumbency, as required by the Institutional Animal Care and Use Committee policy surgical guidelines. Subsequently, they were monitored twice daily for 3-5 d to ensure general health. The specific criteria used to monitor animal health included hunched posture, piloerection, abnormal feeding, drinking, and ambulation. If there were adverse signs that persisted for 24 h postoperatively or a pronounced sharp decrease in body weight (> 25%), the animals were euthanized using excessive anesthesia.

Animals were randomly sham-operated (Sham group, Sham, n = 6) or subjected to pancreatectomy (Px) (Experimental groups). The animals were divided into three groups: ventral pancreatectomy (VPx, n = 7), partial pancreatectomy (PPx, n = 8), and subtotal pancreatectomy (SPx, n = 6). For VPx, PPx, and SPx, different ranges of pancreatic resection were performed, as shown in Figure 1, corresponding to the resection of the right pancreas (VPx, Figure 1, area A, approximately 10% of the total pancreatic volume), the right pancreas and splenic lobe (area C, approximately 65%-75% of the total pancreatic volume) of the left pancreas (PPx, Figure 1, combined resection of areas A + C, approximately 75%-85% of the total pancreatic volume), right pancreas and gastric lobe (area B, approximately 5%-10% of the total pancreatic volume), and splenic lobes of the left pancreas (SPx, Figure 1, combined resection of areas A + B + C, approximately 85%-90% of the total pancreatic volume). The sham-operated animals were handled similarly, but their pancreas was not removed.

Experimental data were collected for each animal (Figure 2). Blood was collected through the submandibular vein 8, 10, 15, 17, 22, and 26 d after the operation, and body weight was measured on postoperative days 5, 11, 18, and 25. Intraperitoneal glucose tolerance test (IPGTT) and blood glucose testing were performed once and twice per week, respectively, after surgery. The average amount of food consumed for 7 consecutive days after surgery was taken as the first week's food intake. The food intake for the second, third, and fourth weeks was calculated in sequence. Bromodeoxyuridine (BrdU) at a dose of 100 mg/kg body weight per day was injected intraperitoneally 3 d before sacrifice. All experimental animals were sacrificed 4 wk after surgery.

Glucose homeostasis

Blood glucose was measured twice a week at approximately 9:00 am on the tail snips using a portable glucometer (190725; TERUMO, Tokyo, Japan). IPGTT was performed when *S. murinus* were injected intraperitoneally with 1 g dextrose/kg body weight after overnight fasting (water not prohibited). Blood glucose concentrations were measured at various time points (0, 10, 30, 60, and 120 min), and blood was collected 30 min after intraperitoneal injection for insulin detection. The area under the curve was used to reflect the overall blood glucose level during IPGTT.

Immunofluorescence staining

Immediately after euthanizing the animals, systemic perfusion was performed using 4% paraformaldehyde. Pancreatic tissue specimens were then collected, immersed, and fixed in 4% PFA at 4 °C overnight. The specimens were then washed

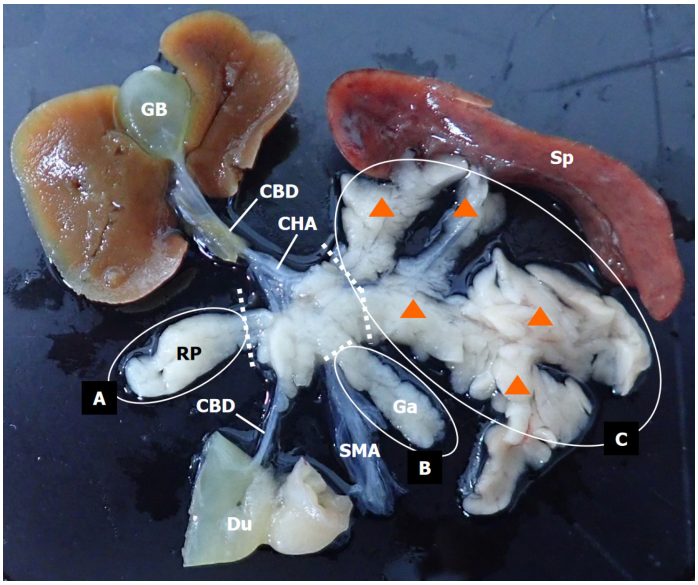

Figure 1 Diagram of the extent of pancreatic resection in *Suncus murinus*. Arrowheads indicate the splenic lobe of the left pancreas (area C). CBD: Common bile duct; CHA: Common hepatic artery; Du: Duodenum; Ga: Gastric lobe of the left pancreas (area B); GB: Gallbladder; RP: Right pancreas (area A); SMA: Superior mesenteric artery; Sp: Spleen.

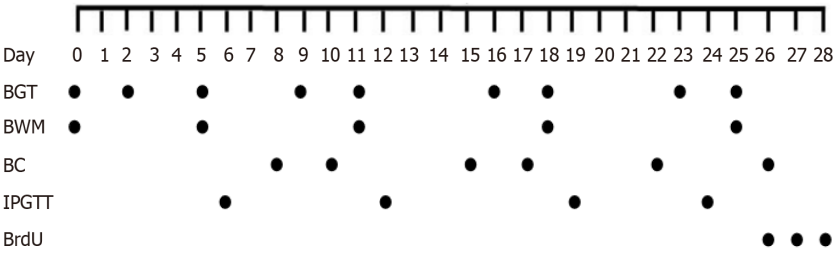

Figure 2 The schedule of experimental data collection. BC: Blood collection; BGT: Blood glucose testing; BrdU: Bromodeoxiuridin; BWM: Body weight measurement; IPGTT: Intraperitoneal glucose tolerance test.

thoroughly for 4-5 h under running tap water, dehydrated, and routinely embedded in paraffin. Sections (5 μm) were cut and placed on gelatin-coated glass slides. Immunohistochemical procedures for double fluorescence staining were performed as previously described[24]. Briefly, the tissue sections were deparaffinized with xylene and rehydrated in a graded ethanol series. The sections were then treated for 15 min in a methanol solution containing 0.3% (v/v) hydrogen peroxide. Rinsing was performed in 0.01 M PBS. After this, the sections were blocked with protein block (X0909; Dako, Nowy Sącz, Poland) for 1 h and incubated with 2 M hydrochloric acid for 45 min at RT. Next, the sections were incubated overnight at 4 °C with guinea pig anti-insulin antibody (ready to use) (IR00261-2J; Dako) in a humidified chamber, and then incubated with mouse anti-BrdU antibody (B35128; Invitrogen, ThermoFisher Scientific, Waltham, MA, United States) diluted to 1:50 in 0.01 M PBS in the same way. Thereafter, two types of corresponding secondary antibodies, Alexa Fluor 488-conjugated goat anti-guinea pig IgG (A11073; Invitrogen) and donkey anti-mouse IgG TRITC (sc-2300; Santa Cruz Biotechnology, Dallas, TX, United States), were diluted 1:100 in 0.01 M PBS and then incubated for 1 h at RT with the slides. Sections were then coverslipped with Fluoromount (K-024; Diagnostic Biosystems, Pleasanton, CA, United States) and viewed under a fluorescence microscope (Axio Imager M1; Zeiss, Oberkochen, Germany).

Detection of insulin, PP, SST, and GLP-1 in serum

S. murinus were fasted (water not restricted) for 12 h, and blood was collected 30 min after feeding. After blood collection, samples were allowed to stand at RT for approximately 2 h to coagulate, then centrifuged at 3000 rpm for 10 min, and the serum was stored at -20 °C until the next experiment. These serum samples were used to measure insulin using the Insulin Eliza kit (10-1113-01; Mercodia AB, Uppsala, Sweden), PP using the Pancreatic Polypeptide ELISA kit (EK-054-02; Phoenix Pharmaceuticals, Mannheim, Germany), SST using the Somatostatin ELISA kit (NBP2-80269; Novus Biologicals, Centennial, CO, United States), and GLP-1 using a GLP-1 ELISA kit (10-1278-01; Mercodia AB). For the detailed steps, refer to the corresponding product protocols.

Statistical analysis

Data are expressed as the mean ± standard deviation. To determine statistical significance, a Mann–Whitney test was

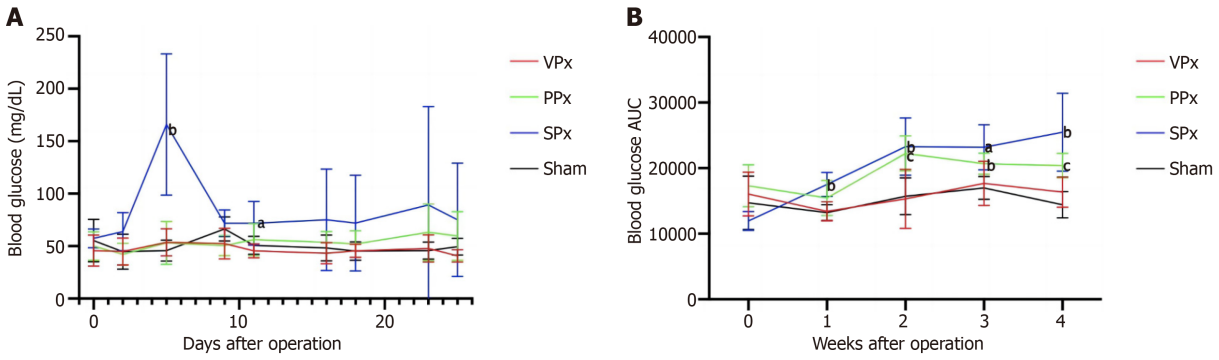

Figure 3 Variations in blood glucose levels and intraperitoneal glucose tolerance test outcomes over time in *Suncus murinus* with different pancreatic resection ranges. A: Blood glucose level; B: Intraperitoneal glucose tolerance test outcomes. $^{a}P < 0.05$ *vs* Sham; $^{b}P < 0.01$ *vs* Sham; $^{c}P < 0.001$ *vs* Sham. AUC: Area under the curve; PPx: Partial pancreatectomy group; SPx: Subtotal pancreatectomy group; VPx: Ventral pancreatectomy group.

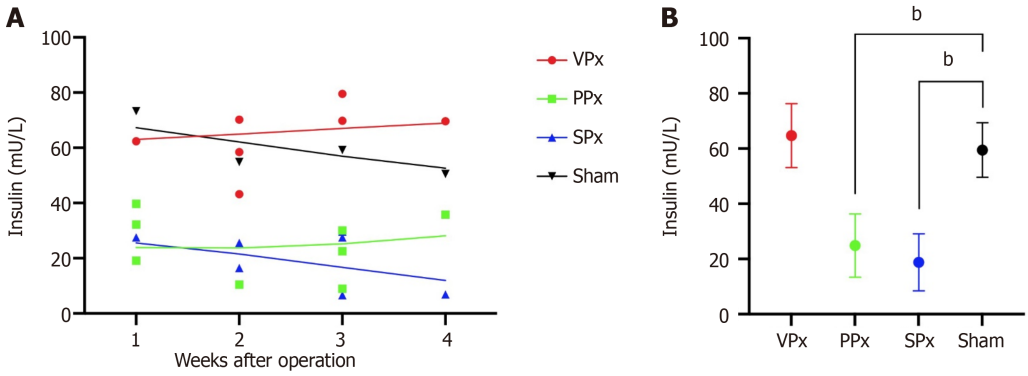

Figure 4 Variations over time and comparisons in insulin release. A: Insulin release at 30 min after the intraperitoneal glucose tolerance test (IPGTT) in *Suncus murinus* with different pancreatic resection ranges; B: Comparisons in insulin release at 30 min after the IPGTT between the pancreatectomy (Px) groups and the Sham group. Second-order smoothing was used to describe the trend of value variation over time. $^{b}P < 0.01$. PPx: Partial pancreatectomy group; SPx: Subtotal pancreatectomy group; VPx: Ventral pancreatectomy group.

used for comparisons between two groups. Second-order smoothing was used to describe the trend of value variation over time. Data visualization was conducted using GraphPad Prism Version 9.0.0 (La Jolla, CA, United States). Differences were considered statistically significant at $P < 0.05$.

RESULTS

Effects on blood glucose and glucose tolerance

S. murinus in the SPx group experienced a temporary increase in blood glucose levels in the first 2 wk after surgery and then recovered to the same level as the Sham group (Figure 3A and Supplementary Table 1). Only one (1/6) animal maintained a sustained and stable hyperglycemic state, with an average postoperative blood glucose level of 151 mg/dL after surgery. *S. murinus* in both the PPx and SPx groups showed varying degrees of impaired glucose tolerance after surgery, which remained stable over time (Figure 3B and Supplementary Table 2).

Insulin release at 30 min after the IPGTT in the PPx and SPx groups was significantly reduced and relatively stable over time in comparison to the Sham group (Figure 4 and Supplementary Table 3). *S. murinus* subjected to PPx and SPx both suffered from varying degrees of stable impaired glucose tolerance due to insufficient insulin secretion, but only a small proportion of *S. murinus* in the SPx group developed diabetes.

At the end of the experiment, no abnormally active proliferation of pancreatic endocrine cells was observed in any of the three surgical groups compared with the Sham group (Figure 5). Thus, it does not support the explanation of β-cell proliferation as a compensatory process for glucose homeostasis after Px in *S. murinus*.

Effects on body weight and food intake

All animals that underwent Px showed varying degrees of weight loss after surgery, with the SPx group exhibiting the most severe weight loss (Figure 6A and Supplementary Table 4). Only *S. murinus* in the SPx group showed a significant decrease in food intake post-surgery (Figure 6B and Supplementary Table 5). The decrease in food intake may be an essential reason for the severe weight loss in the SPx group.

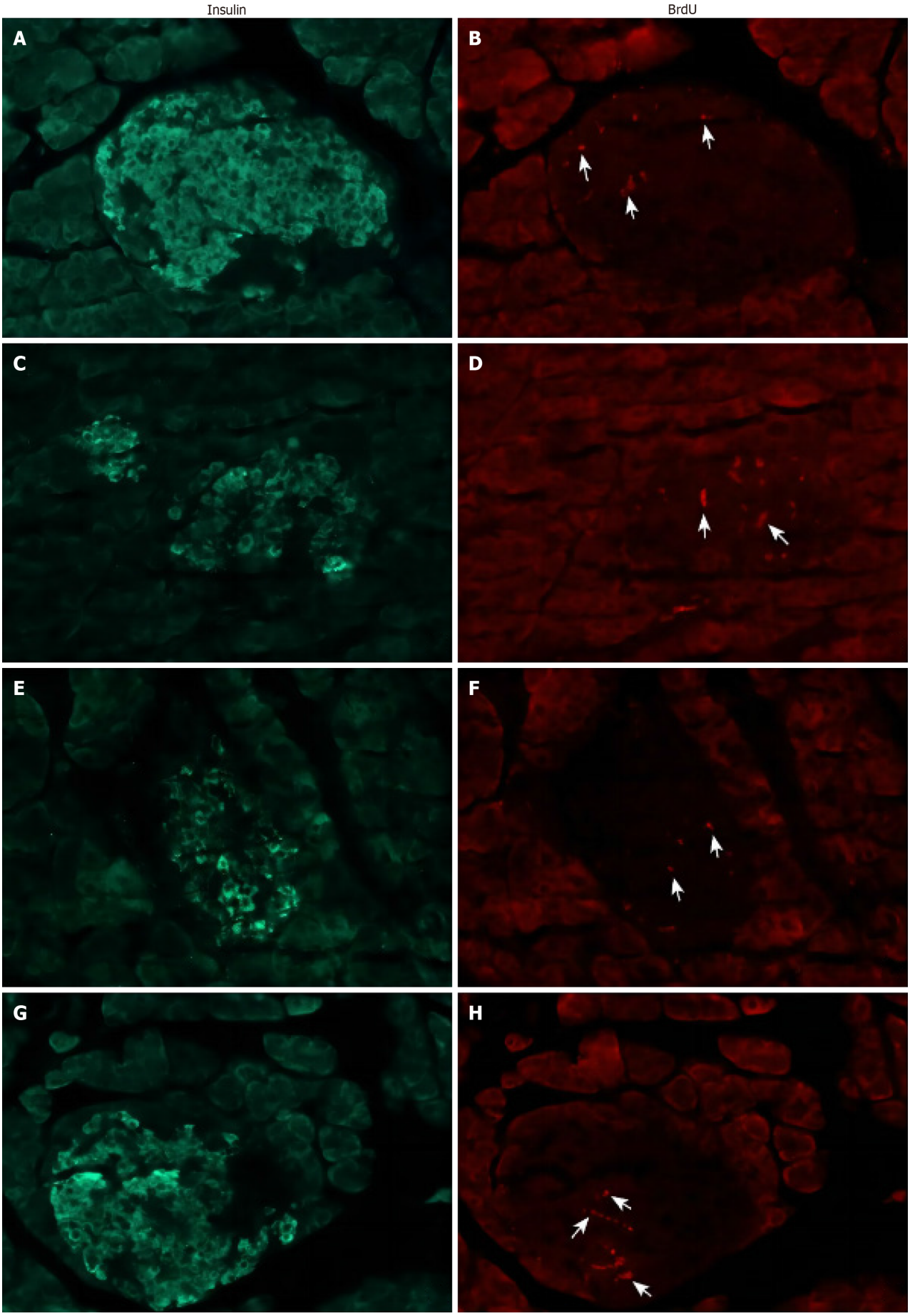

Figure 5 Double fluorescence staining of insulin-positive cells and Bromodeoxyuridine-positive cells in the islets of pancreatic tissue

after pancreatectomy. A: Insulin stained from the ventral pancreatectomy (VPx) group; B: Bromodeoxyuridine (BrdU) stained from the VPx group; C: Insulin stained from the partial pancreatectomy (PPx) group; D: BrdU stained from the PPx group; E: Insulin stained from the subtotal pancreatectomy (SPx) group; F: BrdU stained from the SPx group; G: Insulin stained from the Sham group; H: BrdU stained from the Sham group. Magnification: × 400 in each figure. Arrows indicate BrdU-positive reaction cells.

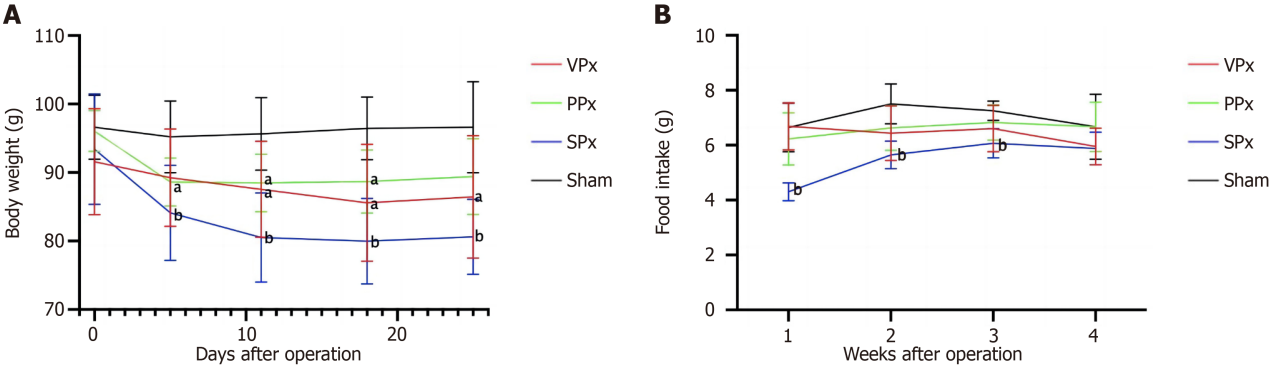

Figure 6 Variations in body weight and food intake over time, and comparisons between the pancreatectomy groups and the Sham group. A: Body weight; B: Food intake. $^{a}P < 0.05$ *vs* Sham; $^{b}P < 0.01$ *vs* Sham. PPx: Partial pancreatectomy group; SPx: Subtotal pancreatectomy group; VPx: Ventral pancreatectomy group.

Effects on endocrine function of S. murinus

Serum insulin levels at 30 min after feeding in both the PPx and SPx groups decreased significantly and remained relatively stable over time (Figure 7A and B, Supplementary Table 6). A 75%-85% Px can lead to insufficient postprandial insulin secretion in *S. murinus*. Serum GLP-1 levels at 30 min after feeding in the SPx group significantly increased and remained relatively stable over time (Figure 7C and D, Supplementary Table 7). SPx can lead to compensatory elevation in postprandial GLP-1 levels in *S. murinus*. The serum PP levels at 30 min after feeding in both the VPx and PPx groups decreased and remained relatively stable over time (Figure 7E and F, Supplementary Table 8), whereas there was no significant change in the SPx group. Partial Px, including that of the ventral pancreas, can cause a decrease in PP levels in the postprandial blood of *S. murinus*. However, when the scope of pancreatic resection expands further, it triggers compensatory mechanisms and rebounds to near-normal levels. Serum SST levels at 30 min after feeding in both the VPx and PPx groups decreased and remained relatively stable over time (Figure 7G and H, Supplementary Table 9), but the decrease was marginal.

DISCUSSION

In the present study, we divided the experimental animals into three Px groups (VPx, PPx, and SPx) and one sham-operated group. We regularly measured postprandial serum insulin, GLP-1, PP, and SST levels, as well as food intake, body weight, blood glucose, and glucose tolerance in all groups. We found that both *S. murinus* treated with PPx and SPx suffered from varying degrees of stable impaired glucose tolerance due to insufficient insulin secretion; however, only a small proportion of *S. murinus* in the SPx group had diabetes. Only *S. murinus* in the SPx group showed a significant decrease in food intake accompanied by severe weight loss. Only the SPx group showed a significant increase in serum GLP-1 levels 30 min after feeding. Postprandial serum PP levels decreased in both the VPx and PPx groups, but not in the SPx group.

We found that PPx (75%-85% Px) can lead to insufficient postprandial insulin release in *S. murinus*. Although insulin release in the SPx group decreased markedly (SPx *vs* Sham, 5.4 *vs* 30.4), only a small proportion of SPx *S. murinus* developed stable diabetes. This may be related to individual differences in the animals and subtle differences in the resection range. Kaufmann and Rodriguez[25] studied the incidence and development process of diabetes 12 mos after subtotal pancreatectomy in five strains of rats and found that only a few animals developed diabetes at the end of the experiment, and the severity of diabetes in different strains was distinct. Several animal experimental studies[26,27] have shown that partial pancreatic resection can lead to compensatory regeneration of pancreatic β cells. Although this study observed an increase in endocrine cells in the pancreatic islets of *S. murinus* after Px, the number of cells was not significantly different from that in the control group. Therefore, we believe that compensatory regeneration of β-cells is not the main reason *S. murinus* resists blood glucose imbalance after Px.

In addition, we observed that serum GLP-1 levels 30 min after feeding in the SPx group were significantly higher than those in the control group. The study by Cabou *et al*[28] showed that systemic glucose utilization and femoral artery blood flow in hyperinsulinemic-hyperglycemic mice were reduced by continuous intracerebral infusion of GLP-1 receptor agonists, demonstrating that this effect was strictly glucose dependent. Further research has indicated that brain GLP-1 signaling activates hypothalamic glucose-dependent PKC-δ to regulate femoral artery blood flow and insulin

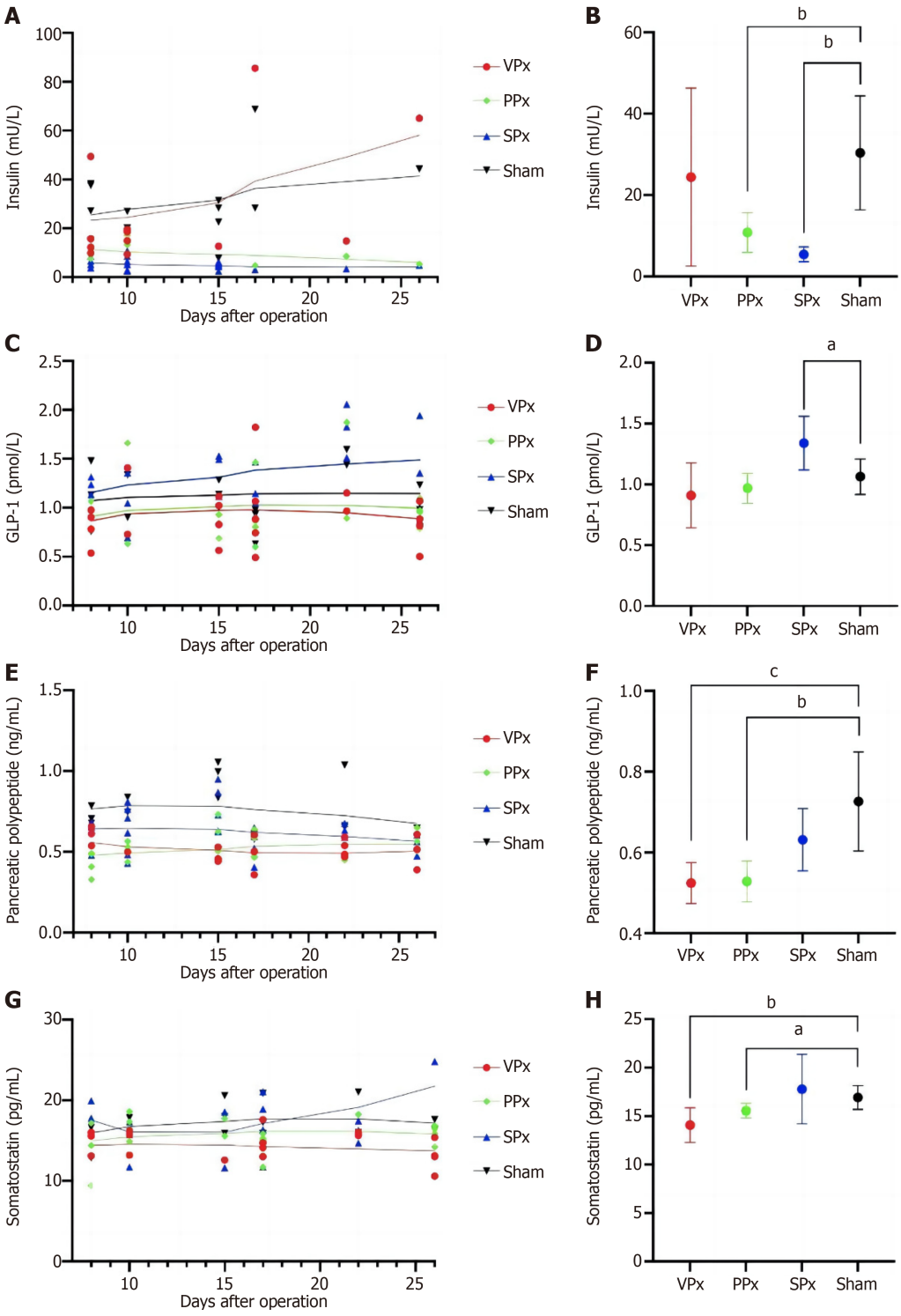

Figure 7 Variations in serum hormone levels at 30 min after feeding over time, and comparisons between the pancreatectomy groups and the Sham group. A: Serum insulin levels; B: Comparisons of insulin; C: Serum glucagon-like peptide-1 (GLP-1) levels; D: Comparisons of GLP-1; E: Serum pancreatic polypeptide (PP) levels; F: Comparisons of PP; G: Serum somatostatin levels; H: Comparisons of somatostatin. Second-order smoothing was used to describe the trend of value variation over time. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$. PPx: Partial pancreatectomy group; SPx: Subtotal pancreatectomy group; VPx: Ventral pancreatectomy group.

sensitivity in mice[29]. Parlevliet *et al*[30] also reported that, in high-fat fed mice, peripheral administration of GLP-1 enhances insulin's ability to inhibit endogenous glucose production and reinforces its ability to stimulate glucose utilization. These studies indicate that GLP-1 can inhibit endogenous glucose production and increase insulin sensitivity under hyperglycemic conditions. The increase in circulating GLP-1 levels and its participation in the regulation of glucose homeostasis may be one of the important reasons that the SPx group that underwent 85%-90% Px only showed a transient increase in blood glucose in the early stage without developing into stable diabetes.

We also found that the serum PP levels in the VPx and PPx groups significantly decreased 30 min after feeding. However, in the SPx group, it rebounded to normal levels in a compensatory manner, with no significant difference from the Sham group. Andersen *et al*[31] reported that the inhibition of hepatic glucose production significantly increased when PP was administered with insulin in dogs with chronic pancreatitis-induced PP deficiency. Seymour *et al*[32] studied male individuals who underwent Px after abdominal trauma, and found that patients with insufficient postoperative PP responses had severely impaired hepatic insulin responses. A few years later, in a study of a rat model of chronic pancreatitis[33], PP deficiency was associated with decreased availability of hepatic insulin receptors, which was reversible after PP administration. Therefore, we believe that the compensatory rebound of PP may contribute to the maintenance of blood glucose homeostasis in the SPx group by increasing liver sensitivity to insulin.

This study showed that *S. murinus* in the SPx group experienced severe weight loss accompanied by a decrease in food intake and an increase in postprandial serum GLP-1 levels. Punjabi *et al*[34] suggested that a regular chow meal transiently increased plasma active GLP-1 levels in the hepatic portal vein but not in the vena cava. However, an unphysiologically large postprandial release of GLP-1, for example, after gastric bypass surgery[35], may reach the circumventricular organs, and dipeptidyl peptidase 4 (DPP-4)-resistant GLP-1 receptor agonists clearly have central actions. Punjabi[34] also reported that intrameal hepatic portal vein GLP-1 infusion specifically reduced ongoing meal size by almost 40%. Peripherally administered GLP-1 receptor agonists reach the brainstem nuclei and hypothalamus, acting on the GLP-1 receptors of neurons in the arcuate nucleus that express proopiomelanocortin/cocaine and amphetamine-regulated transcript; the neurons are then depolarized by GLP-1 receptor stimulation and inhibit appetite producing NPY/appetite related peptide neurons, leading to decreased appetite and delayed eating[36,37], which are associated with reduced appetite and delayed initiation of meals. These studies indicate that abnormal increases in circulating GLP-1 are associated with reduced food intake and weight loss, which is consistent with our findings. Our study suggests that the effects of GLP-1 on weight loss in *S. murinus* after Px deserve further attention.

This study showed that the serum PP levels 30 min after feeding in both the VPx and PPx groups decreased, whereas there was no significant change in the SPx group. Our previous study[9] showed that PP-producing cells were extremely abundant in the right lobe of the pancreas of *S. murinus*, whereas they were absent in the left lobe. Thus, we believe that the distribution characteristics of PP cells were the main reason for the decrease in PP in the VPx and PPx groups. Moreover, we previously reported[24] that PP family (peptide Y) immunoreactive cells of the GI tract in *S. murinus* were predominantly distributed in the rectum. This may be the main site of compensatory increase in PP secretion in *S. murinus* that underwent a SPx. However, Dammann *et al*[38] reported that PP was undetectable in 8 patients who underwent total Px. This implies the absence of a significant number of normally functioning PP cells at extrapancreatic sites in humans. Therefore, it should be noted that there may be differences in compensatory ability for PP secretion between humans and animals.

We also observed a decrease in postprandial serum SST levels in the VPx and PPx groups, but the decrease was minimal (VPx and PPx *vs* Sham, 14.1 and 15.6 *vs* 16.9). We have not found any studies suggesting a correlation between Px and changes in postprandial serum SST levels. In this study, we were not sure whether a slight decrease in SST after pancreatic surgery would affect the physiological function of *S. murinus*.

In summary, the maintenance of glucose homeostasis in *S. murinus* after Px is the result of the combined action of multiple hormones, among which PP and GLP-1 may play a non-negligible role, and severe weight loss may be related to poor appetite caused by the compensatory elevation of GLP-1.

CONCLUSION

This study suggests that severe weight loss after Px, in addition to easy-to-understand factors such as large surgical trauma and a sharp decrease in digestive enzymes, may be related to loss of appetite caused by compensatory elevation of GLP-1, and that PP and GLP-1 may play a non-negligible role in resisting blood glucose imbalance after Px. Our results provide a new direction for the treatment and prevention of diabetes after Px. It is suggested that this animal model can be used for research related to impaired glucose tolerance or diabetes, weight loss, and endocrine dysfunction after Px.

FOOTNOTES

Author contributions: Li RJ and Yi SQ acquired funding and designed and conceived the study; Li RJ, Yang T, and Zeng YH participated in experiments; Li RJ, Yi SQ, Ren K, and Li J analyzed the data; Li RJ wrote the article; Yi SQ revised the manuscript accordingly; All authors have contributed to the final version of the manuscript, and have read and approved the final manuscript.

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