Pancreatic and Gastric Somatostatin Release in Response to Intragastric and Intraduodenal Nutrients and HCl in the Dog

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ABSTRACT The effects of the instillation of glucose, fat, casein hydrolysate, and HCl into the gastrointestinal tract upon plasma levels of somatostatin-like immunoreactivity (SLI) in the venous effluent of the pancreas, fundus and antrum of the stomach, and in the inferior vena cava (IVC) were determined in normal laparotomized dogs. Fasting SLI levels in the effluent plasma from these sites were significantly greater than IVC levels. The intragastric administration of glucose elicited a prompt and significant rise in SLI levels in pancreatic, fundic and antral venous plasma, and in IVC plasma; intraduodenal glucose elicited smaller increments. After intragastric fat, a smaller, more gradual increase in the pancreatic and fundic effluents was observed, whereas the rise in antral SLI was minute, and IVC SLI did not rise significantly. Intraduodenal fat elicited a prompt increase in the pancreatic and antral vein SLI levels, and a small but significant increase in fundic and IVC plasma which suggests faster release of enteric factors that influence SLI secretion in the pancreas and antrum. Intragastric casein hydrolysate elicited a prompt increase in SLI in both the pancreatic and fundic veins, the latter being marked, but the antral SLI response was small; IVC SLI rose significantly within 15 min. Intragastric HCl provoked a prompt and marked rise in pancreaticoduodenal and antral vein SLI but no increase in fundic vein SLI; IVC SLI levels rose significantly within 20 min. Intraduodenal HCl elicited an even more prompt and marked pancreatic SLI response, and SLI rose significantly in both the fundic and antral venous effluents; IVC SLI also rose more promptly. In dogs with a gastric fistula that prevented intraduodenal entry of HCl, intragastric HCl elicited only a very small and transient rise in pancreaticoduodenal vein SLI, markedly stimulated the antral SLI response, but completely suppressed fundic venous SLI levels.

The results indicate that all three nutrients stimulate SLI release from the pancreas and stomach. The greater SLI response to intragastric, as opposed to intraduodenal, glucose suggests that unidentified local factors are of importance. The responses to the intraduodenal instillation of HCl and fat suggest a role of enteric hormones in the release of SLI from the pancreas and fundus and antrum of the stomach. Additionally, there is evidence of direct effects of HCl upon gastric SLI release.

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INTRODUCTION

The functional role or roles of the somatostatin-containing δ-cells of the gastrointestinal tract and pancreas (1–8) are not known. It has been suggested that this tetradecapeptide is primarily a "paracrine" substance acting locally upon target cells situated in proximity to δ-cells of the islets and (or) gastrointestinal tract (8–10). However, the demonstration in the isolated canine pancreas that substantial amounts of somatostatin are released into the venous effluent in response to perfused nutrients and gut hormones, together with the presence of circulating somatostatin-like immunoreactivity in the plasma of rats (11), dogs (12), and humans (11) has raised the possibility of an endocrine role of somatostatin (13, 14).

The present study was designed to gain further insight into the in vivo secretory patterns of pancreatic and gastric somatostatin after the intragastric and intraduodenal administration of nutrients and of HCl.

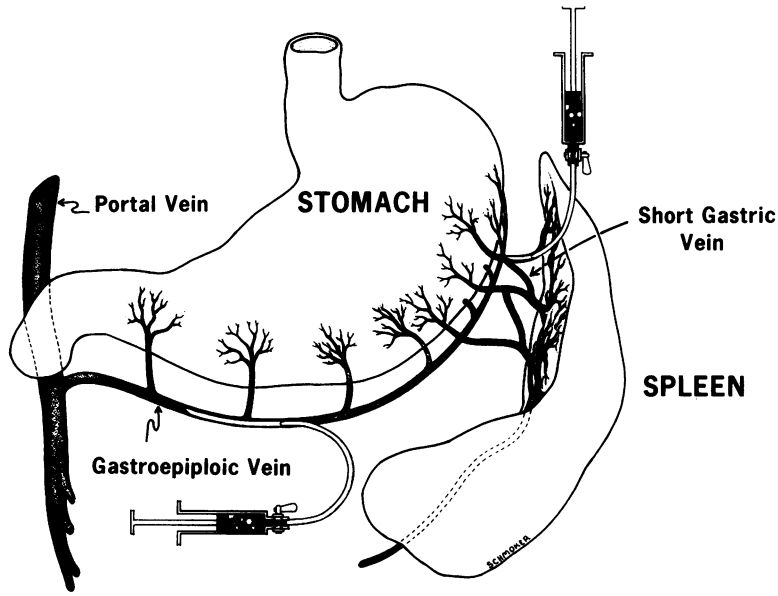


FIGURE 1 Position of silastic catheters in the short gastric vein to obtain blood from the fundus and upper corpus region of the stomach and in the left gastroepiploic vein for blood from the antrum.

METHODS

Experimental protocols. All experiments were performed in healthy mongrel dogs weighing 17–22 kg. After anesthesia (Nembutal; Abbott Laboratories, North Chicago, Ill.) and laparotomy silastic catheters were placed in the pancreaticoduodenal vein, in a short gastric vein draining the fundus and upper corpus of the stomach, and in the lower one-third of the left gastroepiploic vein, which drains the antrum (Fig. 1). A catheter was also placed in the inferior vena cava for sampling. After placement of the catheters, the operating table was tilted in a 35° head-up position to avoid accumulation of administered nutrients in the upper part of the stomach during subsequent experiments. An equilibration period of 1 h preceded each experiment.

In experiments designed to determine the effects of nutrients administered intragastrically, 50 g of glucose (n = 5), 50 g of peanut oil (n = 5), or 50 g of casein hydrolysate (n = 5) were mixed with water to a total volume of 250 ml and instilled via an intragastric tube. In other experiments 250 ml of 0.1 N HCl (n = 5) was instilled into the stomach by a gastric tube.

In experiments designed to determine the effects of the intraduodenal administration of nutrients and HCl, the pylorus was first ligated to prevent reflux into the stomach and a tube was inserted through an incision just below the pylorus. After a 1-h equilibration period, the same amount and concentration of peanut oil (n = 5), glucose (n = 5), or HCl (n = 6) was instilled intraduodenally.

Radioimmunoassay of plasma somatostatin-like immunoreactivity. Somatostatin-like immunoreactivity (SLI)[1] was determined by radioimmunoassay by use of a modification of the methods of Arimura et al. (15) and of Kronheim et al. (16). A 0.05-M sodium phosphate buffer, pH 7.5, that contained 0.1% bovine serum albumin, 0.25% disodium EDTA and 100 Kallikrein Inhibitor Units/ml of aprotinin (Trasylol; FBA Pharmaceuticals, Inc., New York) was used in the assay system. 100 μl of diluted rabbit antisomatostatin serum no. R101, 100 μl of either a reference standard or plasma sample, and 100 μl of ^{125}I-Tyr^{1}-somatostatin (2,000–3,000 cpm) which contained Kallikrein Inhibitor Units of Trasylol were incubated with 400 μl of buffer for 72 h at 4°C. Separation of antibody-bound and free-labeled hormone was carried out with 500 μl of 0.1% charcoal (Norit A, Pfanstiehl Laboratories, Inc. [chemicals], Waukegan, Ill.) coated with 0.01% dextran T-70 in 0.05 M sodium phosphate buffer. 100 μl of sheep serum was added to all tubes that did not contain plasma before the addition of charcoal. After incubation for 40 min at 4°C, the tubes were centrifuged at 2,500 rpm for 20 min at 4°C and the charcoal-adsorbed ^{125}I-Tyr^{1}-somatostatin was counted in the Autogamma Spectrometer.

The minimal sensitivity of the assay (lowest value that could be differentiated from zero with 95% confidence) was 50 pg/ml. Above this level, differences of 15 pg could be detected with 95% confidence. The coefficient of variation within and between assays was 6 and 18%, respectively. Gastrin-heptadecapeptide (kindly provided by Dr. Morton Grossman), cholecystokinin-pancreozymin, cholecystokinin-octapeptide, secretin, vasoactive inhibitory peptide, gastric inhibitory polypeptide pancreatic polypeptide (kindly provided by Dr. Ronald Chance) glucagon, and insulin in concentrations 10–30 times the maximum molar concentrations of somatostatin used in the standard curve did not cross-react in the assay. Serial dilution curves of endogenous plasma SLI paralleled those of synthetic somatostatin in plasma-free buffer and in plasma after its subcutaneous injection (1 mg) in dogs. Recovery of synthetic somatostatin added to canine plasma and incubated for 3 h at room temperature was 96±8%. Gel filtration on P-10 bio-gel columns (Bio-Rad Laboratories, Richmond, Calif.), followed by rechromatography on G-200 Sephadex (Pharmacia Fine Chemicals, Inc., Piscataway, N. J.) columns at pH 8.8, revealed the molecular size of both en-

[1] *Abbreviation used in this paper*: SLI, somatostatin-like immunoreactivity.

dogenous plasma SLI and synthetic somatostatin added to plasma to be in the 150,000–200,000 range, while at pH 2.5 both were eluted from P-10 columns in the 1,600-mol wt range (17, 18), which indicated that both circulate in the plasma bound to large proteins (18). Although proof of the biologic activity of circulating endogenous SLI is not available, it is known that biologically active synthetic somatostatin exerts its activity while circulating in plasma bound presumably to the same large proteins (18). Affinity chromatography with immobilized antibodies directed against the central portion of the somatostatin molecule (antiserum S-27 of Dr. Wylie Vale) removed approximately 95% of plasma SLI (17). The assay technique and evidence of the validity of measurements of plasma SLI are reported in greater detail elsewhere (17). Glucagon and insulin were determined by previously described techniques (19, 20). For statistical comparisons, the Student *t* test for paired and nonpaired data was employed.

RESULTS

Effects of intragastric and intraduodenal administration of glucose. The intragastric administration of glucose in a group of five dogs was followed by a prompt and significant increase in the pancreaticoduodenal

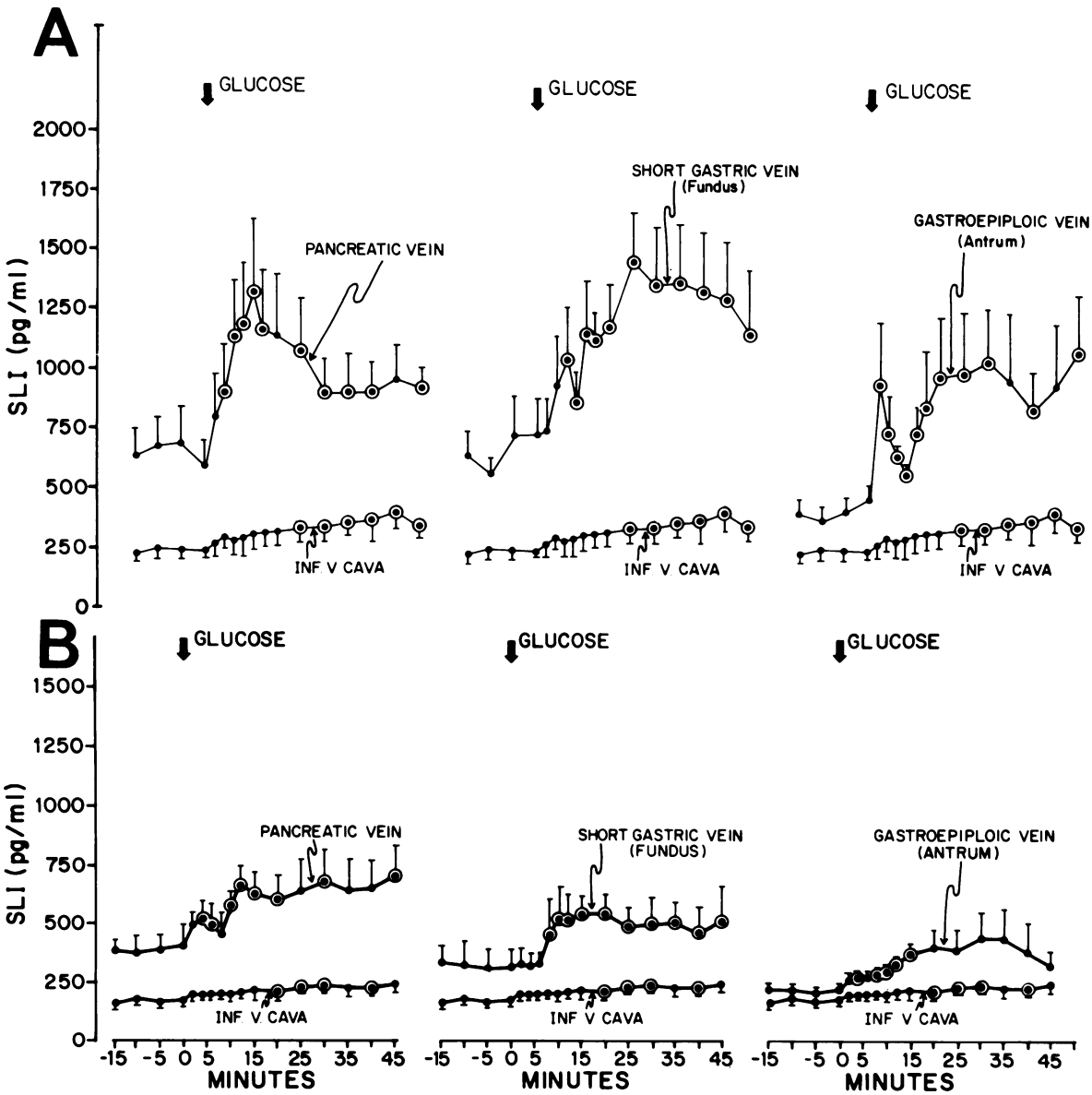


FIGURE 2 SLI in pancreatic, short gastric, and gastroepiploic vein and in the inferior vena cava (inf. v. cava) in response to intragastric ($n = 5$) (A) and intraduodenal ($n = 5$) (B) administration of glucose (50 g). ⊙ indicates significant differences ($P < 0.05$ or less) compared to base-line levels.

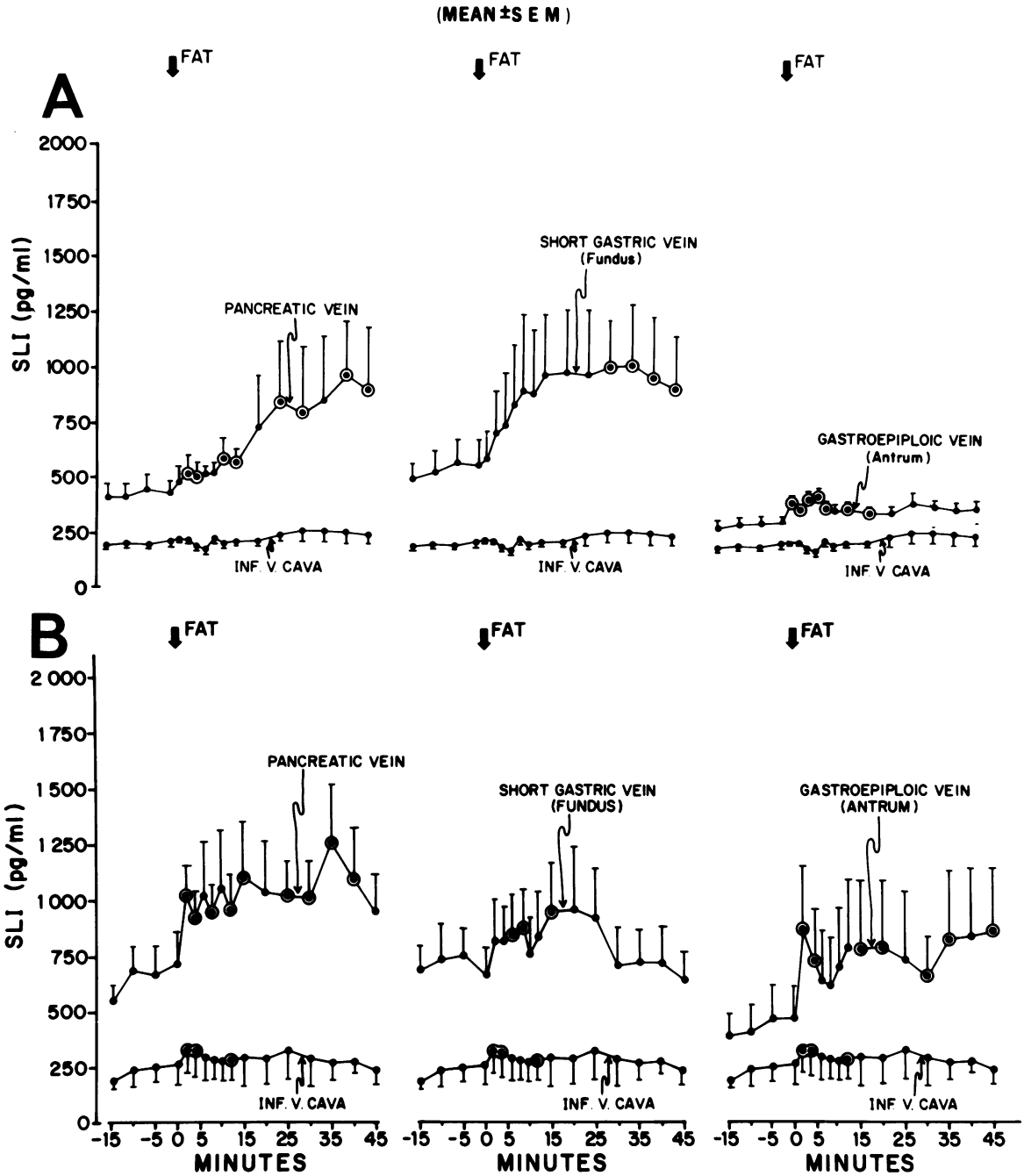


FIGURE 3 SLI in pancreatic, short gastric, and gastroepiploic vein and in the inferior vena cava (inf. v. cava) in response to intragastric ($n = 5$) (A) and intraduodenal ($n = 5$) (B) administration of fat (50 g). ⊙ indicates significant differences ($P < 0.05$ or less) compared to base-line levels.

vein levels of SLI from a mean base-line value of 647±117 pg/ml to a peak value of 1,332±322 pg/ml at 10 min ($P < 0.05$) (Fig. 2A). Thereafter, SLI levels declined to a plateau of about 900 pg/ml for the remainder of the experiment. Fundic SLI secretion increased significantly within 6 min from a base-line level of 678±128 to 1,000±226 pg/ml ($P < 0.05$) and a peak of 1,470±219 pg/ml ($P < 0.001$) at 20 min; it remained above 1,100 pg/ml for the rest of the experiment. Antral SLI levels formed a biphasic pattern with a rise from

the base line of 404±59 pg/ml to an initial peak of 950±267 pg/ml within 2 min after the glucose load, a return almost to base-line levels about 5 min later, and then a rise to levels above 900 pg/ml for the rest of the experiment. Inferior vena caval SLI levels rose from a base line of 243±30 pg/ml to a value of 335±49 pg/ml at 20 min ($P < 0.02$) and remained significantly elevated for the ensuing 25 min ($P < 0.05$). SLI measurements in the effluent plasma of the pancreas, fundus, and antrum were significantly greater than in the inferior vena caval plasma ($P < 0.05$). The vena caval insulin concentrations rose at 30 min and glucagon levels did not change.

After the intraduodenal administration of glucose in a group of five dogs (Fig. 2B), the pancreaticoduodenal vein SLI rose from a base line of 386±77 to 518±79 pg/ml within 4 min ($P < 0.02$) and was in the 700-pg/ml range during the final 35 min of the experiment. Fundic vein SLI concentration rose significantly from a base line of 324±92 to 460±181 pg/ml at 8 min ($P < 0.05$) and remained in the 500-pg/ml range for the entire experimental period. The incremental SLI values were significantly below those observed in the fundic effluent after the intragastric administration of glucose ($P < 0.01$). Antral vein SLI levels rose only slightly after intraduodenal administration of glucose, although the rise was statistically significant between 4 and 15 min ($P < 0.05$–0.02); again, incremental SLI was significantly below the antral vein response after intragastric glucose ($P < 0.02$). Vena caval SLI rose from a base line of 167±24 pg/ml to 201±25 pg/ml at 20 min ($P < 0.02$). The maximum levels were below those of the intragastric experiments but the difference was not significant. SLI levels in the pancreaticoduodenal vein and in the fundic vein were significantly greater than those in the inferior vena cava at all points both before and after the intraduodenal administration of glucose ($P < 0.05$–0.001), but a significant SLI gradient across the antrum was observed only after the glucose administration. Insulin and glucagon levels in the inferior vena cava increased after 30 min.

Effects of the intragastric and intraduodenal administration of fat. After the intragastric administra-

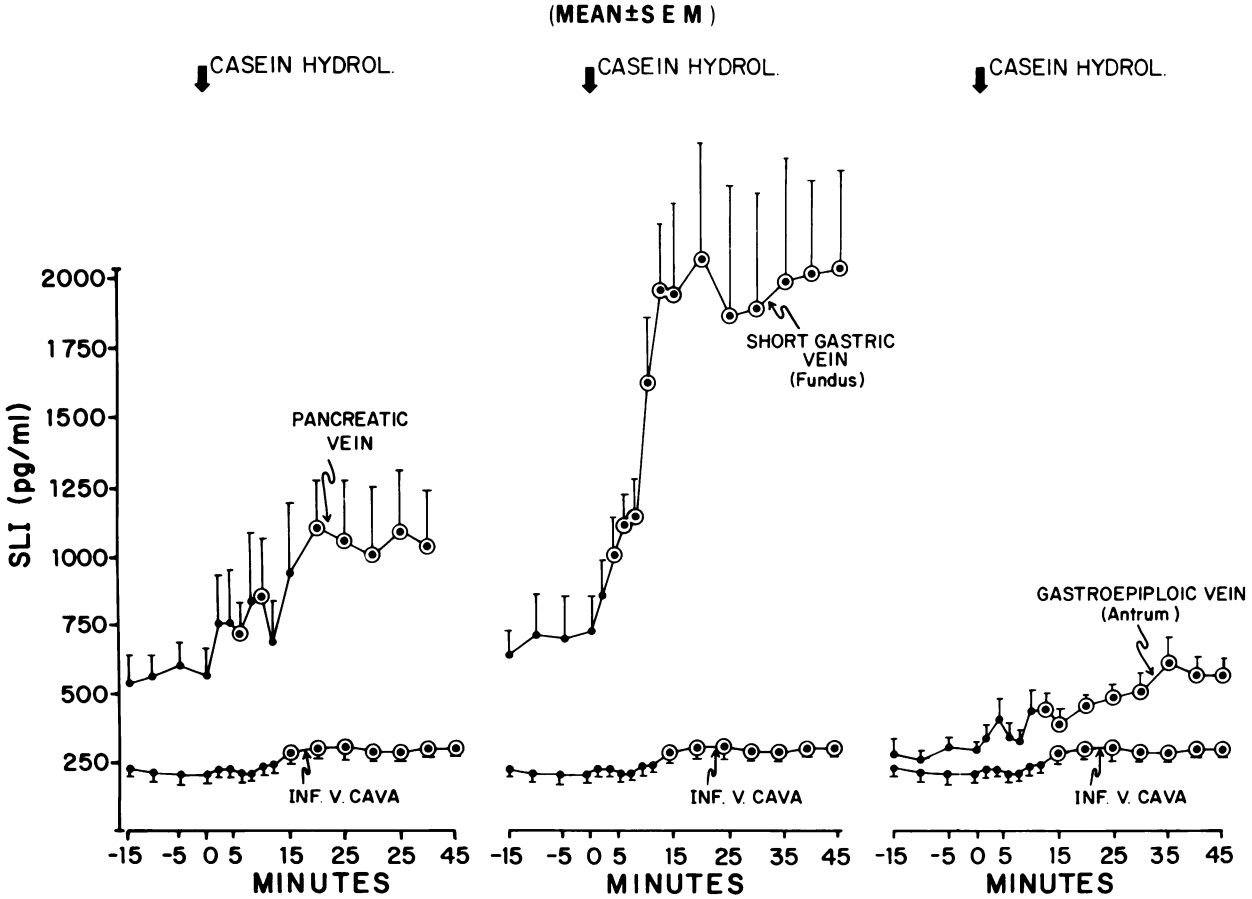
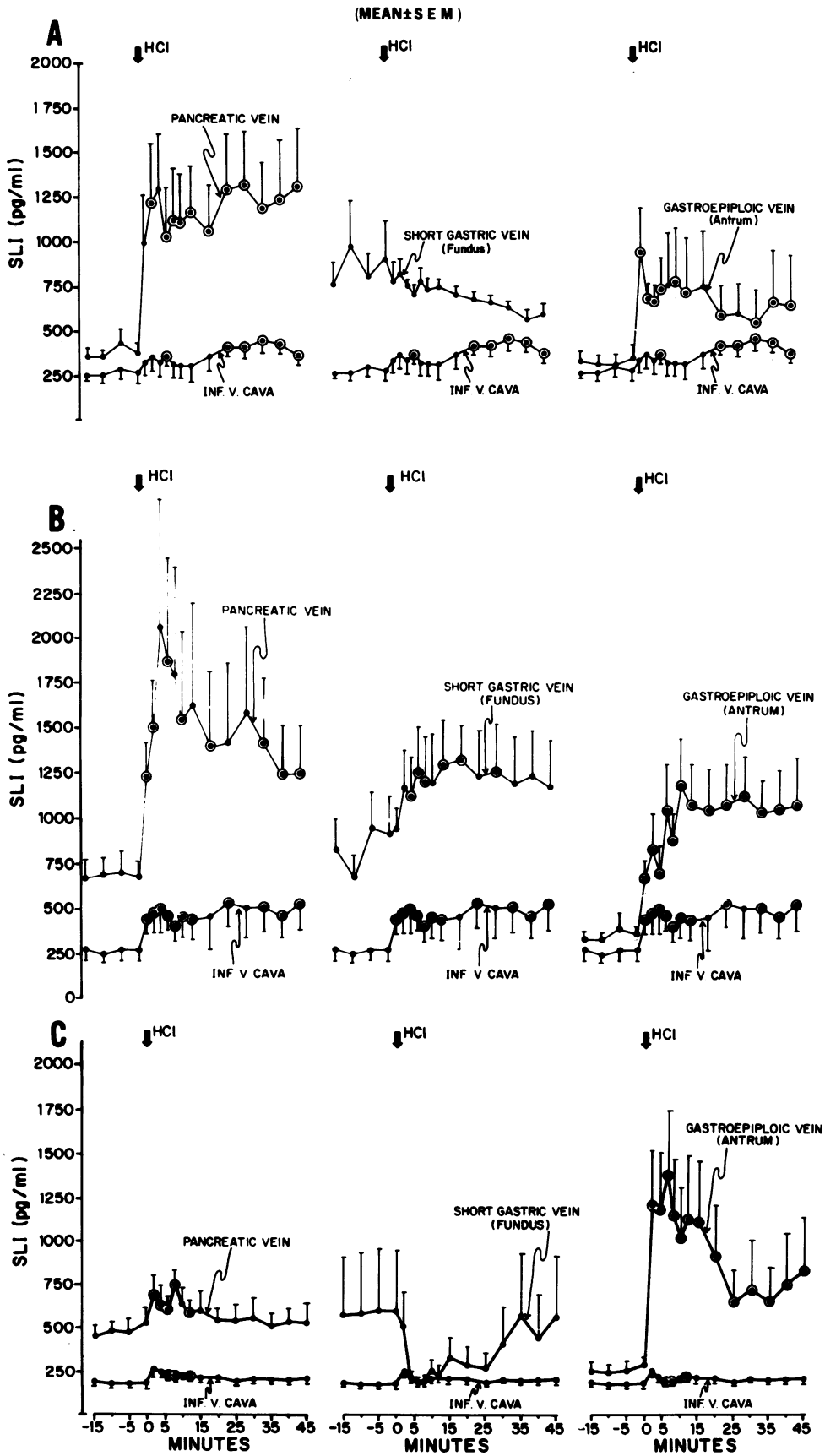


FIGURE 4 SLI in pancreatic, short gastric, and gastroepiploic vein and in the inferior vena cava (inf. v. cava) in response to intragastric administration of casein hydrolysate (50 g), ($n = 5$). ⊙ indicates significant differences ($P < 0.05$ or less) compared to base-line levels.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tion of 50 g of peanut oil pancreaticoduodenal vein SLI rose from a base-line level of 423±62 to 516±86 pg/ml at 4 min ($P < 0.05$) and remained above 750 pg/ml thereafter (Fig. 3A). Fundic vein SLI levels rose from 533±95 to 1,013±223 pg/ml at 30 min, but these changes were significant ($P < 0.05$) between 30 and 45 min only. SLI values in the antral vein rose very slightly during the first 20 min ($P < 0.05$–0.02) and thereafter returned to base-line levels. Pancreaticoduodenal fundic, and antral vein SLI levels were significantly above the vena caval values at virtually all points ($P < 0.05$). Glucagon levels rose after 20 min and insulin concentrations did not change.

The intraduodenal instillation of fat was followed by a rise in pancreaticoduodenal vein SLI levels from a base line of 656±114 to 1,030±137 pg/ml within 2 min ($P < 0.01$) and a peak of 1,260±260 pg/ml at 35 min (Fig. 3B). Fundic vein SLI rose from a mean base line of 708±126 to 851±183 pg/ml ($P < 0.05$) within 6 min. Antral values increased within 2 min to a peak of 868±289 pg/ml ($P < 0.05$), declined soon thereafter, and rose again towards the end of the experimental period. This rise after intraduodenal instillation of fat was significantly greater than that observed in the antral vein after its administration via the intragastric route ($P < 0.05$). Vena caval SLI levels were significantly elevated above the base line at only three time points, 6, 40, and 45 min ($P < 0.05$). Inferior vena cava insulin and glucagon levels rose after 20 min.

Effects of the intragastric administration of casein hydrolysate. After the intragastric administration of casein hydrolysate, SLI levels in the pancreaticoduodenal vein rose within 6 min from a mean base-line level of 576±99 to 720±122 pg/ml ($P < 0.05$) and reached values above 1,000 pg/ml between 20 and 45 min ($P < 0.05$) (Fig. 4A). Fundic vein SLI levels rose sharply from the base line of 713±154 pg/ml to 1,005±116 pg/ml within 4 min ($P < 0.001$) and reached a plateau of about 2,000 pg/ml thereafter ($P < 0.01$). In the antral vein, the rise in SLI concentration was modest and remained below 700 pg/ml throughout; it reached its highest concentration towards the end of the 45-min period of observation; all values between 12 and 45 min were significantly above the base line ($P < 0.05$–0.01). Inferior vena caval SLI levels rose from a base line of 218±32 pg/ml to between 270 and 305 pg/ml after 15 min ($P < 0.05$–0.005). Both the pancreaticoduodenal and fundic vein SLI levels were significantly above those in the inferior vena caval plasma at all points before and after the meal ($P < 0.05$), but in the antral effluent SLI levels were significantly greater only during the final 20 min of the experiment ($P < 0.05$–0.02). Glucagon levels rose after 25 min in the inferior vena cava; insulin levels did not change.

The effect of intraduodenally administered casein hydrolysate was not examined.

The intragastric and intraduodenal administration of HCl. Within 4 min after the intragastric instillation of HCl, pancreaticoduodenal vein SLI rose significantly from a mean base-line value of 382±65 to 1,224±335 pg/ml ($P < 0.05$) and remained above 1,000 pg/ml thereafter ($P < 0.05$–0.02) (Fig. 5A). Fundic vein SLI levels did not increase. Antral vein levels rose within 2 min from 319±65 to 940±250 pg/ml ($P < 0.05$) and, although they declined thereafter, they remained significantly above base-line levels for the rest of the experimental period ($P < 0.05$–0.01). Vena caval levels of SLI increased from a base line of 271±45 to 406±84 pg/ml at 25 min and remained significantly elevated thereafter ($P < 0.05$–0.005). Almost all pancreaticoduodenal and fundic vein SLI levels were significantly above those in the vena cava ($P < 0.05$–0.01), but antral vein SLI values were significantly higher only during the first 15 min after the administration of the HCl. Glucagon levels in the inferior vena cava rose within 2 min; insulin levels did not change.

The intraduodenal administration of HCl was also followed by a sharp rise in pancreaticoduodenal SLI from a base line of 685±112 to 1,230±190 pg/ml within 2 min (Fig. 5B); it reached a peak concentration at 6 min of 2,070±764 pg/ml ($P \pm 0.05$) and declined thereafter. In contrast to the lack of response after intragastric administration of HCl, fundic vein SLI levels increased significantly within 4 min from a base-line value of 830±165 to 1,177±200 pg/ml ($P < 0.05$), remained elevated thereafter, and reached a peak of 1,325±206 pg/ml ($P < 0.01$) at 20 min. Antral vein SLI levels also rose significantly within 2 min ($P < 0.005$) and reached a peak concentration of 1,195±256 pg/ml at 12 min ($P < 0.02$). SLI levels in the inferior vena caval plasma rose from a base-line level of 266±62 to 448±80 pg/ml at 2 min ($P < 0.02$) and remained significantly elevated throughout the entire experiment ($P < 0.05$–0.02), in contrast to the slower response to HCl administered via the intragastric route. They were significantly below the SLI concentrations in the pancreaticoduodenal, fundic, and antral veins before and after the administration of HCl at all points ($P < 0.05$–0.005). Glucagon levels increased significantly within 20 min and insulin levels within 30 min of HCl administration.

FIGURE 5 SLI in pancreatic, short gastric, and gastroepiploic vein and in the inf. v. cava in response to intragastric ($n = 5$) (A) and intraduodenal ($n = 6$) (B) administration of 0.1 N HCl, and in response to intragastric administration of HCl into dogs with a gastric fistula ($n = 5$) (C).⊙ indicates significant differences ($P < 0.05$ or less) compared to base-line levels.

To differentiate between gastric and duodenal effects of HCl administered via the intragastric route upon SLI release from the various sites, the pylorus was ligated and bissected proximally in five dogs to create a gastric fistula and prevent the emptying of gastric contents into the duodenum. HCl was instilled into the stomach 1 h later. As shown in Fig. 5C, pancreaticoduodenal vein SLI rose from a base-line value of 485±75 to a level of only 690±106 pg/ml within 2 min ($P < 0.05$), and the period of significant elevation was of only 12 min duration. The rise was significantly less than after both the intragastric ($P < 0.05$) and intraduodenal ($P < 0.05$) administration of HCl in dogs without the gastric fistula. Fundic vein SLI decreased sharply within 2 min down to inferior vena caval levels. Antral vein SLI rose from a base line of 257±51 to 1,212±323 pg/ml within 2 min ($P < 0.02$) and remained significantly above base-line levels thereafter ($P < 0.05$–0.01). Fundic vein SLI levels were significantly less than after the intraduodenal instillation of HCl ($P < 0.05$), while the antral vein response did not differ significantly from the values observed after intragastric or intraduodenal administration in the dogs without a gastric fistula. Glucagon levels rose within 10 min and insulin did not change.

DISCUSSION

Although measurements of somatostatin-like immunoreactivity in unextracted plasma have been unsuccessful until recently (14, 16), the assay employed in the present study appears to measure in dog plasma a material that is indistinguishable from synthetic somatostatin added to dog plasma by either comparison of dilution slopes or molecular size (17, 18). The validity of plasma SLI measurements is further supported by the fact that virtually all circulating native SLI is removed from plasma by passage through a column of immobilized antibodies directed against the central portion of the somatostatin molecule, and that positive plasma SLI gradients are observed across tissues known to be rich in somatostatin. Furthermore, the qualitative similarity between the observations in vivo of pancreatic SLI release in response to nutrients and those in plasma-free systems in vitro (12, 21, 22), suggests that changes in plasma SLI reflect real changes in somatostatin release from the various organs studied.

The results of the present study reveal that glucose, fat, and protein instilled into the gastrointestinal tract of anesthetized dogs stimulate SLI release from the pancreas and stomach. Glucose administered via the stomach elicited a prompt and substantial increase of SLI in the effluent plasma of the pancreas, fundus, and antrum, followed by a later increase of approximately 80 pg/ml in peripheral venous SLI levels. When the glucose was given intraduodenally, the SLI increments from the foregoing sites and in the peripheral venous plasma were smaller, which suggests that unidentified local gastric factors somehow influence gastric and pancreatic SLI release in response to glucose.

Fat administered via the stomach similarly stimulated pancreatic and fundic vein SLI release, but the antral vein response was considerably greater when the fat was given intraduodenally. Inferior vena caval SLI levels rose by approximately 40 pg/ml. The greater antral vein SLI response when the fat was administered intraduodenally suggests an enteric influence upon the antral δ-cells, perhaps via gut hormones.

Casein hydrolysate was administered only via the stomach and it stimulated the release of pancreatic, fundic and antral SLI. The concentrations of SLI in the fundic vein were higher than after glucose and fat, whereas those in the antral vein were lower than after glucose and similar to those after fat. Inferior vena caval SLI levels rose by approximately 80 pg/ml.

The rapidity of the responses of pancreatic SLI to the nutrient loads indicate stimulation by factors other than a rise in the circulating concentration of the nutrient. Indeed, in all glucose experiments the peak SLI rise preceded a change in plasma glucose concentration. No changes in plasma triglyceride concentrations were observed in any of the fat experiments. Because gastrin, pancreozymin-cholecystokinin, secretin and gastric inhibitory polypeptide all stimulate pancreatic vein SLI in vitro (21, 22), these gut hormones are candidates for mediators of certain of the effects and would also explain, at least in part, the rapidity of the observed changes (23–25). This possibility is supported by the fact that HCl, which stimulates secretin (25, 26) and pancreozymin-cholecystokinin (27) release, elicited prompt increases in SLI release from the pancreas and the antrum, and inferior vena caval SLI levels were approximately doubled. The intraduodenal route of HCl administration, but not the intragastric route, resulted in a small but significant increase of fundic vein SLI levels. In dogs with a gastric fistula, the intragastric administration of HCl not only failed to elicit the striking rise in pancreatic vein SLI release observed in the intact dogs, but appeared to suppress completely SLI secretion by the fundus, while inducing a marked response of antral vein SLI. This provides strong evidence that the pancreatic SLI response to HCl is mediated by factors originating in the small bowel and suggests that release of SLI from the antrum is stimulated both by the presence of acid in the stomach and by enteric factors, possibly gut hormones. Additionally, it appears that fundic SLI release is inhibited by acid in the stomach.

Base-line levels of SLI in all 41 experiments averaged 671±71 pg/ml in the fundic vein plasma, 578±45 pg/ml in the pancreatic effluent, and 317±23 pg/ml in the antral plasma. All were significantly greater

than the mean base line of 228±15 pg/ml in the inferior vena cava ($P < 0.01$–0.001), indicating a contribution from these sites to the circulating SLI.

The physiologic implications of the foregoing results remain to be established. The rises in circulating SLI levels observed in the venous drainage of somatostatin-containing tissues do not necessarily distinguish between an "overflow" of locally active somatostatin and secretion designed to fulfill a hormonal role upon remote target tissues. The demonstration of varying SLI gradients across these three somatostatin-containing regions is, therefore, compatible with local or paracrine functions and(or) with remote endocrine actions.

Inasmuch as somatostatin in high doses inhibits gastric emptying (28), HCl (29, 30), and pepsin (30) secretion as well as gastrin release (29), local or paracrine actions of gastric somatostatin, might, therefore, include influences upon any or all of these processes. Somatostatin also inhibits insulin and glucagon (31–37) secretion, and a paracrine role of somatostatin within the islet upon the regulation of α- and β-cell activities has been suggested.

The rise in SLI in peripheral venous plasma is compatible with endocrine actions on peripheral sites. Comparable increments produced by intraportal infusion of synthetic somatostatin reportedly retard the postprandial rise in nutrient levels (38), and support possible endocrine functions beyond the liver, while endocrine effects upon the liver are suggested by the studies of Sacks et al. (39), who demonstrated that somatostatin reduces the glycogenolytic activity of glucagon and may influence hepatic metabolism.

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