

# Gastric and Pancreatic Release of Somatostatin-like Immunoreactivity During the Gastric Phase of a Meal

## Effects of Truncal Vagotomy and Atropine in the Anesthetized Dog

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### SUMMARY

The postprandial release of gastric and pancreatic somatostatin-like immunoreactivity (SLI) was examined in anesthetized dogs during the gastric phase of a meal, and the role of vagal and atropine-sensitive mechanisms in the responses was assessed. The intragastric instillation of liver extract at pH 7 elicited a significant rise in antral vein SLI (~300 pg/ml) and gastrin concentration. After truncal vagotomy, both baseline and postprandial antral vein SLI and gastrin concentration increased significantly compared with the control group. The infusion of atropine (100 µg/kg/h) abolished the postprandial rise in antral vein SLI but not in gastrin. The liver meal at pH 2 elicited a sustained sixfold greater rise of antral SLI (~2000 pg/ml) than that at pH 7, while gastrin concentrations did not rise significantly. The latter antral SLI response was not influenced by truncal vagotomy, but atropine infusion reduced it by about 50%. In response to the meal at pH 7, fundic vein SLI concentrations rose by about 300 pg/ml. The rise was augmented slightly by truncal vagotomy but was abolished completely by atropine infusion. In response to the meal at pH 2, fundic SLI decreased sharply below baseline levels. The response was not altered significantly by vagotomy, but was reversed completely by atropine infusion, during which fundic vein SLI concentrations rose significantly. Pancreatic vein SLI concentrations rose by about 350 pg/ml in response to the gastric meal at pH 7. That rise was not altered significantly by vagotomy but was abolished by atropine infusion. In response to the meal at pH 2, pancreatic SLI concentrations rose by about 1000 pg/ml above baseline, significantly greater than the response to the meal at pH 7. The pancreatic vein SLI response to the meal at pH 2 was not altered by vagotomy. It was reduced considerably by atropine infusion.

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It is concluded that SLI is released from the antrum, fundus, and pancreas during the gastric phase of a meal and that these responses are modified by acidification of the intragastric contents and by truncal vagotomy and atropine infusion. The greatly augmented release of antral SLI in response to the acidified meal raises the possibility of a role for somatostatin in acid-induced suppression of gastrin release. *DIABETES* 28:658-663, July 1979.

**S**omatostatin-like immunoreactivity (SLI) is released from the stomach and pancreas after intragastric or intraduodenal administration of nutrients;<sup>1,2</sup> its possible role in the regulation of certain gastrointestinal functions and in the homeostasis of ingested nutrients has been suggested.<sup>3-6</sup> However, the mechanism of these SLI responses is unclear. To examine the role of the gastric phase of a meal in the food-induced responses of splanchnic SLI, the release of SLI from the antrum and fundus of the stomach and from the pancreas was determined during the gastric phase of test meals at pH 7 and at pH 2, and the influence of vagotomy and atropine on these responses was assessed.

### MATERIALS AND METHODS

Studies were performed in 35 normal mongrel dogs (17-25 kg body wt). After anesthesia with pentobarbital (Nembutal) and laparotomy, silastic catheters were placed in the pancreaticoduodenal vein, the left gastroepiploic vein (antrum), and a short gastric vein (fundus-corpora), and a catheter was placed in the inferior vena cava as described previously.<sup>1</sup> The pylorus was bisected to prevent nutrients from entering the duodenum and a gastric fistula was created to permit the efflux of gastric contents.

In 13 dogs, a bilateral intrathoracic truncal vagotomy, including section of all ramifications, was performed 2 h before the instillation of the liver meal at pH 7 or pH 2.

After an equilibration period of 1 h after the completion of these surgical procedures, 250 ml of 20% liver extract (Reheis Chemicals, Chicago, Illinois), adjusted to pH 7 or to

pH 2, was instilled via a gastric tube. Frequent blood samples were taken from the catheterized veins before and after the test meal.

Somatostatin-like immunoreactivity was measured by radioimmunoassay using a modification<sup>7</sup> of previously described techniques by Arimura et al.<sup>8</sup> and Kronheim et al.<sup>9</sup> and using Arimura's antisomatostatin serum R101 (Dr. A. Arimura, New Orleans, Louisiana). The minimal sensitivity of the assay, which has been validated in previous reports,<sup>1,7</sup> is 50 pg/ml. The coefficient of variation within and between assays is 6% and 18%, respectively. No cross reactivity was observed with gastrin-17, gastric inhibitory polypeptide, cholecystokinin, secretin, pancreatic polypeptide, vasoactive intestinal polypeptide, glucagon, or insulin. Considerable variation in baseline values for SLI was observed, which is not unusual in this type of procedure.

Gastrin concentrations were determined by a modification of the method of Yalow and Berson<sup>10</sup> using the Squibb Immutope gastrin kit.

The Student's *t* test for paired and nonpaired data was used for comparisons within and between experimental groups, respectively; mean baseline levels represent the average of the four baseline values that precede the instillation of the meal. Values of *P* < 0.05 or less were considered to be significant.

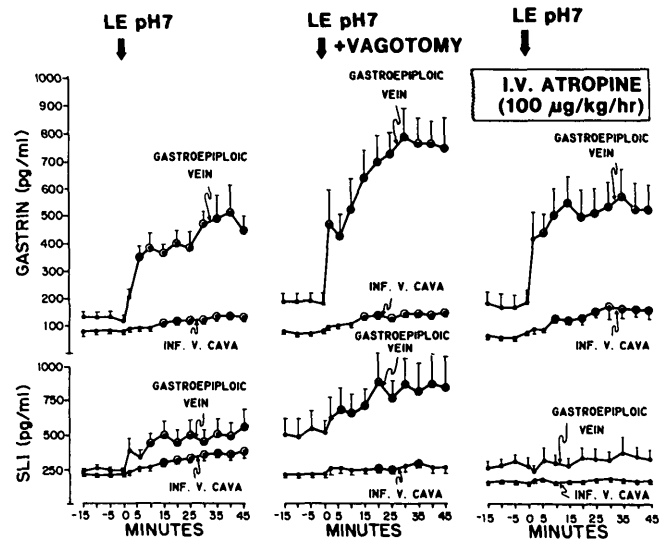
## RESULTS

### ANTRAL VEIN RESPONSES

**Antral vein SLI and gastrin concentration in response to a liver meal at pH 7 and the effects of vagotomy and atropine infusion.** In a group of five dogs, the intragastric instillation of liver extract at pH 7 elicited a gradual increase in antral vein SLI concentrations from a mean baseline of  $240 \pm 28$  pg/ml to  $562 \pm 116$  pg/ml ( $P < 0.01$ ) at 45 min (Figure 1). Inferior vena cava SLI concentrations rose from a mean baseline of  $210 \pm 35$  pg/ml to  $396 \pm 82$  pg/ml at 45 min ( $P < 0.01$ ). Plasma gastrin concentrations in the antral vein increased from a mean baseline of  $135 \pm 20$  pg/ml to a peak concentration of  $512 \pm 103$  pg/ml ( $P < 0.05$ ) at 40 min (Figure 1). Inferior vena cava gastrin rose significantly from  $75 \pm 10$  pg/ml to  $108 \pm 17$  pg/ml ( $P < 0.05$ ) in 15 min, reaching a maximum of  $140 \pm 24$  pg/ml ( $P < 0.01$ ) at 40 min (Figure 1).

To study the role of the vagus as a possible mediator of the foregoing changes in antral SLI release, 13 dogs were subjected to a bilateral truncal vagotomy. In these 13 dogs, mean baseline SLI concentrations in the antral vein were significantly higher than in the 10 normal dogs ( $514 \pm 39$  pg/ml vs.  $268 \pm 16$  pg/ml,  $P < 0.001$ ), as were antral vein gastrin concentrations ( $209 \pm 25$  pg/ml vs.  $147 \pm 21$  pg/ml,  $P < 0.001$ ) (Figure 2).

In the six vagotomized dogs that received liver extract at pH 7, antral vein SLI rose from a mean baseline of  $500 \pm 150$  pg/ml to a peak of  $887 \pm 253$  pg/ml ( $P < 0.05$ ) at 20 min (Figure 1). Incremental antral vein SLI concentrations for the 45-min period of the experiment averaged  $2398 \pm 560$  pg/ml, which is significantly above the value of  $949 \pm 540$  pg/ml in the normal animals ( $P < 0.025$ ). Inferior vena cava SLI concentrations rose from a mean baseline  $220 \pm 30$  pg/ml to  $294 \pm 86$  pg/ml at 35 min ( $P < 0.05$ ); but only three out of 10 time points were significantly above the baseline, and

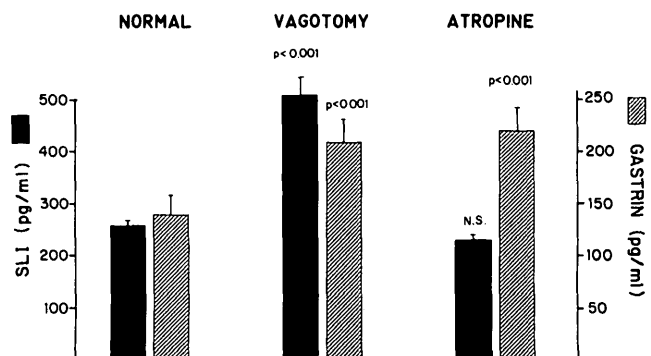


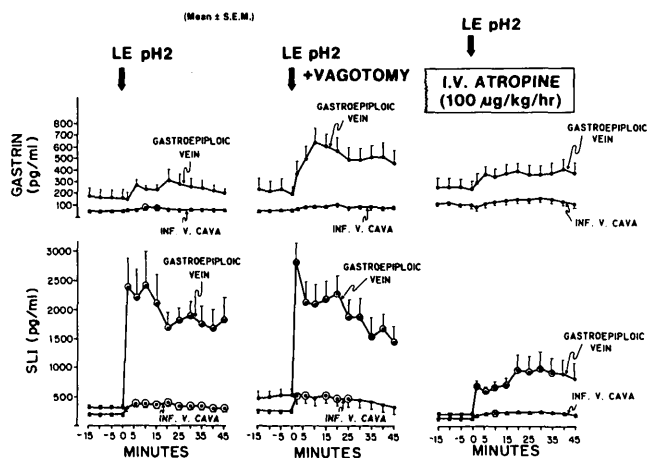
**FIGURE 1.** Somatostatin-like immunoreactivity (SLI) and gastrin concentrations in gastroepiploic vein and inferior vena cava in response to a gastric liver extract (LE) test meal at pH 7 in normal dogs ( $N = 5$ ), after truncal vagotomy ( $N = 6$ ), and during atropine infusion ( $N = 5$ ) (mean  $\pm$  SEM).  $\odot$  indicates significant differences of  $P < 0.05$  or less versus baseline levels.

the incremental inferior vena cava SLI concentration of  $322 \pm 163$  pg/ml was significantly less than that of the normal dogs ( $1150 \pm 280$  pg/ml,  $P < 0.05$ ) (Figure 1). After vagotomy, antral vein gastrin rose from a mean baseline of  $180 \pm 30$  pg/ml to a maximum concentration of  $783 \pm 100$  pg/ml at 30 min ( $P < 0.01$ ) (Figure 1) in response to a meal at pH 7. The mean incremental antral vein gastrin value in response to the liver extract at pH 7 was  $4752 \pm 637$  pg/ml, significantly higher than the value of  $2644 \pm 272$  pg/ml in the normal dogs ( $P < 0.02$ ). This was paralleled by an increase in inferior vena cava gastrin from a mean baseline value of  $75 \pm 10$  pg/ml to a maximum of  $141 \pm 21$  pg/ml ( $P < 0.025$ ) at the end of the experiment. The mean inferior vena cava incremental gastrin concentration was  $532 \pm 96$  pg/ml after vagotomy and only  $398 \pm 104$  pg/ml in the controls ( $P < 0.05$ ).

The infusion of atropine at a rate of  $100 \mu\text{g/kg/h}$  in 12 dogs did not change baseline SLI concentration in the antral vein, although baseline gastrin levels were significantly higher than in the controls (Figure 2). The postprandial rise in

**FIGURE 2.** Basal antral vein somatostatin-like immunoreactivity (SLI) and gastrin concentrations in normal dogs ( $N = 10$ ), after truncal vagotomy ( $N = 13$ ), and during atropine infusion ( $100 \mu\text{g/kg/h}$ ) ( $N = 12$ ).





**FIGURE 3.** Somatostatin-like immunoreactivity (SLI) and gastrin concentrations in gastroepiploic vein and inferior vena cava in response to a gastric liver extract (LE) test meal at pH 2 in normal dogs (N = 5), after truncal vagotomy (N = 7), and during atropine infusion (N = 7) (mean ± SEM). ⊙ indicates significant differences of P < 0.05 or less versus baseline levels.

SLI was abolished completely by atropine infusion (Figure 1), and postprandial antral vein gastrin concentrations rose from  $180 \pm 45$  pg/ml to a peak of  $580 \pm 114$  pg/ml at 35 min. This was not significantly different from that of the controls, where incremental gastrin concentrations averaged  $3280 \pm 904$  pg/ml during atropine and  $2644 \pm 272$  pg/ml in the control state (NS). In the inferior vena cava, incremental gastrin concentrations were  $729 \pm 200$  pg/ml compared with  $398 \pm 104$  pg/ml in the control groups (NS).

**Antral vein SLI and gastrin concentrations in response to a liver meal at pH 2 and the effects of vagotomy and atropine infusion.** The intragastric instillation of liver extract at pH 2 was associated with a much greater increase in antral vein SLI concentrations from a mean baseline value of  $325 \pm 33$  pg/ml to a peak of  $2420 \pm 550$  pg/ml in 2 min ( $P < 0.001$ ). They remained between 1600 pg/ml and 2000 pg/ml during the entire experiment. Inferior vena cava SLI rose significantly from  $200 \pm 30$  pg/ml to  $372 \pm 72$  pg/ml in 4 min ( $P < 0.05$ ), reaching a maximum of 406 pg/ml at 20 min (Figure 3). The increases in antral vein gastrin values were not significant at any point, and inferior vena cava gastrin concentrations rose significantly above the baseline at only two time points.

The effects of truncal vagotomy on antral vein SLI and gastrin values in response to the liver meal at pH 2 are shown in Figure 3. Antral vein SLI rose from  $510 \pm 100$  pg/ml to a peak of  $2820 \pm 336$  pg/ml ( $P < 0.001$ ) in 2 min and remained between 1600 and 2000 pg/ml for the remainder of the experiment (Figure 3), which is not different from the normal group. Inferior vena cava SLI rose from a mean baseline of  $270 \pm 55$  pg/ml to  $524 \pm 140$  pg/ml in 2 min ( $P < 0.05$ ) and remained elevated for the next 25 min (Figure 3). Although the gastrin response to the liver extract at pH 2 ( $240 \pm 100$  pg/ml to a peak of  $641 \pm 129$  pg/ml at 10 min) was greater than in the normal group, the increase was not significant because antral vein gastrin levels did not rise in two dogs. Inferior vena cava gastrin values did not change significantly (Figure 3).

During the infusion of atropine, the response of antral

vein SLI concentrations to the liver test meal at pH 2 was markedly reduced; they rose from a mean baseline of  $200 \pm 20$  pg/ml to a peak concentration of only  $980 \pm 309$  pg/ml at 30 min ( $P < 0.05$ ) (Figure 3). Incremental antral vein SLI concentrations averaged  $6088 \pm 2016$  pg/ml, significantly below the  $17,466 \pm 3240$  pg/ml value of the control animals ( $P < 0.01$ ). Antral vein and inferior vena cava gastrin concentrations did not change significantly from their respective baselines (Figure 3).

**FUNDIC VEIN RESPONSES**

**Fundic vein SLI concentrations in response to a liver meal at pH 7 and the effects of vagotomy and atropine infusion.** SLI concentrations in the fundic vein rose from a mean baseline of  $600 \pm 145$  pg/ml to  $868 \pm 185$  pg/ml in 6 min ( $P < 0.05$ ) and remained elevated in this range for the remainder of the experiment (Figure 4). This response to liver extract at pH 7 was not influenced by vagotomy but was abolished completely by atropine (Figure 4).

**Fundic vein SLI concentrations in response to a liver meal at pH 2 and the effects of vagotomy and atropine infusion.** In response to the intragastric liver test meal at pH 2, fundic vein SLI concentrations decreased significantly in 6 min from a mean baseline of  $1000 \pm 270$  pg/ml to  $554 \pm 190$ , reaching a nadir of  $380 \pm 99$  pg/ml at 25 min ( $P < 0.05$ ) (Figure 5).

Truncal vagotomy did not alter the suppressive effect of a low pH test meal on fundic SLI concentrations (Figure 5).

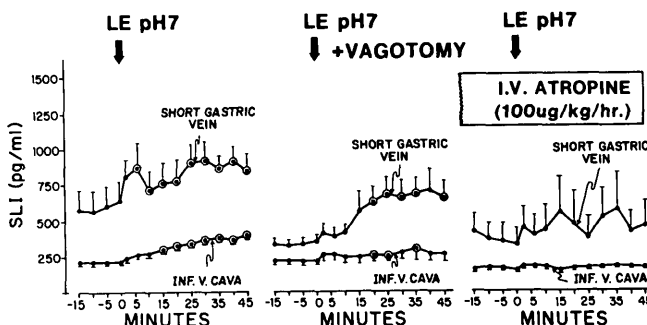
The infusion of atropine not only abolished this decrease, but it was associated with a rise in fundic SLI from a mean baseline of  $400 \pm 105$  pg/ml to a maximum of  $704 \pm 175$  pg/ml at 15 min ( $P < 0.01$ ) (Figure 5).

**PANCREATIC VEIN RESPONSES**

**Pancreatic vein SLI in response to a gastric liver meal at pH 7 and the effect of vagotomy and atropine infusion.** After intragastric instillation of the liver meal at pH 7, pancreatic vein SLI rose gradually from a mean baseline of  $540 \pm 140$  pg/ml to  $940 \pm 266$  pg/ml in 40 min ( $P < 0.05$ ) (Figure 6).

This rise was not changed significantly by truncal vagotomy; pancreatic vein SLI levels increased from a mean baseline of  $485 \pm 80$  pg/ml to a maximum concentration of  $782 \pm 113$  pg/ml at 35 min ( $P < 0.05$ ) (Figure 6).

**FIGURE 4.** Somatostatin-like immunoreactivity (SLI) in the short gastric vein (fundus-corporis) and inferior vena cava in response to a gastric liver extract (LE) test meal at pH 7 in normal dogs (N = 5), after truncal vagotomy (N = 6), and during atropine infusion (N = 5) (mean ± SEM). ⊙ indicates significant differences of P < 0.05 or less versus baseline levels.



During the infusion of atropine, the basal pancreatic vein SLI in all 12 experiments averaged  $322 \pm 22$  pg/ml, significantly below the value of  $520 \pm 36$  pg/ml in the control dog ( $P < 0.01$ ), and the postprandial rise in response to the liver meal at pH 7 was abolished completely (Figure 6).

#### Pancreatic vein SLI in response to a gastric liver meal at pH 2 and the effect of vagotomy and atropine infusion.

The liver meal at pH 2 elicited a much sharper rise in pancreatic vein SLI concentrations, which increased from a mean baseline of  $490 \pm 75$  pg/ml to  $1398 \pm 246$  pg/ml in 15 min ( $P < 0.005$ ) (Figure 7). Incremental pancreatic vein SLI concentrations for the 45-min period averaged  $6538 \pm 1420$  pg/ml, significantly greater than the value of  $2098 \pm 455$  pg/ml after the liver meal at pH 7 ( $P < 0.02$ ).

After truncal vagotomy, pancreatic vein SLI rose significantly in 2 min from a mean baseline of  $650$  pg/ml to  $1033 \pm 137$  pg/ml ( $P < 0.01$ ) and remained elevated for the entire experiment (Figure 7). After vagotomy, the incremental SLI concentration was  $4051 \pm 1285$  pg/ml, which is not different from that of the normal dogs.

During atropine infusion, pancreatic vein SLI rose slightly from a mean baseline of  $270 \pm 40$  pg/ml to  $491 \pm 94$  pg/ml at 15 min ( $P < 0.01$ ) (Figure 7); the incremental SLI concentration was  $1575 \pm 704$  pg/ml, significantly below that of the normal ( $P < 0.001$ ) and vagotomized ( $P < 0.005$ ) dogs.

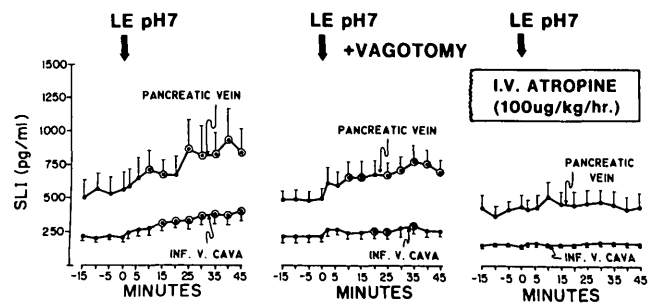
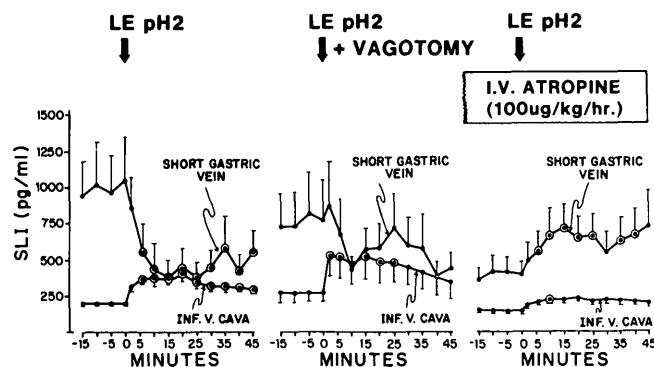
#### DISCUSSION

The present study is a comparison of the release of gastric and pancreatic SLI in anesthetized dogs during the gastric phase of a protein meal, at neutral and low pH in otherwise intact, laparotomized dogs and in dogs after truncal vagotomy and during atropine infusion.

In the intact group, the meal at pH 7 elicits a small, gradual increase of antral and fundic vein SLI, associated with a marked rise in antral and peripheral vein gastrin levels. At pH 2, the amount of postprandial gastrin released is reduced, as described previously,<sup>11-14</sup> in association with a sixfold increase in the response of antral vein SLI levels, while fundic vein SLI is decreased sharply.

A role for somatostatin as a local or paracrine modulator of gastrin and HCl secretion from the antrum and fundus-corporus region of the stomach was postulated previously.<sup>15-17</sup>

**FIGURE 5.** Somatostatin-like immunoreactivity (SLI) in the short gastric vein (fundus-corporus) and inferior vena cava in response to a gastric liver extract (LE) test meal at pH 2 in normal dogs ( $N = 5$ ), after truncal vagotomy ( $N = 7$ ), and during atropine infusion ( $N = 7$ ) (mean  $\pm$  SEM).  $\odot$  indicates significant differences of  $P < 0.05$  or less versus baseline levels.



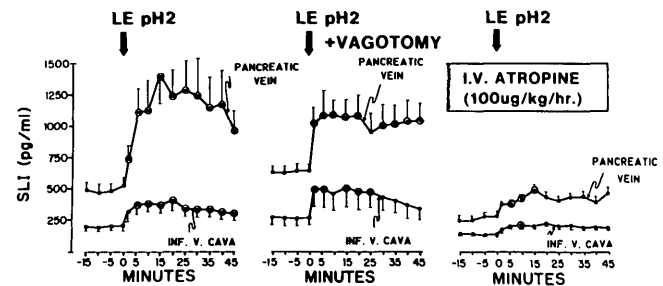
**FIGURE 6.** Somatostatin-like immunoreactivity (SLI) in the pancreatic vein and inferior vena cava in response to a gastric liver extract (LE) test meal at pH 7 in normal dogs ( $N = 5$ ), after truncal vagotomy ( $N = 6$ ), and during atropine infusion ( $N = 5$ ) (mean  $\pm$  SEM).  $\odot$  indicates significant differences of  $P < 0.05$  or less versus baseline levels.

The foregoing data are consistent with the idea that the acid-induced reduction of the amount of postprandial gastrin released may be mediated by the rise in antral somatostatin, but the decrease in fundic vein SLI does not necessarily support a role of locally released fundic somatostatin in acid-induced inhibition of gastric acid secretion during the gastric phase of a meal.<sup>14,18,19</sup> The results are also compatible with a postulated endocrine role of somatostatin,<sup>3</sup> for which evidence was reported recently,<sup>5,6</sup> the peripheral vein SLI concentrations in response to a gastric meal at pH 2 reach the levels observed when synthetic somatostatin is infused at  $0.5-0.7$   $\mu\text{g/kg/h}$ ,<sup>20</sup> a rate that can inhibit gastric acid secretion in dogs.<sup>21</sup>

We reported previously that pancreatic vein SLI concentrations rise in response to a fat-protein meal<sup>2</sup> and after intraduodenal administration of various nutrients.<sup>1</sup> The present results indicate that unidentified gastric factors influence this postprandial pancreatic SLI release. The fact that the acidified meal induces a much greater rise in pancreatic SLI levels than the meal at pH 7 in normal dogs suggests that, in addition to gastrin, which was suggested previously to be a mediator of the gastroinsular axis,<sup>22-28</sup> another factor, or factors, present in the stomach and stimulated by low pH acts as a mediator of this effect. A similar effect of low-pH intragastric meals on glucagon and insulin release was reported elsewhere.<sup>29</sup> While vagotomy does not change this effect, the infusion of atropine reduces it substantially.

In the stomach, truncal vagotomy results in an increased antral SLI release in response to the meal at pH 7, while the

**FIGURE 7.** Somatostatin-like immunoreactivity (SLI) in the pancreatic vein and inferior vena cava in response to a gastric liver extract (LE) test meal at pH 2 in normal dogs ( $N = 5$ ), after truncal vagotomy ( $N = 7$ ), and during atropine infusion ( $N = 7$ ) (mean  $\pm$  SEM).  $\odot$  indicates significant differences of  $P < 0.05$  or less versus baseline levels.



antral response to the meal at pH 2 is not altered significantly. Despite the increase in the postprandial antral vein SLI response to the meal at pH 7, the rise in peripheral vein SLI in response to this meal was considerably reduced, possibly because of the reduction in absolute fundic vein SLI levels or a loss of somatostatin release from somatostatin-containing peptidergic nerve fibers that are contained in the vagal nerve.<sup>30</sup> Basal and postprandial gastrin levels increased after vagotomy as described previously.<sup>31-35</sup>

The infusion of atropine changed both antral and fundic SLI responses to the meals at pH 7 and pH 2. Both antral and fundic SLI released in response to the meal at pH 7 were virtually abolished during atropine infusion, whereas the antral vein SLI response to the meal at pH 2 was reduced considerably but was still substantial, suggesting that both atropine-sensitive and atropine-insensitive mechanisms are needed for the antral SLI response to acid. The decrease of the postprandial fundic vein SLI response to the meal at pH 2 was converted to a significant increase, indicating that atropine-sensitive cholinergic mechanisms might mediate the suppression of fundic vein SLI by acid during the gastric phase of a meal and demonstrating an opposite effect of muscarinic cholinergic mechanisms in the modulation of antral and fundic D-cell functions.

The question of what is the true anatomic source of immunoreactivity recovered in effluent plasma can be posed legitimately in view of studies by Taylor and Torrance,<sup>36</sup> which suggest a portal system in the stomach through which antral blood might pass directly to the oxyntic tissue. However, the marked differences between antral and fundic vein SLI responses to the acidified liver meal, observed in the intact and in the vagotomized dogs, suggest that, at least in these circumstances, the two effluents were separate. The antrum contains a higher tissue concentration of somatostatin.<sup>37</sup>

In summary, the following conclusions can be made. Firstly, the intragastric administration of a protein meal alters gastric D-cell activity and this response varies with change in pH. Secondly, the release of gastric SLI can be modified by vagotomy and atropine infusion, which suggests a close neuroendocrine interrelationship between the somatostatin-containing D-cells and intragastric neural elements. Thirdly, the stomach influences pancreatic D-cell activity through atropine-sensitive pathways.

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