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Research Article

To investigate the effect of acute elevation of plasma free fatty acids (FFA) on the secretion of splanchnic somatostatin-like immunoreactivity (SLI), the peripheral venous, pancreatic, and gastric venous effluent levels of SLI were measured in normal and chronic alloxan diabetic dogs before and after the infusion of a fat emulsion supplemented with heparin. In normal conscious dogs heparin injected during the infusion of a fat emulsion elevated FFA levels from a mean (\pm SE) base-line level of 0.7 ± 0.1 meq/liter to a peak value of 1.5 ± 0.1 meq/liter ($P < 0.001$) and plasma SLI rose from a mean (\pm SE) base-line value of 145 ± 7 pg/ml to a peak of 253 ± 44 pg/ml ($P < 0.05$). Neither the infusion of glycerol, of fat emulsion without heparin, of heparin alone nor of saline itself had an effect on either the plasma level of FFA or SLI. In another group of anesthetized dogs with surgically implanted catheters the administration of fat emulsion plus heparin was accompanied by more than a two-fold rise in the concentration of SLI in the venous effluent of the pancreas and of the gastric fundus and antrum in association with an elevation of FFA levels. In a group of conscious diabetic dogs fat emulsion plus heparin raised FFA from a mean base-line level of 1.2 ± 0.2 to 1.6 ± 0.3 meq/liter ($P < 0.05$) and SLI rose [...]

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ABSTRACT To investigate the effect of acute elevation of plasma free fatty acids (FFA) on the secretion of splanchnic somatostatin-like immunoreactivity (SLI), the peripheral venous, pancreatic, and gastric venous effluent levels of SLI were measured in normal and chronic alloxan diabetic dogs before and after the infusion of a fat emulsion supplemented with heparin. In normal conscious dogs heparin injected during the infusion of a fat emulsion elevated FFA levels from a mean (\pm SE) base-line level of 0.7 ± 0.1 meq/liter to a peak value of 1.5 ± 0.1 meq/liter ($P < 0.001$) and plasma SLI rose from a mean (\pm SE) base-line value of 145 ± 7 pg/ml to a peak of 253 ± 44 pg/ml ($P < 0.05$). Neither the infusion of glycerol, of fat emulsion without heparin, of heparin alone nor of saline itself had an effect on either the plasma level of FFA or SLI. In another group of anesthetized dogs with surgically implanted catheters the administration of fat emulsion plus heparin was accompanied by more than a two-fold rise in the concentration of SLI in the venous effluent of the pancreas and of the gastric fundus and antrum in association with an elevation of FFA levels. In a group of conscious diabetic dogs fat emulsion plus heparin raised FFA from a mean base-line level of 1.2 ± 0.2 to 1.6 ± 0.3 meq/liter ($P < 0.05$) and SLI rose from a mean base-line level of 185 ± 9 pg/ml to a peak value of 310 ± 44 pg/ml ($P < 0.01$). Although SLI levels were significantly greater than in normal dogs at several time points after the rise in FFA, the magnitude of the increment in diabetic dogs did not differ from normal. These results demonstrate that a rise in FFA levels is a potent stimulus for SLI secretion from the pancreas

and stomach and raise the possibility that FFA is an important physiological regulator of SLI secretion.

INTRODUCTION

Free fatty acids (FFA)¹ influence the secretion of insulin and glucagon; a rise in their concentration is associated with an increase in insulin (1-4) and a suppression of glucagon (4-7). The present studies were designed to determine if a change in FFA concentration also influences the secretion of pancreatic and gastric somatostatin in normal and chronic alloxan diabetic dogs.

METHODS

For various studies of the response of somatostatin-like immunoreactivity (SLI) levels in peripheral venous plasma, 14 normal mongrel dogs (body wt 20.0-26.0 kg) and 4 dogs with alloxan diabetes of 6 mo to 3 yr duration (body wt 29.0-32.0 kg) were studied in a conscious state. Except for the diabetes in the latter group, all dogs were in apparent good health at the time of their experiments, and their leukocyte counts and hematocrits were within normal range. When the same dog was used in more than one experiment, after each study, it was transfused with its own erythrocytes suspended in 0.9% sterile saline to avoid anemia and it received a prophylactic antibiotic, Distrycillin (E. R. Squibb & Sons, Inc., Princeton, N. J.). The alloxan diabetic dogs had been maintained on 8-18 U neutral protamine Hagedorn insulin administered twice daily with meals, but 2 d before the study only the morning dose of insulin was given, and no further insulin was administered until after the experiment ~48 h later. Meals were given as usual until the day of the study.

To raise plasma FFA levels, in eight of the dogs a triglyceride emulsion (10% Intralipid, Cutter Laboratories, Inc., Berkeley, Calif.) was infused intravenously at a rate of 1

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¹ Abbreviations used in this paper: FFA, free fatty acids; SLI, somatostatin-like immunoreactivity.

ml/min for 2 h using a Harvard peristaltic pump (Harvard Apparatus Co., Inc., S. Natick, Mass.) after a 20 ml priming bolus of the emulsion, and 1,500 U of heparin sodium (Abbott Laboratories North Chicago, Ill.) was given intravenously 30, 50, and 70 min after the start of the infusion. In control experiments, the triglyceride emulsion was infused without heparin, heparin was given without triglycerides, or saline alone was infused at a rate of 1 ml/min. In these studies, six of the dogs served as their own control, and the order of experiments was randomized. To minimize volume loss during these studies, 250 ml of normal saline was infused by drip over the 3.5 h experimental period. In another group of six normal conscious dogs glycerol was infused at a rate of 100 mg/kg per h, after a priming bolus of 32.5 mg/kg.

In experiments designed to determine the source of any rise in plasma SLI levels another group of 12 healthy mongrel dogs weighing 19.0–26.5 kg were subjected to laparotomy under Nembutal (sodium pentobarbital; Abbott Laboratories) anesthesia. A silastic catheter was placed, as previously described (8), in the superior pancreaticoduodenal vein, in a major short gastric vein draining the fundus and upper corpus of the stomach, in the left gastroepiploic vein draining the antrum, and in the inferior vena cava through the right jugular vein. After placement of the catheters, an equilibration period of 1 h preceded each experiment. To minimize volume loss 1,000 ml of normal saline was infused by constant drip during these experiments. In seven of the dogs FFA levels were raised by triglyceride emulsion plus heparin as described above, and in five dogs saline was infused as a control at a rate of 1 ml/min.

Blood samples were collected in tubes containing 6 mg EDTA and 500 kallikrein inhibitor units Trasylol/ml blood. The samples were kept chilled in an ice bath and were centrifuged at 2,000 rpm for 20 min at 4°C within 1 h after collection of blood. The plasma was stored at –20°C until assayed.

Plasma SLI was measured by a modification (9) of previously reported methods (10, 11), using antiserum R101 supplied by Dr. A. Arimura, Veterans Administration Hospital, New Orleans, La. This assay has been previously validated for measurements in unextracted canine plasma (12, 13). Recovery of synthetic somatostatin added to canine plasma containing varying concentrations of Intralipid (10–300 mg/dl, as triglycerides) or sodium salt of oleic acid (0.5–3.3 mmol/liter) averaged $94 \pm 4\%$ and $92 \pm 5\%$ (mean \pm SE) at somatostatin concentration of 450 pg/ml, respectively. These recovery rates were not significantly different from those in control plasma samples. Insulin and glucagon were measured by previously described methods (14, 15). Glucose was determined by the glucose oxidase method using the Auto-Analyzer (Technicon Instruments Corp., Tarrytown, N. Y.). Plasma FFA concentrations were determined by the colorimetric microdetermination method of Soloni and Sardina (16) as modified by Howard et al. (17).

For statistical analysis, an analysis of variance was employed. When results of this analysis of variance were significant, the Newman-Keuls multiple comparison procedure was applied to locate the specific differences.

RESULTS

Effect of increased FFA levels on plasma SLI in normal dogs. The administration of triglyceride plus heparin to eight conscious normal dogs caused FFA to rise from a mean (\pm SE) basal value of 0.67 ± 0.09 meq/liter to a peak value of 1.53 ± 0.11 meq/liter ($n = 6$, $P < 0.001$) at 60 min. This was accompanied by

a rise in plasma SLI from a base-line value of 144.9 ± 7.2 pg/ml to a maximum of 252.5 ± 44.4 pg/ml ($n = 8$, $P < 0.05$) at 80 min (Fig. 1). The rise occurred within 10 min after heparin injection, thus coinciding with the increase in plasma FFA, and it remained elevated above control levels until the infusion of triglycerides was terminated, whereupon it declined significantly ($P < 0.05$). In the same dogs neither fat emulsion without heparin, heparin alone nor normal saline altered the levels of either FFA or SLI from the base-line values (Fig. 1). The mean plasma glucagon level tended to fall, but this failed to reach statistical significance ($0.05 < P < 0.1$) (Fig. 3). Insulin levels did not change significantly in any of the studies (not shown).

Effect of glycerol infusion on plasma SLI. To determine if the observed effects of the triglyceride plus heparin on SLI levels could be the result of increased glycerol levels, glycerol was infused for 120 min at a rate of 100 mg/kg per h after a priming injection of 32.5 mg/kg. This dose of glycerol was 20% more than

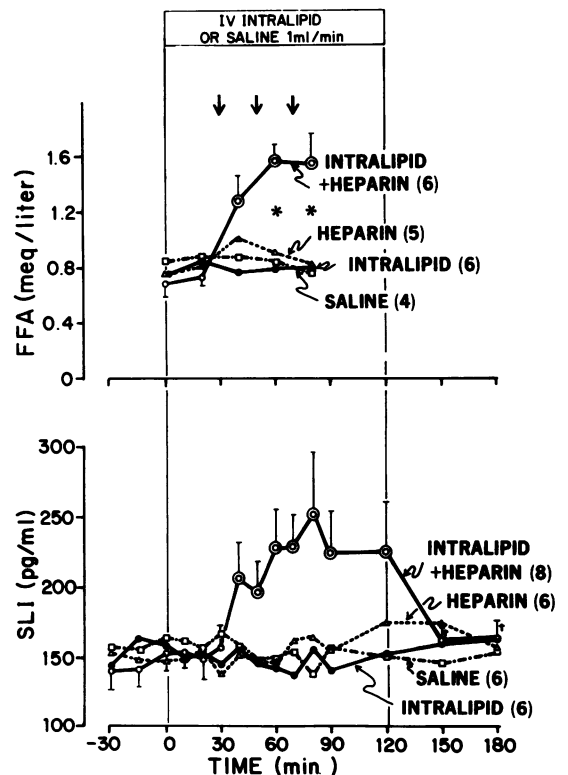


FIGURE 1 Effect of intravenous infusion of fat emulsion (10% Intralipid), at a rate of 1 ml/min after a 20 ml priming bolus plus heparin, fat emulsion without heparin, heparin without emulsion, or saline alone on plasma levels of FFA and SLI in a group of conscious normal dogs. The number of dogs is in parentheses. © and * indicate significant differences ($P < 0.05$) from each base-line value (–30 to 0 min) and from each control group, respectively. Dagger (†) indicates a significant ($P < 0.05$) decline from the time 120 min. Arrows indicate 1,500 U heparin i.v. Mean \pm SE.

the amount estimated to be available from total hydrolysis of the fat emulsion administered in the present study (18). As shown in Fig. 2, no effect on SLI was observed.

Effect of increased FFA levels on plasma SLI levels of alloxan diabetic dogs. In four insulin deprived alloxan diabetic dogs, the fasting FFA levels averaged 1.17 ± 0.22 meq/liter (mean \pm SE), and rose during the triglyceride-heparin administration to 1.60 ± 0.25 meq/liter ($P < 0.05$) at 60 min and then declined gradually. The mean base-line SLI level was 184.6 ± 9.2 pg/ml and it rose to a maximum of 310 ± 44.2 pg/ml ($P < 0.01$) at 60 min (Fig. 3). The mean plasma SLI level was significantly higher than in normal dogs at times -30, 20, 150, and 180 min ($P < 0.05$ or less), but the mean integrated SLI increment above the base line from 30 to 180 min did not differ from that of the normal dogs.

Plasma glucagon levels, which were significantly above those in the normal dogs at all time periods, declined significantly ($P < 0.001$) within the first 10 min of the heparin injection from a mean basal level of 211.3 ± 27.3 pg/ml and reached a nadir of 130.3 ± 24.1 pg/ml ($P < 0.05$) at 90 min. They remained low for the ensuing 180 min.

Effect of increased FFA levels on plasma SLI levels in pancreatic and gastric veins. To determine the source of the increase in SLI observed when plasma FFA levels were elevated, SLI was measured in the venous effluent of the pancreas and stomach of anesthetized, laparotomized nondiabetic dogs during triglyceride-heparin infusions. Plasma FFA increased from a mean base-line level of 0.34 ± 0.07 meq/liter to a mean maximum of 1.21 ± 0.16 meq/liter ($P < 0.005$) at 10 min after heparin injection. Plasma SLI in the inferior vena caval plasma rose from a base-line level of 164.8 ± 13.5 pg/ml to a maximum value of 358.6 ± 53.3 pg/ml ($P < 0.005$) at 90 min and returned to the base-line range by 180 min (Fig. 4A). In the pancreatic

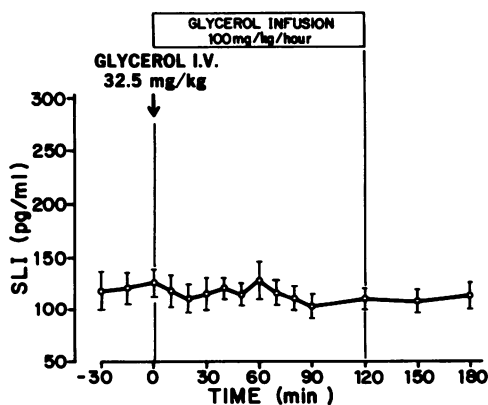


FIGURE 2 Effect of intravenous infusion of glycerol (100 mg/kg/h after a priming bolus of 32.5 mg/kg) on the plasma SLI levels in six normal dogs. Mean \pm SE.

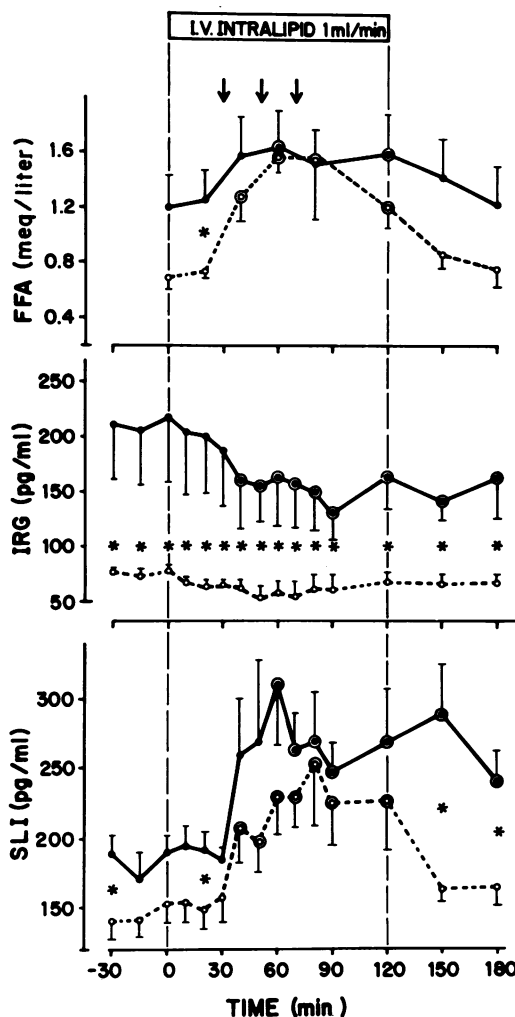


FIGURE 3 Effects of acute elevation of plasma FFA on the plasma levels of immunoreactive glucagon (IRG) and SLI in eight normal (---) and in four alloxan diabetic (—) dogs. Circled symbols (⊙, ⊙) indicate significant differences ($P < 0.05$) from each base-line value (-30 to 0 min) and asterisks indicate a significant difference ($P < 0.05$) from normal dogs. Arrows indicate 1,500 U heparin i.v. Mean \pm SE.

effluent, plasma SLI increased from a base line of 244.0 ± 18.6 pg/ml to a peak of 529.3 ± 108.8 pg/ml ($P < 0.01$) at 120 min (Fig. 4B). The rise occurred within 20 min after heparin injection, and after cessation of triglyceride infusion, declined to the base-line range. In the fundic vein plasma SLI also increased from a base-line level of 211.7 ± 24.6 pg/ml to a peak of 545.0 ± 98.6 pg/ml ($P < 0.01$) at 90 min and thereafter gradually declined (Fig. 4C). In the venous effluent of the antrum, SLI rose from a base-line value of 179.2 ± 18.1 pg/ml to a level of 402.9 ± 65.7 pg/ml ($P < 0.005$) at 120 min (Fig. 4D). In control studies in which only saline was infused (Fig. 4) there were no significant increases in plasma SLI levels in any of the four veins.

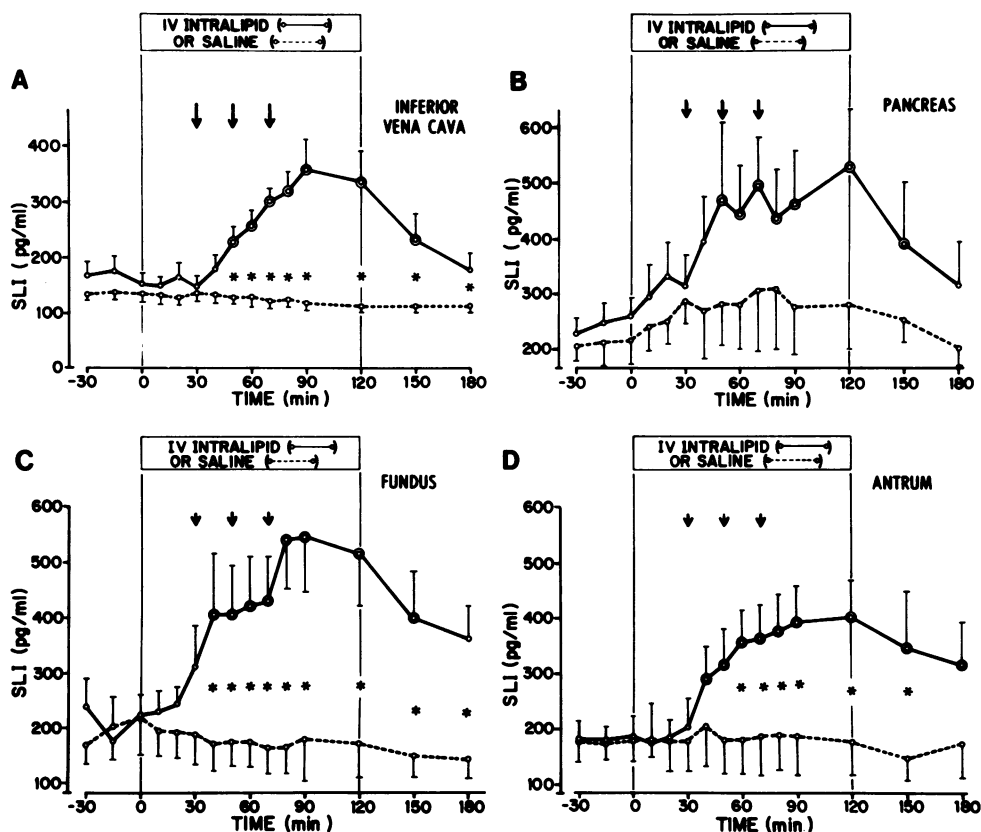


FIGURE 4 Plasma SLI levels in the inferior vena cava (A), the paracretoduodenal vein (pancreas, B), the short gastric vein (fundus, C), and the left gastroepiploic vein (antrum, D) after intravenous infusion of fat emulsion plus heparin ($n = 7$) or saline ($n = 5$). \odot indicates a significant difference ($P < 0.05$) from each base-line value (-30 to 0 min) and * indicate a significant difference ($P < 0.05$) between fat emulsion plus heparin and saline control groups ($P < 0.05$). Arrows indicate 1,500 U heparin i.v. Mean \pm SE.

DISCUSSION

The present study suggests that FFA² is a potent stimulus of SLI release by the pancreas and by the fundus and antrum of the stomach. A doubling of plasma levels of FFA by injecting heparin during an infusion of a fat emulsion was associated with a rise in the mean peripheral SLI level of approximately 100 pg/ml in both nondiabetic and diabetic dogs. The fasting SLI levels and SLI response to acute elevation of plasma FFA in alloxan diabetic dogs were greater than normal, and the elevation was more prolonged in the diabetic dogs. But the magnitude of the response of SLI estimated by the sum of increments above base-line level was almost identical in normal and diabetic dogs.

A SLI increase of the magnitude observed in this study may be of physiologic importance in nutrient homeostasis, considering that a rise in venous plasma

SLI to only 35–80 pg/ml above the postprandial levels produced by the intraportal infusion of synthetic somatostatin reduces the rise in triglyceride and xylose levels resulting from a fat or a xylose meal (19). These effects have been attributed (20, 21) to actions of somatostatin in slowing a spectrum of rate-limiting gastrointestinal (22, 23)³ and pancreatic exocrine functions (24, 25) and in reducing portal venous flow (26). Considering that a relatively small rise in FFA is capable of raising plasma SLI levels to a biologically meaningful degree, a role of plasma FFA in the regulation of SLI secretion may be suspected. Perhaps the high levels of FFA that occur during exercise or starvation, by raising SLI levels, reduce gastrointestinal activity, which would be superfluous in such circumstances.

² The possibility that monoglycerides rather than, or in addition to FFA play a role in these responses has not been excluded in this study.

³ Johansson, C., A. Aly, O. Wisen, K. Uvnäs-Wallensten, and S. Efendic. Effects of somatostatin on gastrointestinal preparation and absorption of oral glucose in man. Submitted for publication.

Other fuels appear to be less effective than FFA in stimulating SLI secretion. Glycerol failed to stimulate SLI secretion. Glucose lowers peripheral SLI levels in normal dogs despite increased pancreatic SLI release (13, 27), although it has been reported to stimulate somatostatin in some (28–30) but not other (31, 32) *in vitro* studies. Amino acid mixture stimulates SLI release from the canine pancreas (29) but not from the stomach and peripheral venous levels of SLI do not rise after intravenous infusion of a 15-amino acid mixture in conscious normal dogs (unpublished observation).

Somatostatin may itself influence FFA levels through two possible mechanisms. First, it may indirectly modulate lipolysis via its inhibitory actions on insulin (33–35) and glucagon (35, 36) secretion. In the present studies, glucagon suppression occurred in diabetic dogs concomitantly with the rise in SLI, but it is not clear if somatostatin contributes to the glucagon-suppressing effect of FFA. Second, SLI might be important in determining the postprandial FFA levels after the ingestion of fat. Conceivably, as suggested by Bilheimer,⁴ somatostatin protects against too rapid an influx of chylomicrons from the gut, which in the presence of normal lipoprotein lipase activity might result in excessively high elevations of FFA levels with possible adverse effects (37–44). By regulating the rate of fat entry from the gut, such putative perturbations may be avoided.

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⁴ D. Bilheimer. Personal communication.

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