Insulin Inhibits Somatostatin-Like Immunoreactivity Release Stimulated by Intragastric HCl

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SUMMARY

To determine the effect of an increase in insulin levels within the range occuring under physiologic conditions on the protein- and acid-induced release of splanchnic somatostatin, insulin was infused in dogs for 1 h following the intragastric instillation of a neutral protein load (20% liver extract at pH 7), a weak stimulus of somatostatin-like immunoreactivity (SLI), and after an intragastric HCl, a strong stimulus of SLI release, instilled 30 min later. Insulin levels between 50 and 60 μU/ml significantly reduced the rise in peripheral venous SLI levels elicited by the acid load from a mean integrated incremental value of 1705 ± 182 pg/ml in controls to 840 ± 312 in the insulin-infused group ($P < 0.05$). Prevention of the insulin-induced hypoglycemia and the secondary rise in glucagon, a known stimulus of pancreatic somatostatin secretion, by means of a concomitant infusion of glucose, did not modify the reduction in acid-induced increase in plasma SLI concentration associated with hyperinsulinemia. Insulin-glucose infusion significantly lowered the SLI in the pancreaticoduodenal vein, and in the gastroepiploic vein draining the antrum ($P < 0.02$; $P < 0.05$), but not in the short gastric veins draining the fundus of the stomach in response to the acid load. It is concluded that a physiologic elevation of insulin levels causes significantly reduced response of SLI to an intragastric acid load in dogs. This reduction is explained by a diminished increment of SLI in the venous effluent of the pancreas and the antrum.

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Hormones of the islets have the capacity to influence the secretion of other islet hormones. Samols first demonstrated that glucagon stimulates insulin secretion[1] and that insulin inhibits glucagon secretion,[2] while others have observed that somatostatin inhibits insulin[3] and glucagon secretion[4] and that glucagon stimulates somatostatin secretion.[5]

However, an effect of insulin upon somatostatin release has been more difficult to establish. Patton et al. were unable to demonstrate any action of insulin on somatostatin release from the perfused canine pancreas.[5] Yet in vivo studies in diabetic dogs[6] and in vitro studies by Schauder et al.[7] and Rothman[8] were consistent with a somatostatin-suppressing action of insulin, while Gerber et al.[9] observed insulin-induced suppression in the isolated rat pancreas. Nevertheless, Honey et al.[10] noted stimulation of somatostatin by insulin in the perfused chicken pancreas.

The present study was designed to determine the in vivo effects of physiologic increments of plasma insulin upon the response of splanchnic somatostatin-like immunoreactivity (SLI) to a test meal.

MATERIALS AND METHODS

The experiments were performed in 22 mongrel dogs (body wt 25–30 kg). After anesthesia (Nembutal) and laparotomy, silastic catheters were placed in the inferior vena cava, the pancreaticoduodenal vein, a short gastric vein draining the fundus of the stomach, and the left gastroepiploic vein draining the antrum.[11] An equilibration of 1 h followed the surgical procedure. In one group of dogs, 250 ml of a 20% liver extract (Reheis Chemicals, Chicago, Illinois) at pH 7, a weak stimulus of SLI,[11] was administered intragastrically over a 1-min period. At the same time, an infusion of either crystalline insulin (0.03 U/kg/h) diluted in saline containing 0.5% albumin or of a control (Eli Lilly, Indianapolis, Indiana) saline-albumin solution was administered via a crural vein and continued throughout the project. Thirty minutes later, 200 ml of 1 N HCl, a strong stimulus of SLI,[11] was administered intragastrically over a 1-min period. Glucose levels were monitored at 5-min intervals. In half of the dogs receiving insulin, glucose levels were maintained at a level comparable to those of the controls by infusing glucose via a jugular vein at a rate determined by glucose monitoring of inferior vena caval plasma at 5-min intervals. Frequent

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blood samples were also drawn from the catheterized effluent veins before and after the instillation of the test meals.

Insulin and glucagon were measured according to previously described techniques[12,13] and somatostatin by a modification[14] of the methods of Arimura et al.[15] and Kronheim et al.[16]

Statistical analysis between groups was carried out by the Student's *t* test for paired data. Incremental changes in SLI and glucagon were calculated by averaging the sum of their increments above the prestimulation baseline for 30 min in each dog.

RESULTS

Effect of insulin infusion on peripheral SLI release during a neutral protein meal and an acid load. The infusion of insulin in a group of 7 dogs increased the peripheral levels of insulin from a mean baseline of 15.6 ± 4.1 μU/ml to 48.1 ± 7 μU/ml within 20 min and maintained them in this range until the end of the experiment (Figure 1). In the saline control experiments in 8 dogs, insulin levels remained below 20 μU/ml for 30 min after the protein meal but rose significantly to about 35 μU/ml after the acid meal. Glucose levels dropped slowly to levels about 35 mg/dl below the baseline values.

The intragastric administration of the liver extract at pH 7 failed to raise SLI levels in the peripheral blood in either the control group or the insulin-infused group. However, the administration of the acid load elicited in the controls a sharp rise in SLI from a baseline value of 238 ± 48 pg/ml to a peak of 528 ± 76 pg/ml at 20 min (Figure 1). In the insulin-infused group, by contrast, SLI rose from a baseline level of 161 ± 15 pg/ml to only 316 ± 78 pg/ml within 10 min, significantly less than in the controls ($P < 0.05$) (Figure 1). The incremental SLI after the acid load was 840 ± 312 pg/ml in the insulin-infused group, significantly less than the value of 1705 ± 182 pg/ml in the controls ($P < 0.05$).

To assess the possibility that hypoglycemia and/or the rise in glucagon, a known stimulus of pancreatic somatostatin secretion,[5] contributed to the foregoing results, the insulin experiments were repeated in another group of seven dogs with a concomitant glucose infusion designed to prevent hypoglycemia and to reduce glucagon secretion. When glucose was co-infused with insulin (Figure 2), the mean incremental glucagon in response to HCl was only 54 ± 47 pg/ml, significantly below both the 386 ± 131 pg/ml value observed in the saline control group ($P < 0.05$) and the 281 ± 86 pg/ml value observed when insulin was infused without glucose (Figure 3) (the latter was not significantly different from the controls). Nevertheless, despite this marked difference in both the glucagon and glucose levels in the two insulin experiments, in each incremental SLI was equally suppressed below the control value (Figure 2). This

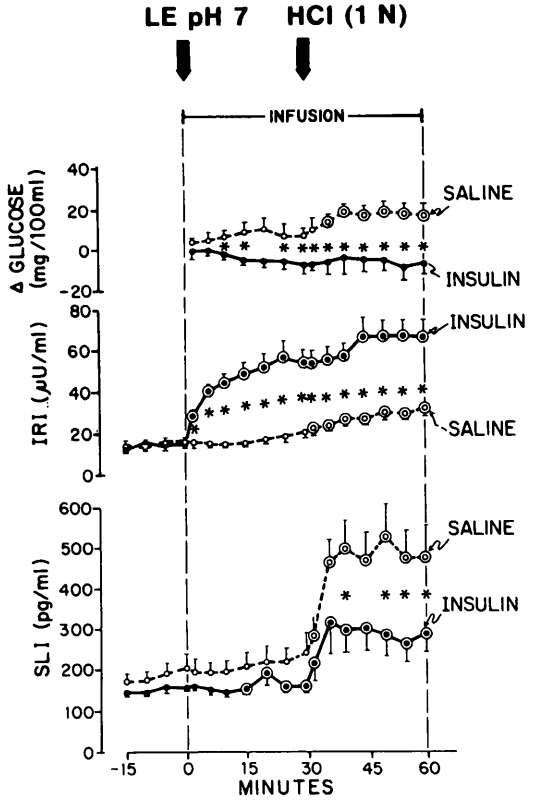


FIGURE 1. The effect of insulin infusion (0.03 U/kg/h) on the level of plasma SLI, insulin, and glucose in a group of 7 dogs following the intragastric instillation of 250 ml of 20% liver extract (LE) at pH 7 and 200 ml of 1 N HCl (mean ± SEM). A group of 8 dogs received the liver extract and HCl, but saline was used as a control. Circled points are statistically ($P < 0.05$) different from the mean of baseline values. Asterisks (*) indicate a significant ($P < 0.05$) difference between values observed during insulin infusion and those observed during saline controls.

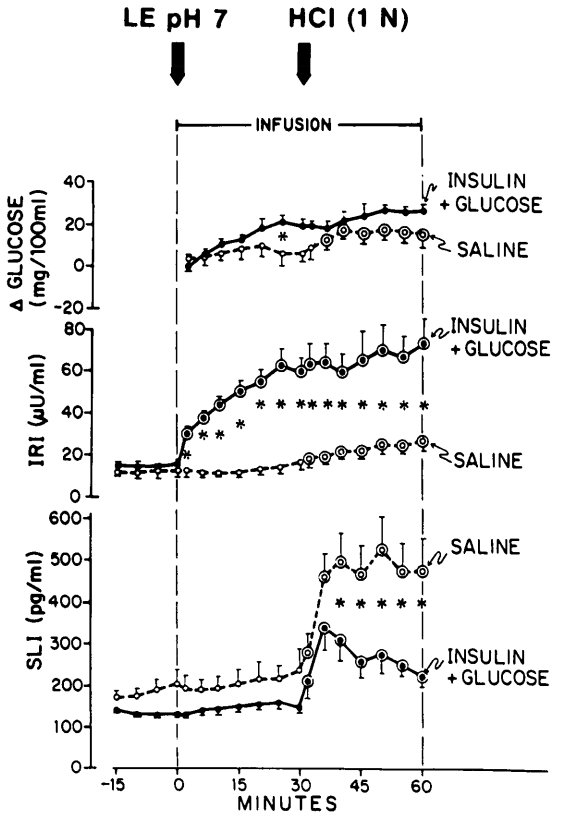


FIGURE 2. The effect of the infusion of insulin plus glucose in a group of 7 dogs upon plasma levels of somatostatin-like immunoreactivity (SLI), insulin, and glucose following the intragastric instillation of liver extract (LE) at pH 7 and HCl (mean ± SEM). Circled points are statistically different ($P < 0.05$) from the mean of the baseline values. Asterisks (*) represent statistically significant differences between values observed during the infusion of insulin and glucose and those observed during the eight saline control experiments.

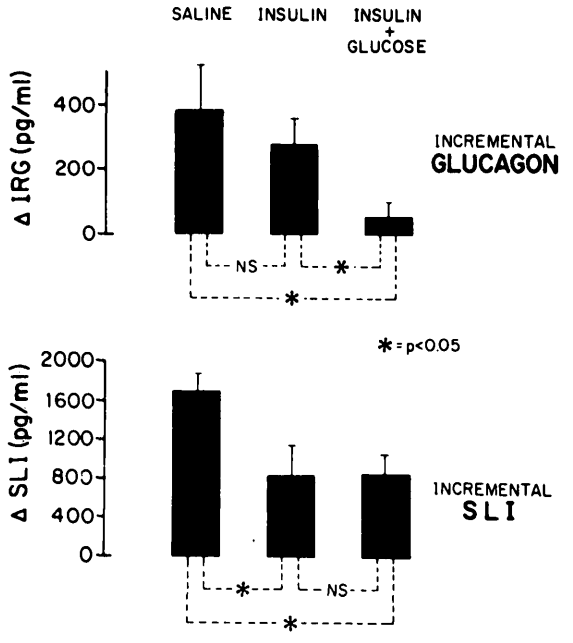


FIGURE 3. The integrated incremental glucagon levels during insulin suppression of acid-stimulated SLI release (mean ± SEM). The saline group contained 8 dogs, the insulin group 7 dogs, and the insulin plus glucose group 7 dogs.

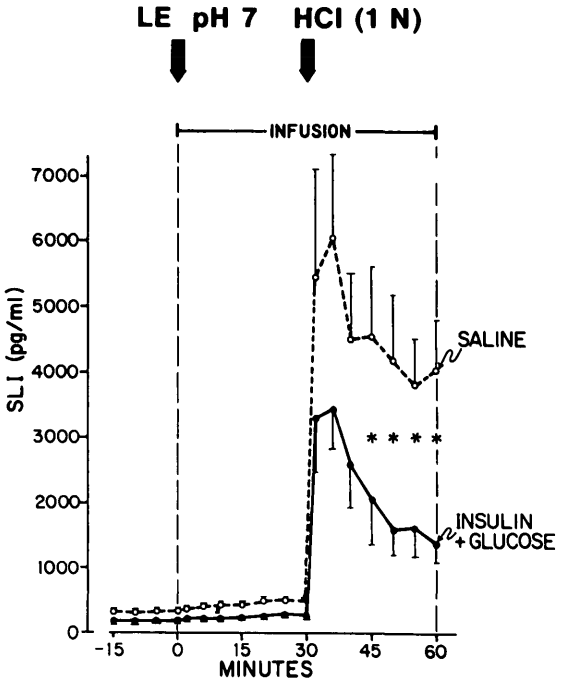
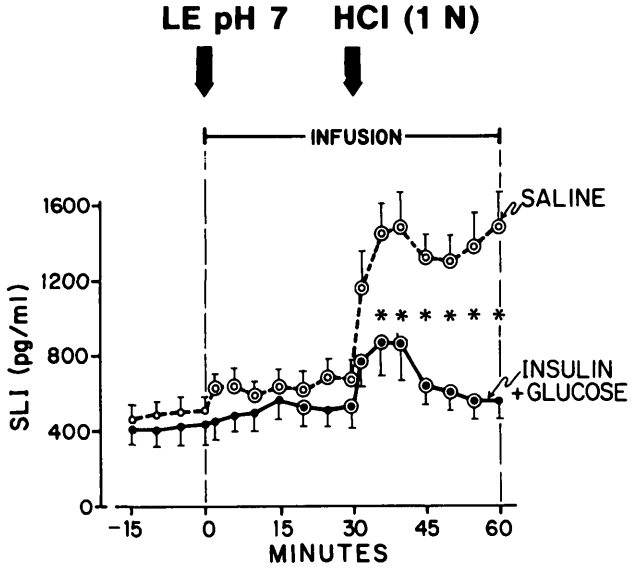


FIGURE 5. Effect of intravenously infused insulin and glucose upon SLI levels in the gastroepiploic vein draining the antrum in the same 7 dogs of Figure 2. Asterisks (*) represent statistically significant differences (P < 0.05) between values observed during insulin and glucose infusion and those noted during the eight saline control infusions.

suggests that the insulin-induced reduction in the SLI response to intragastric HCl was not dependent on either a fall in glucose or a rise in glucagon.

Site of the insulin-mediated reduction in SLI levels. The increase in SLI after an intragastric acid load is known to originate from both pancreas and stomach.[11] To determine which of these sites was inhibited during the insulin-induced reduction of the SLI response, SLI levels were measured in specimens of the venous effluent of the pancreas and the gastric antrum and fundus obtained in the foregoing experiments.

FIGURE 4. The effect of intravenously infused insulin and glucose on pancreatic vein SLI values (mean ± SEM) in the same 7 dogs of Figure 2. Circled points represent statistically significant (P < 0.05) differences from the mean of the baseline values. Asterisks (*) represent differences between values observed during insulin plus glucose infusion and during the eight saline control experiments.



In the pancreatic vein, a small but significant rise in SLI occurred after liver extract administration in the eight control experiments, but this was less prominent during the infusion of insulin and glucose (Figure 4). In the eight control experiments, HCl induced a rise in pancreatic vein SLI from a baseline of 673 ± 140 pg/ml to a peak of 1487 ± 189 pg/ml, whereas in the seven insulin and glucose infusion experiments, pancreatic vein SLI rose from 531 ± 111 pg/ml to a peak of only 874 ± 197 pg/ml, decreasing thereafter (Figure 4). This was significantly less than in the controls ($P < 0.02$).

In the gastroepiploic vein draining the antrum of the stomach, SLI levels, which did not rise after the liver extract at pH 7 (Figure 5), increased after the acid load from 498 ± 120 pg/ml to a peak of 6044 ± 1297 pg/ml and decreased slowly thereafter. During the infusion of insulin and glucose they rose from 252 ± 19 pg/ml to only 3443 ± 609 pg/ml within 10 min, significantly below the controls at four time points ($P < 0.05$–$P < 0.02$) (Figure 5).

In a short gastric vein draining the fundus of the stomach, the levels stimulated by the acid load were slightly lower during the insulin and glucose infusion than in the controls, but the differences were not significant at any point.

DISCUSSION

The data indicate that the somatostatin secreted by the D-cells of the pancreas and antrum of the dog in response to a test meal is diminished by an elevation of insulin levels to within the range found under physiologic conditions.

These results corroborate previous in vivo studies in al-

loxan-diabetic dogs,[6] showing that insulin completely inhibits the postprandial rise in SLI, and the in vitro studies of Schauder et al.[7] and of Gerber and co-workers.[9] They further indicate that the effect is not mediated or demonstrably influenced by concomitant changes in glycemia or glucagon levels.

However, these results do not indicate whether the in vivo effect of insulin on the SLI response to these stimuli is a direct one on the D-cells of the islets and stomach or whether it is mediated by possible insulin-induced suppression of D-cell secretagogues[17,18] released from the gut, such as gastrin, cholecystokinin, secretin, and gastric inhibitory polypeptide. The finding of Gerber et al.[9] that insulin suppresses the SLI response of the perfused rat pancreas is consistent with a direct action on D-cells, but it does not exclude a concomitant reduction in meal-induced release of D-cell secretagogues.

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