Effect of Somatostatin on Meal-stimulated Pancreatic Exocrine Secretions in Dogs

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SUMMARY

The effect of exogenously administered somatostatin (SRIF) on meal-stimulated secretions of the exocrine pancreas was studied in dogs with chronic pancreatic fistulas. Dogs were fed 600 gm. of raw meat, and pancreatic output of water, bicarbonate, and protein was measured. Bicarbonate and protein secretions rose markedly postfeeding in all control animals. Four hundred micrograms or 100 μg. of SRIF infused for one hour together with a meal completely prevented the postfeeding rise in pancreatic secretions. SRIF (100 μg./hr.) infused one hour after a meal suppressed pancreatic secretions to basal levels within 30 minutes. Pancreatic secretions rose promptly after discontinuation of SRIF in all dogs. These data indicate (1) SRIF completely prevents pancreatic bicarbonate and enzyme responses when given together with a meal; (2) it completely suppresses already initiated pancreatic responses when given one hour after a meal; (3) 100 μg. of SRIF is as effective as 400 μg. in suppressing the postprandial rise in pancreatic secretions. We conclude that SRIF severely interferes with pancreatic secretions during normal alimentation and that this observation should be considered if SRIF is to be used as a therapeutic agent.
DIABETES *26*:7-10, January, 1977.

Somatostatin (somatotropin-release-inhibiting factor, SRIF) has been demonstrated to inhibit the release of growth hormone,[1] thyrotropin,[2] insulin,[3] glucagon,[4] gastrin,[5] secretin,[6] and glucagon-like immunoreactivity (GLI).[7] It has been used in patients with acromegaly,[8] diabetes,[9,10] and islet-cell tumors[5] and has been proposed as a therapeutic agent for these conditions. However, other reported effects of SRIF suggest that its long-term administration may result in undesired side effects. Some of these additional effects of SRIF are its inhibition of gastric acid secretion,[5] gallbladder contractility,[11] and secretion of the exocrine pancreas whether stimulated by the intravenous infusion of exogenous secretin and cholecystokinin (CCK) or the intraduodenal administration of HCL.[6] The purpose of this study was to determine in dogs the effect of exogenously administered SRIF on the secretions of the exocrine pancreas under the physiologic stimulus of a protein meal.

Presented at the national meeting of the American Federation for Clinical Research, Atlantic City, New Jersey, 1976 (Clin. Res. *24*:293A, 1976).

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Accepted for publication July 14, 1976.

METHODS

All studies were performed on conscious mongrel dogs weighing between 17 and 20 kg. that were fasted for 20 hours. All dogs had chronic pancreatic fistulas prepared three weeks prior to study according to a previously described modification[6] of the Herrera technique.[12] In the morning of the day of the experi-

ment, the dogs were fed 600 gm. of lean, raw meat that was consumed within three minutes. Pancreatic secretions were collected from the fistulas in 15-min. aliquots for four hours. Four groups of dogs were studied. The first group (n = 6) received an infusion of saline without somatostatin and served as control. The second (n = 6) and third (n = 7) groups were given SRIF at the beginning of the meal (group II, 400 μg./hr.; group III, 100 μg./hr.). Group IV received 100 μg./hr. SRIF one hour after feeding.

Somatostatin (the cyclic form, given to us through the courtesy of Dr. Norman Grant of the Wyeth Co., Philadelphia) was dissolved in saline and administered intravenously by a Harvard pump for one hour; beginning at −15 minutes for group II, at zero time for group III, and at +60 minutes for group IV.

Pancreatic flow rate and bicarbonate and protein outputs were determined as previously described.[5,13]

Results are expressed as total output/15-min. interval, and values are expressed as mean ± S.E.M. Statistical evaluation was performed by the one-tailed Student *t* test for paired samples.

RESULTS

Pancreatic secretions after a meal (figure 1). The output of water, bicarbonate, and protein increased significantly ($P < 0.01$) within the first 15 minutes after the meal, reached a peak within 90 min., and thereafter declined gradually over the next two and one-half hours, but was still elevated above basal after four hours.

Effect of SRIF given together with a meal (figures 2 and 3). When 400 μg. SRIF was infused beginning 15 min. prior to feeding no rise in pancreatic output was

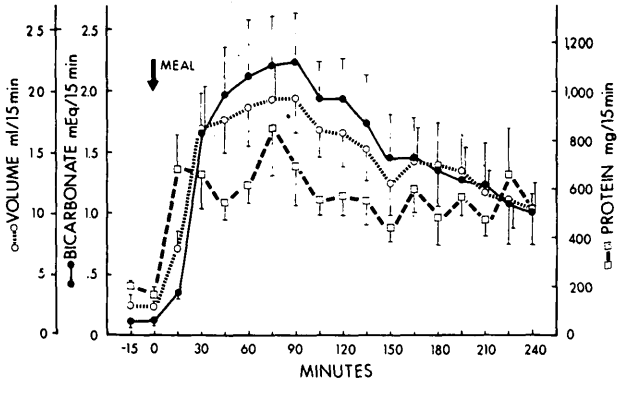

FIG. 1. Pancreatic flow rate and bicarbonate and protein secretion in six dogs following a 600-gm. protein meal. Values represent total output/15 minutes and are expressed as means ± S.E.M.

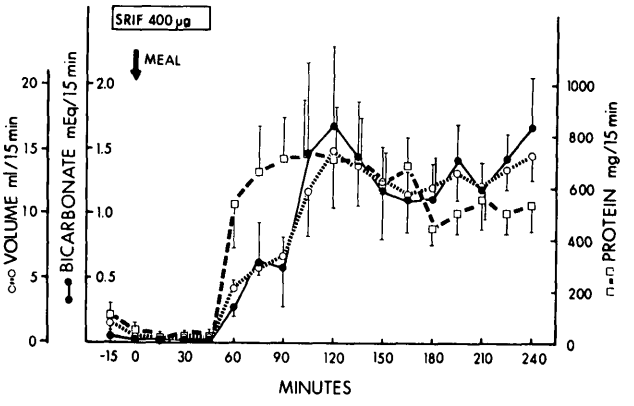

FIG. 2. Effect of SRIF (400 μg.) on meal-stimulated pancreatic flow rate and bicarbonate and protein secretion in six dogs. The SRIF was infused for one hour beginning 15 minutes prior to a 600-gm. protein meal.

observed. As shown in figure 2, pancreatic secretions were completely suppressed throughout the infusion. The mean values for volume and protein output were significantly ($P < 0.01$) lower than basal levels. Mean bicarbonate values were also lower than basal levels, but the difference did not achieve statistical significance. Within 15 minutes after cessation of the infusion there was a prompt rise in water, bicarbonate, and protein outputs. Within one hour after discontinuation of the infusion, pancreatic secretions had reached levels comparable to those of controls. During the infusion of SRIF no apparent untoward effects were observed; however, three of six animals became extremely agitated within 30 minutes after the discontinuation of the infusion, and one dog vomited undigested gastric contents approximating one half of the ingested meal. No similar reactions had ever been observed in our laboratory following ingestion of a protein meal. In an attempt to avoid these untoward effects seen with the 400-μg. dose, 100 μg. SRIF was infused into another seven dogs. During these experiments no adverse effects were noted. As seen in figure 3, the 100-μg. dose also completely suppressed the rise in pancreatic secretions. After discontinuation of the SRIF there was again a prompt rise in the outputs of water, bicarbonate, and protein, and these outputs remained elevated throughout the period of observation.

Effect of SRIF given after a meal (figure 4). To determine the effect of SRIF on pancreatic secretions already initiated, SRIF (100 μg. for one hour) was infused beginning one hour after feeding. Within 30 minutes of the onset of the SRIF infusion, the meal-stimulated secretion of water, bicarbonate, and pro-

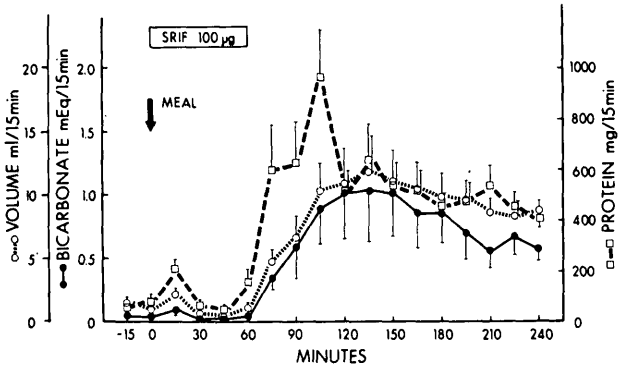

FIG. 3. Effect of SRIF (100 μg.) on meal-stimulated pancreatic flow rate and bicarbonate and protein secretion in seven dogs. The SRIF was infused for one hour beginning at the time of feeding.

tein was completely suppressed. Furthermore, secretions remained suppressed throughout the infusion and rose promptly after its cessation.

DISCUSSION

These data clearly demonstrate that SRIF effectively suppressed exocrine pancreatic secretions in response to a protein meal. Suppression was seen regardless of when the SRIF was given. SRIF was capable of preventing the onset of meal-stimulated pancreatic secretions and could suppress already initiated secretions from peak levels to basal levels. The onset of the effect was always immediate, and the duration was limited to the time of infusion. The 100-μg. dose was as effective as the 400-μg. dose in inhibiting the postprandial rise in secretion. There was an initial rise in secretions seen with the 100-μg. dose that was not seen with the 400-μg. dose; however this is most likely due to the fact that in the 100-μg. experiment the SRIF infusion was begun at the time of feeding, whereas in the 400-μg. experiment the SRIF infusion was begun 15 minutes earlier. It is noteworthy that the 100-μg. dose is less than the doses that have been used by others in dogs and man to demonstrate the effects of SRIF on plasma glucagon, glucose, and ketoacids.[7,9,10,14]

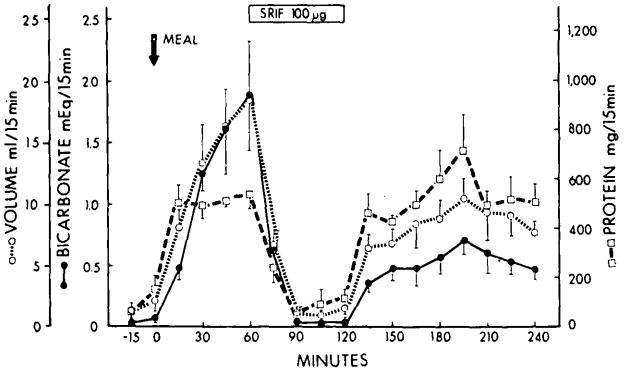

FIG. 4. Effect of SRIF (100 μg.) on meal-stimulated pancreatic flow rate and bicarbonate and protein secretion in seven dogs. SRIF was infused for one hour beginning 60 minutes after feeding.

The mechanism of the suppressive effect of SRIF on the exocrine pancreas appears to be multifactorial. First, SRIF has been shown to inhibit the release of secretin,[6] assumed to be the most important physiologic stimulus for pancreatic bicarbonate secretion. Second, Creutzfeldt et al.[11] have shown that SRIF suppresses pancreatic secretions during exogenous secretin and CCK infusions, suggesting a direct suppressive effect on the exocrine pancreas. Third, SRIF appears to affect gastrointestinal motility[15] and delay gastric emptying.[16] Delayed gastric emptying would delay and diminish release of any humoral agent from the intestine essential for the pancreatic response to a meal.

Whatever the mechanism of SRIF's action, the observation that SRIF completely inhibits meal-stimulated pancreatic secretions is important for at least two reasons. First, this observation, coupled with the discovery that immunoreactive SRIF is found in abundant amounts in the pancreas and duodenum,[17,18] suggests that SRIF may have a physiologic role in the control of exocrine pancreatic secretions. Second, this observation is important if SRIF is to be used as a therapeutic agent. While the present study was performed in dogs, there are data in humans that also demonstrate a suppressive effect of SRIF on pancreatic secretions.[11] The observation that SRIF blocks gastric and biliary secretions,[5,11] together with the results of the present study, suggests that SRIF would seriously interfere with normal digestive processes if given with meals or during the four-hour period after a meal. These undesired effects would seriously curtail its usefulness in the treatment of diabetes mellitus.

The question can also be raised whether the previously noted blood-sugar-lowering effect of SRIF on the postprandial hyperglycemia of diabetics could in part be due to the effects of SRIF on digestion. In a study by Gerich et al.,[10] α-amino nitrogen levels 30 minutes and 60 minutes after a meal were significantly lower in diabetics who were treated with SRIF prior to a meal than in diabetics who were not given SRIF. This effect on α-amino nitrogen levels was not

observed in dogs treated with SRIF when a protein hydrolysate was administered directly into the duodenum,[7] suggesting that SRIF interferes with the digestion of ingested protein at a point prior to its absorption from the small intestine. Furthermore, Wahren and Felig have recently presented data that suggest that the improvement in glucose tolerance in diabetics who are given SRIF during an oral glucose tolerance test is due to an effect of SRIF on the gastrointestinal absorption of glucose rather than to an effect on the metabolism of glucose.[19]

Finally, we are led to the conclusion that, as the list of undesired effects of SRIF continues to grow, the therapeutic use of SRIF will depend on the development of analogues of SRIF that lack these unwanted effects.

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