

Circulating Somatostatin

Physiological Regulator of Pancreatic Function?

Klaus Gyr, Christoph Beglinger, Erich Köhler, Urs Trautzl, Ulrich Keller, and Stephen R. Bloom

Division of Gastroenterology and Department of Research, University Hospital, CH-4031 Basel, Switzerland, and Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom

Abstract

The present study was designed to determine whether somatostatin is released into the circulation in sufficient amounts to regulate exocrine and endocrine pancreatic function and to evaluate the possible role of somatostatin as a hormonal regulator of the pancreas. Mean plasma somatostatin levels (SLI) increased from 11 ± 2 pmol liter⁻¹ to peak concentrations of 18 ± 2 in six healthy male volunteers after a steak meal ($P < 0.05$). Infusion of somatostatin inhibited hormone-induced exocrine pancreatic secretion and suppressed cerulein-stimulated pancreatic polypeptide (PP) secretion, but did not significantly change arginine-stimulated insulin and glucagon release at mean plasma somatostatin concentrations within the range seen after a meal. The amount of somatostatin released after a meal thus was of sufficient magnitude to inhibit exocrine pancreatic function and PP release. On the other hand, basal and arginine-stimulated glucagon and insulin secretions were not significantly affected by these plasma concentrations of intravenous somatostatin suggesting that the exocrine pancreas might be more sensitive to somatostatin than the islet cells. We conclude that somatostatin in concentrations within the range seen after a meal is a potent inhibitor of stimulated acinar cell function in man. The findings support the hypothesis that somatostatin acts as a true hormonal regulator.

Introduction

Somatostatin, a tetradecapeptide originally isolated from hypothalamic extracts (1) and named for its ability to inhibit growth hormone secretion, has been identified mainly in the brain and the gut by immunocytochemical techniques. When infused at pharmacological doses, somatostatin has been shown to inhibit a variety of gastrointestinal functions (2, 3). Recently an inhibitory effect of somatostatin on fasting plasma insulin and glucagon levels has been demonstrated in man (4), when synthetic somatostatin-14 (S-14)¹ was infused at concentrations that produced a rise of plasma somatostatin levels comparable to physiological levels observed after a meal. Two further human studies

showed that such physiological amounts of S-14 as reaching the systemic circulation after a meal was sufficient to inhibit gastric acid secretion (5, 6). Taken as a whole, these studies suggest an hormonal role of S-14 on the gastrointestinal tract.

Whether the amount of somatostatin released into the blood after a meal is of sufficient magnitude to affect the exocrine pancreas, is not known since the hypothesis that circulating somatostatin represents a physiological inhibitory principle in exocrine pancreatic function, has not been thoroughly investigated. The present study was therefore undertaken to elucidate the inhibitory effects of circulating S-14 on exocrine and endocrine pancreatic function in man.

Methods

Materials. Synthetic S-14 was kindly provided by Diamalt, Munich, Federal Republic of Germany. Synthetic secretin (Sekretolin) was a gift of Hoechst Pharma, Zurich, Switzerland, and synthetic cerulein (Takus) of Carlo Erba Farmitalia, Berne, Switzerland.

Subjects. Six healthy fasting volunteers (all males, age 23–30) with no history of gastrointestinal or endocrine disorder were studied. Their average weight was 75 kg (range 64–88 kg). No subject was taking any medication and all gave written, informed consent to participate. Studies were approved by the local Ethical Human Research Committee.

Experimental procedure. Each subject was studied on seven different days in random order.

Meal study. After an overnight fast, all subjects ate a meal consisting of 200 g beefsteak, 150 g potatoes, a green salad, and 3 dl of apple juice within 20 min. The meal contained 45 g protein, 65 g carbohydrates, and 15 g fat (575 kcal). Blood samples were obtained from an indwelling catheter in a forearm before and in regular intervals after taking the meal for 3 h. The blood samples were collected into ice-chilled tubes containing 150 µg EDTA and 5,000 kallikrein inhibiting units (KIU) aprotinin per 5 ml blood. Samples were immediately centrifuged at 4°C and the plasma stored at -20°C until it was assayed.

Exocrine pancreatic secretion studies. After fasting overnight, the subjects swallowed a multilumen tube using standard methods previously described (7). Briefly, gastric and duodenal secretions were collected separately and continuously, and divided into 15-min aliquots. Polyethylene glycol (PEG) 4,000 was perfused as a nonabsorbable marker to correct for intestinal volume losses (2 ml min⁻¹ in a concentration of 2 g liter⁻¹). After an equilibration period, exocrine pancreatic secretion was stimulated with intravenous secretin (50 ng kg⁻¹ h⁻¹ = 16.4 pmol kg⁻¹ h⁻¹) throughout the experiments. Starting from the second hour, synthetic cerulein (a cholecystokinin analogue) was given simultaneously in a dose of 10 ng kg⁻¹ h⁻¹ (equating 7.4 pmol kg⁻¹ h⁻¹) for an additional 90 min. These doses have been shown before to produce submaximal pancreatic enzyme secretion (7, 8).

After pilot experiments with different doses of S-14, the following three tests were performed in random order: either 0.154 M NaCl (saline) or human S-14 in two different doses (50 and 100 ng kg⁻¹ h⁻¹ = 31 or 61 pmol kg⁻¹ h⁻¹, respectively) were infused through an indwelling catheter in one forearm throughout the experiments. Peptides were dissolved in saline containing 0.1% human albumin (Humanalbumin, SRK, Berne, Switzerland).

Address reprint requests to Dr. Gyr, Division of Gastroenterology, University Hospital, Basel, Switzerland.

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1. Abbreviations used in this paper: AUC, area under the curve; KIU, kallikrein inhibiting units; PP, pancreatic polypeptide; SLI, somatostatin-like immunoreactivity; S-14, somatostatin-14.

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Gastric and duodenal secretions were measured to the next ml; gastric juice samples were then assayed for hydrogen ion and PEG concentration, while the duodenal aliquots were assayed for bicarbonate (9), trypsin (10), amylase (11), and PEG (12) concentrations using standard methods previously described.

For somatostatin and pancreatic polypeptide (PP) determinations, blood samples were obtained at regular intervals as described above from a similar indwelling catheter in the opposite arm throughout the three experiments.

Islet cell function tests. Islet cell secretion was stimulated by intravenous arginine infusions (13). After an overnight fast, indwelling catheters were inserted into both cubital veins, one for blood sampling, one for infusions. 30 min later, blood samples were drawn at 15-min intervals over a basal period of 30 min, during arginine administration and for 30 min thereafter. Arginine-HCl (2.8 mmol kg⁻¹) diluted in 400 ml isotonic saline was infused over 30 min.

All subjects received either S-14 in the same doses mentioned above (31 or 61 pmol kg⁻¹ h⁻¹) or isotonic saline as a control throughout the experiments. S-14 and control infusions contained 0.1% human albumin. The three studies were done on separate days.

Islet cell hormones and blood glucose. Coded plasma samples were assayed for insulin (14), glucagon (14), somatostatin (15), and PP (16) concentrations by using previously described methods. Levels of SLI were measured in ethanol-extracted plasma by radioimmunoassay, which used an ¹²⁵I-tyrosine¹¹-somatostatin tracer and an antibody that detects the S-14 as well as the S-28 molecule (15). No other related peptide showed any significant cross-reactivity. Synthetic somatostatin-14 standards were used. The antibody bound 50% of labeled peptide in the assay system at a final dilution of 1:240,000 and 2 fmol of standard peptide reduced this binding to 40%. Extracted plasma samples (1.5 ml) were incubated in the assay system as described previously (15). Plasma glucose levels were measured enzymatically using a glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, OH).

Calculations and statistical analyses. In general, values are expressed as mean ± SEM unless stated otherwise. In exocrine pancreatic secretion studies, outputs were calculated for bicarbonate (millimoles), trypsin (KIU), and amylase (KIU). The PEG solution perfused to the duodenum served as nonabsorbable marker to calculate the duodenal volume for a given period (17). The recovery of PEG from duodenal samples averaged 72 ± 2%, whereas the average percentage of PEG recovered from the stomach was 3 ± 1%. Blood hormone levels were always assayed in duplicate. During somatostatin infusion studies, blood hormone concentrations of each infusion period were averaged and the mean value for each S-14 infusion period was compared with that during the corresponding NaCl infusion period. For exocrine pancreatic secretion studies, the cumulative responses to secretin alone or secretin plus cerulein were compared under the different treatments.

Several mathematical approaches were used in an attempt to analyse the effects of somatostatin on arginine-stimulated hormone responses. The area under the plasma concentration time curves (AUC) was calculated in each subject for all tests for blood glucose, insulin and glucagon concentrations. In addition, the peak plasma concentration (C_{max}) and times to reach peak plasma concentrations (T_{max}) were determined for each parameter in each subject. Furthermore, ratios of AUC glucose/AUC insulin were calculated. Group means and SEM were determined from these individual subject values and used for statistical analysis. The significance of differences between mean AUC, mean C_{max}, and mean T_{max} concentrations was tested using Student's paired *t* test; additionally, AUC of insulin, glucagon, and glucose concentrations were compared in a multivariate analysis of variance using a commercial SAS program. Differences were considered significant if *P* was < 0.05.

Results

Basal plasma somatostatin levels (SLI). Basal SLI levels were similar in the four experiments. The values are given in Table I.

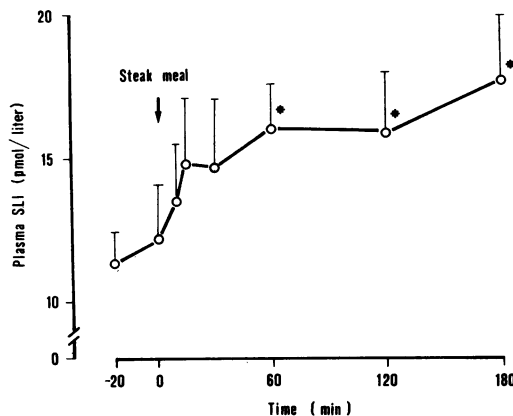


Figure 1. Effect of a steak meal on plasma SLI concentrations in six healthy volunteers (data are mean ± SEM). By 60 min after taking the meal, SLI concentrations were significantly greater than basal in every subject (**P* < 0.05 vs. basal concentration at 0 min).

Plasma SLI in response to a steak meal. The steak meal induced a significant increase over basal levels reaching a plateau at 60 min after taking the meal. The rise of SLI was sustained at 180 min (Fig. 1). The peak response over basal concentrations ranged from 4 to 12 and averaged 6 ± 1 pmol liter⁻¹, whereas the mean postprandial rise of SLI over 180 min amounted to an average of 4 ± 1 pmol liter⁻¹ (Table I). Gel-permeation chromatographical studies of pooled postprandial plasma samples revealed that roughly 50% of the postprandial SLI eluted at the position of S-14 and the remainder at the position of S-28 (15). Adapting these findings to the above SLI concentrations indicates that the postprandial S-14 concentrations range from 2 to 6 pmol liter⁻¹, with an average increase of ~ 3 pmol liter⁻¹.

Effect of intravenous S-14 on plasma SLI. Infusion of synthetic S-14 in two doses induced a dose-related increase in plasma SLI, whereas NaCl (control) did not significantly alter basal SLI levels (Fig. 2). When somatostatin was infused at a dose of 31 pmol kg⁻¹ h⁻¹, a mean rise of 4 ± 1 pmol liter⁻¹ was obtained in the venous circulation which was within the range seen after the steak meal. The higher dose of S-14 (61 pmol kg⁻¹ h⁻¹) produced circulating SLI that were above the mean postprandial S-14 concentrations (mean rise 7 ± 1 pmol liter⁻¹).

Table I. Increment in Plasma SLI Concentration in Response to Two Doses of Exogenous Human Synthetic S-14 and to a Meal

Dose of S-14	Basal SLI	Increment in plasma SLI
pmol/kg per h	pM	pM
0 (control)	12 ± 2	2 ± 1
31	12 ± 2	4 ± 1
61	12 ± 2	7 ± 1
Meal	11 ± 2	4 ± 1

The increment in SLI concentration was calculated by subtracting basal values from all plasma concentrations following meal stimulation or S-14 infusions. The meal response represents the mean of six samples drawn over a period of 180 min after taking the meal, whereas the response to S-14 infusions represents the average of five blood samples drawn at 30-min intervals.

Secretin	16.4 pmol/kg/h
NaCl	Cerulein 7.4 pmol/kg/h
NaCl or S-14	

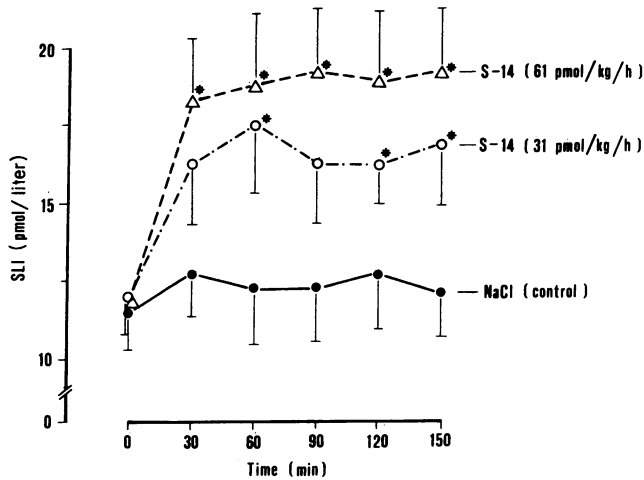


Figure 2. Effect of two doses of intravenously infused human synthetic somatostatin-14 or 0.154 M NaCl (control) on mean (\pm SEM) plasma SLI concentrations in six healthy volunteers intubated with a multilumen duodenal tube to measure stimulated exocrine pancreatic secretion. S-14 infusion produced a dose-related increase in mean plasma SLI above NaCl control ($*P < 0.05$).

Effect of intravenous S-14 on exocrine pancreatic secretion. Secretin ($16.4 \text{ pmol kg}^{-1} \text{ h}^{-1}$) produced, as expected, an immediate stimulation of pancreatic fluid and bicarbonate secretion. The addition of cerulein in a submaximal dose ($7.4 \text{ pmol kg}^{-1} \text{ h}^{-1}$) elicited a strong pancreatic trypsin and amylase response, which for trypsin secretion had a tendency to decline towards the end of the experiment (Fig. 3). S-14 produced a dose-dependent inhibition of pancreatic trypsin and amylase outputs (Fig. 3). The cumulative amylase and trypsin outputs were significantly suppressed by both doses of S-14, whereas the cumulative bicarbonate output was only suppressed by the upper dose of S-14 (Table II). The bicarbonate concentration was dose dependently inhibited by the two S-14 doses (Table III). Duo-

Table II. Cumulative Pancreatic Secretory Responses to Combined Stimulation with Secretin and Cerulein

	S-14, pmol/kg per h		
	0 (NaCl)	31	61
Bicarbonate output (mmol/90 min)	65 \pm 8	58 \pm 9	44 \pm 5*
Amylase output (KIU/90 min)	60 \pm 11	35 \pm 6*	28 \pm 3*
Trypsin output (KIU/90 min)	5.0 \pm 0.7	2.5 \pm 0.6 [‡]	1.7 \pm 0.6 [‡]

For each test and each test person, the sum of the secretory responses to combined stimulation with secretin and cerulein was taken. Group means (\pm SEM) were calculated from these summated responses. $n = 6$, * $P < 0.05$ compared to control (no S-14), [‡] $P < 0.01$.

Secretin	16.4 pmol/kg/h
NaCl	Cerulein 7.4 pmol/kg/h
NaCl or S-14	

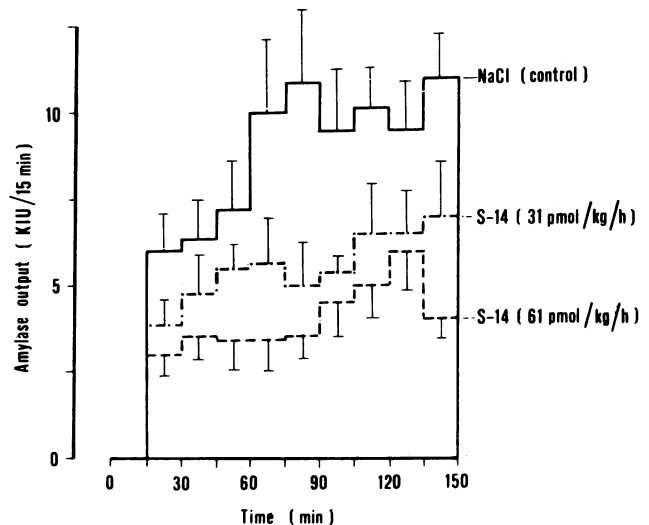
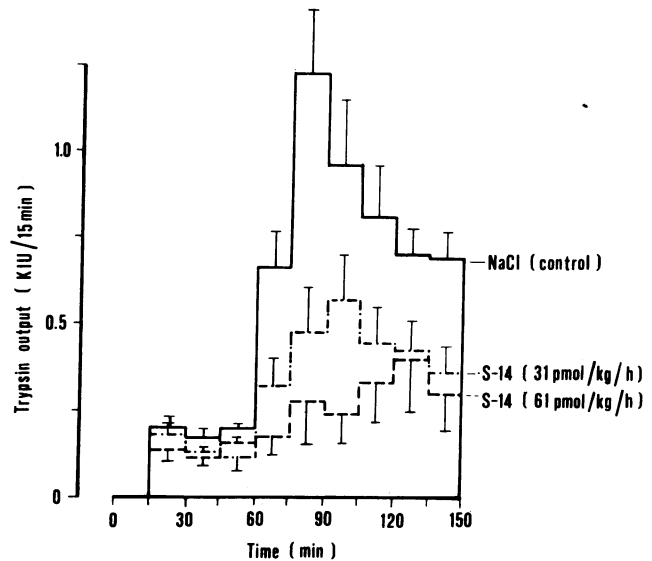


Figure 3. Trypsin and amylase outputs (KIU/15 min) in response to combined stimulation with secretin and cerulein with and without background infusion of synthetic S-14. The symbols in the key indicate background doses of S-14. Data are mean \pm SEM in six healthy volunteers.

denal fluid output was slightly decreased during S-14 infusion, this was, however, only significant for the higher dose ($61 \text{ pmol kg}^{-1} \text{ h}^{-1}$).

Effect of intravenous S-14 on cerulein-stimulated PP release. Mean fasting plasma levels of PP were comparable in the different experiments (Fig. 4). Cerulein infusion produced a significant increase in plasma PP concentration that was suppressed by both doses of S-14, but no dose dependency was observed. Statistical analyses were done on logarithmically transformed data, because plasma PP data fitted a log normal distribution.

Table III. Effect of S-14 on Mean (\pm SEM) Duodenal Fluid Output and Duodenal Bicarbonate Concentration in Six Healthy Volunteers

S-14 <i>pmol/kg per h</i>	Fluid output <i>ml/15 min</i>		HCO ₃ concentration <i>mmol/liter</i>
0 (NaCl)	125 \pm 9	86 \pm 3	
31	116 \pm 8	81 \pm 2*	
61	97 \pm 7*	72 \pm 2 [‡]	

Fluid output and bicarbonate concentration were calculated from six 15-min collection periods during combined stimulation with secretin and cerulein.

* $P < 0.05$ vs. NaCl control, [‡] $P < 0.01$ vs. control.

Effect of S-14 on islet cell function. Arginine infusions produced a rapid and significant ($P < 0.01$) increase in plasma glucagon concentrations. Both doses of S-14 failed to affect basal and arginine-stimulated plasma glucagon levels (Table IV). While 31 $\text{pmol kg}^{-1} \text{h}^{-1}$ S-14 had no significant effect on fasting plasma insulin concentrations, the higher dose of 61 $\text{pmol kg}^{-1} \text{h}^{-1}$ reduced fasting insulin concentrations from 22 ± 4 to $14 \pm 3 \mu\text{e ml}^{-1}$ at 30 min ($P < 0.05$). Both doses slightly reduced the early insulin peak after 15 min of arginine stimulation, but plasma insulin responses were not statistically different from control values in a variety of statistical tests (Fig. 5).

Basal PP concentrations were not significantly decreased by either dose of S-14 infusion. Arginine failed to increase plasma PP levels in any treatment group.

Effect of S-14 on plasma glucose. Fasting plasma glucose measurement for the different experiments ranged from 3.9 to 5.5 mmol liter^{-1} . Plasma glucose concentrations had a tendency to increase during the initial 30 min of S-14 administration, this was, however, not significant for any dose. During arginine infusion, plasma glucose increased significantly with both doses of S-14 (Table IV; $P < 0.05$), but the area under the curve of glucose concentrations did not show any significant difference from control experiments.

Discussion

Our data indicate that infusion of exogenous synthetic S-14 at concentrations that produce plasma levels equal to postprandial levels causes (a) Inhibition of exogenous secretin and cerulein-

Secretin	16.4 pmol/kg/h
NaCl	Cerulein 7.4 pmol/kg/h
NaCl or S-14	

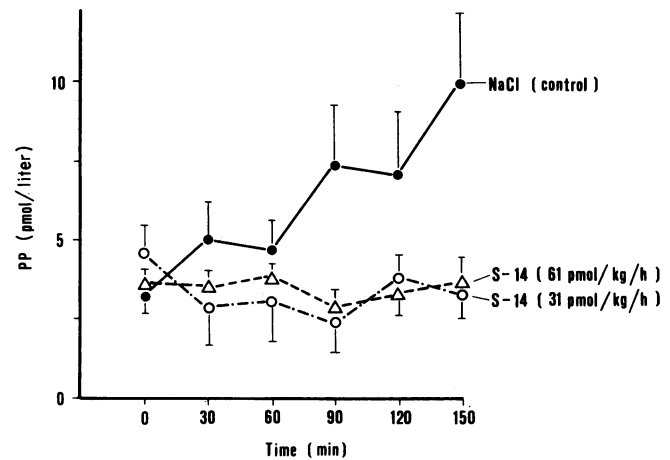


Figure 4. Effect of intravenous S-14 on cerulein-stimulated PP release. $n = 6$, data are mean \pm SEM. Both S-14 doses fully suppressed ($P < 0.05$) cerulein-stimulated PP release.

induced duodenal bicarbonate and fluid secretion, (b) Marked suppression of cerulein-stimulated trypsin and amylase secretion, and (c) Total suppression of cerulein-stimulated PP release.

Several studies have shown that pharmacological amounts of exogenous somatostatin inhibit exocrine pancreatic secretion (18, 19). Our interest was to determine if the increment in circulating plasma SLI after a steak meal is of sufficient magnitude to affect the exocrine and endocrine pancreas. The present study indicates that an intravenous infusion of synthetic human S-14 produced mean circulating plasma SLI concentrations that were within the range observed after a steak meal, and which significantly inhibited pancreatic functions. These findings support the hypothesis that somatostatin acts as a true hormonal regulator of the exocrine pancreas in man.

There are now numerous reports of postprandial increases of circulating SLI in response to varying test meals in man (4, 16, 20–23). Our results closely agree with other reports showing a similar postprandial SLI increase (4, 5, 16). Gel-filtration chromatography performed in this laboratory, indicated that roughly 50% of the postprandial SLI corresponded to S-14 in the volunteers under study (15). Infusing 31 $\text{pmol kg}^{-1} \text{h}^{-1}$ of S-14

Table IV. Plasma Concentrations of Glucagon, PP, and Glucose in Response to Arginine Stimulation in Six Healthy Volunteers (Mean \pm SEM)

Dose of S-14 <i>pmol kg⁻¹ h⁻¹</i>	Glucagon		PP		Glucose	
	Basal (0 min) <i>pg/ml</i>	Arginine (15 min) <i>pg/ml</i>	Basal (0 min) <i>pmol/liter</i>	Arginine (15 min) <i>pmol/liter</i>	Basal (0 min) <i>mmol/liter</i>	Arginine (15 min) <i>mmol/liter</i>
0 (NaCl) = control	32 \pm 2	207 \pm 69*	8 \pm 3	8 \pm 2	4.7 \pm 0.1	4.7 \pm 0.2
31	32 \pm 2	208 \pm 58*	6 \pm 1	5 \pm 1	4.6 \pm 0.3	5.4 \pm 0.3*
61	33 \pm 6	206 \pm 68*	6 \pm 1	5 \pm 1	4.7 \pm 0.2	5.5 \pm 0.2*

* $P < 0.01$ vs. basal.

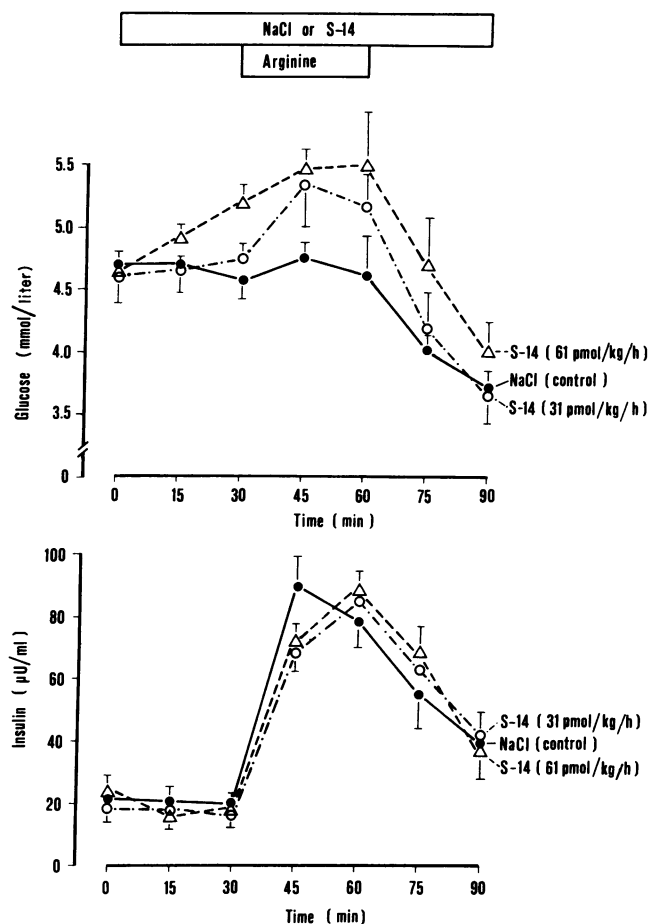


Figure 5. Effect of intravenous S-14 on arginine-stimulated plasma glucose and insulin release. $n = 6$, data are mean \pm SEM.

produced plasma S-14 concentrations which mimicked the postprandial results. The effect of such a small dose of exogenous S-14 on stimulated exocrine pancreatic secretion has, however, not been reported previously.

The mechanism by which somatostatin inhibits exocrine pancreatic secretion is unknown. S-14 could directly act on acinar cells to block the effects of peptides and acetylcholine; it could release another inhibitor that might have these actions or it could decrease the levels of regulatory peptides and acetylcholine by blocking their secretion. At present, there is no evidence that S-14 releases any other potential inhibitors. PP is one of the regulatory peptides that inhibit exocrine pancreatic secretion at plasma concentrations termed "physiological" and is therefore considered a prime candidate for a role as inhibitory regulator of exocrine pancreatic function (24). However, PP levels are suppressed by infusion of S-14 at doses producing postprandial SLI concentrations as indicated in this study, making it unlikely that the reduced pancreatic secretory response was due to PP release. A recent study from the Toulouse group has demonstrated somatostatin receptors at the human acinar cell indicating that S-14 does have a direct effect on exocrine pancreatic cells (25). In this *in vitro* system, a biphasic effect was observed with S-14 with stimulation of acinar cell function at very low doses and inhibition at higher doses of somatostatin. Therefore, the exact mechanism by which somatostatin inhibits exocrine pancreatic function *in vivo* cannot be identified at present.

Endocrine action of S-14 via the systemic circulation is supported by several recent studies (4–6, 16). Colturi and coworkers (5) and Holst's group (6) have both independently studied the effects of low dose infusions of somatostatin on meal-stimulated gastric acid and pancreatic islet cell function. Both demonstrated that these low dose S-14 infusions inhibited basal and food-stimulated gastric acid secretion and endocrine pancreatic function suggesting that somatostatin acts as a humoral regulator in man. In another study, low dose somatostatin infusions exerted profound metabolic effects (4). In this present study, an intravenous infusion of 31 pmol kg⁻¹ h⁻¹ of synthetic S-14 which led to plasma SLI concentrations within the range observed after a meal failed to affect basal and arginine-stimulated islet cell function.

Our plasma insulin data do not support the previous mentioned studies which show the inhibition of postprandial insulin (5, 6) and glucagon release (5), but in which doses of 85 pmol kg⁻¹ h⁻¹ (or 10 µg h⁻¹) or 123 pmol kg⁻¹ h⁻¹ of S-14 were used to simulate the postprandial somatostatin release. Furthermore, both studies do not give any details regarding the proportion of the postprandial SLI corresponding to S-14. Our S-14 infusions may have been too low to suppress basal and stimulated glucagon and insulin secretion. Thus, the exocrine pancreas might be more sensitive to circulating S-14 than islet cell function.

The present study confirms previous reports that part of the circulating SLI is due to the presence of circulating S-28 (26). Especially, it has been shown that S-28 increases after a meal in man (20). Efforts to study the relative biological potencies of S-14 and S-28 have, however, yielded conflicting results (27–30) and might be species dependent. In man, the infusion of equimolar doses of exogenous S-14 and S-28 produced similar inhibition of meal-stimulated insulin, glucagon, and PP release (30).

There are several reasons why we preferred to use S-14 for infusion. First, the human pancreas contains mainly S-14 (31). Second, as S-14 and S-28 exert similar inhibitory effects in man, infusion of S-14 should therefore give qualitatively and probably also quantitatively valid results. Third, it is probably impossible to mimic the adjusted molar amounts of both forms of the peptide to test this hypothesis conclusively. It would, however, be necessary to prove this assumption by further pursuit of the S-28 hypothesis.

In summary, we conclude that exogenous human synthetic S-14 producing postprandial SLI concentrations is a potent inhibitor of stimulated exocrine pancreatic secretion. Whether S-14 is a physiologically important component of a negative feedback loop that regulates pancreatic secretion after feeding, remains to be defined.

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