

Is somatostatin a humoral regulator of the endocrine pancreas and gastric acid secretion in man?

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SUMMARY The effect of low dose infusions of somatostatin on meal stimulated gastric acid secretion was studied in eight healthy volunteers by intragastric titration after a peptone test meal with radioimmunoassay control of the plasma concentrations of somatostatin and the pancreatic hormones glucagon and insulin. Infusion of somatostatin in a dose of 100 ng/kg/h, resulting in a plasma concentration of 13.4 ± 2.1 pmol/l, inhibited acid secretion significantly, and in a dose of 800 ng/kg/h, with corresponding plasma concentration of 66.5 ± 12.0 pmol/l the acid secretion was virtually abolished. Plasma concentrations of insulin and pancreatic glucagon decreased significantly during infusion of 200 ng/kg/h (24.5 ± 7.5 pmol/l) and glucose concentrations increased. Serum gastrin was only significantly decreased during the highest dose of somatostatin. The range of plasma somatostatin concentrations obtained with the lower doses correspond to reported physiological variations. The results support the concept that somatostatin participates in the hormonal control of the pancreatic endocrine and the acid secretion.

The particular localisation and shape of the somatostatin-producing D-cells in the gastric epithelium and the pancreatic islets suggests that somatostatin acts as a paracrine messenger.¹⁻⁴ Studies in dogs by Schusdziarra *et al*⁵ however, have indicated that somatostatin may act as a true hormone with a regulatory role in the homeostasis of ingested nutrients. Furthermore, studies in different experimental animals⁶⁻¹³ and human subjects¹⁴⁻²⁰ have shown that exogenous somatostatin is a potent inhibitor of gastric acid secretion and of the endocrine pancreas, and it has been suggested that somatostatin participates in the physiological control of these secretions as a hormonal mediator.^{5 20-21} The reported effects of somatostatin may be pharmacological, however, because plasma concentrations were generally not controlled.

The present study deals with the effect of increasing doses of somatostatin on meal stimulated gastrin and gastric acid secretion under immunochemical control of the plasma concentrations of somatostatin. In addition we studied the effect on

the pancreatic hormones glucagon and insulin, the secretion of which under these circumstances is moderately stimulated.

Methods

SUBJECTS

Eight healthy volunteers, four men and four women, median age 33 years (range 24-44 years) were studied. All gave informed consent. The study was approved by the ethical committee of Copenhagen County.

EXPERIMENTAL PROCEDURE

Each subject was studied on three separate days. After an overnight fast a Levin tube with a thin welded polyvinyl tube was placed in the stomach under fluoroscopic control. The stomach was emptied. The gastric acid secretion was measured by automatic intragastric titration, using a modification of the method described by Fordtran and Walsh.²² A peristaltic pump was used to mix the stomach contents and to aspirate and reinfuse samples of the stomach contents to and from a titration chamber in which the pH-probe was placed. The pH-probe was connected with an autotitrator (Radiometer, Copenhagen) which maintained a constant pH of 5.5

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in the stomach by infusing 0.5 N NaHCO₃ to the titration chamber. The cumulative volume of bicarbonate used was recorded on a pen writer. The number of mmoles of sodium bicarbonate required per hour to maintain pH at 5.5 is equal to the amount of acid secreted (expressed as mmoles HCl per hour). A test meal, 300 ml of a 10% peptone solution (Peptone Orthana, Orthana Kemisk Fabrik, Kastrup, Denmark) with pH 5.5 was instilled into the stomach, and infused constantly at a rate of 200 ml/h via the polyvinyl tube to maintain a constant volume of the test meal in the stomach during the study.

CONTROL STUDY

On the first day each subject was studied for four hours during intravenous infusion of physiological saline, in order to record the time course of test meal stimulated acid secretion.

SOMATOSTATIN STUDY

On two separate days each subject was studied for three hours. During the first hour physiological saline was infused intravenously and during the next two hours intravenous infusion of somatostatin in increasing doses was given in random order as shown in the Table.

Somatostatin (synthetic somatostatin, Eluka-AG, Buchs, Switzerland) was dissolved in 1 mmol/l HCl and diluted in 0.9% saline containing 1% human albumin (Nordisk Albumin, Denmark) and stored at -20°C. Before every infusion the solution was subjected to sterile filtration by means of Millieux-GS single use filter, 0.22 µm (Millipore, SA, 67 Moijheim, France).

BLOOD SAMPLES

For analyses of somatostatin, glucose, glucagon, insulin and gastrin blood samples were drawn into chilled tubes containing EDTA and aprotinin (Trasylol, Bayer, GFR 500 KIU/ml blood) from a cubital vein every 15 minutes throughout the study. The samples were centrifuged immediately after at 4°C, and plasma stored at -20°C until assay.

Table *Somatostatin study. During intragastric titration in eight healthy human subjects somatostatin was given in different, increasing doses as shown below in random order on two separate days*

Minutes	Intravenous somatostatin µg/kg/h	
	A	B
0-60	0	0
60-120	0.1	0.2
120-180	0.4	0.8

LABORATORY ANALYSES

Somatostatin, glucagon, insulin, and gastrin concentrations were measured radioimmunochemically. For somatostatin, antiserum R213, which is directed against the somatostatin sequence 5-10, was used in a previously described radioimmunoassay^{23, 24} and for determination of glucagon, the glucagon antiserum 4305, which is directed against the 19-29 sequence of glucagon²⁵ was used. The gastrin antiserum used, 2604-8, is highly specific for gastrin and binds the three large molecular forms of gastrin with equimolar potency.²⁶ Insulin was determined as described by Albano²⁷ and blood-glucose by the hexokinase method.²⁸

CALCULATIONS

Acid secretion during somatostatin infusion, given as meq H⁺/30 min, is based on the last 30 min of each infusion period, when the plasma concentration of somatostatin had reached a plateau. For the same reason, all radioimmunoassay results including the somatostatin values are given as the mean of the values from the last 30 min of each infusion period or, for the control experiment, as the mean of the values from the second and third hour. Statistical evaluation of the data was performed using the Wilcoxon's test for pair differences, if preceding analysis of variance (Friedman's two-way analysis) allowed rejection of the null-hypothesis.

Results

The cumulated gastric acid secretion of the control study is shown in Figure 1. The secretory rate was constant throughout the study, even during the fourth hour. The concentration of somatostatin in plasma remained constant throughout the control study (mean value: 5.3±0.2 pmol/l).

The gastric acid secretion during the different somatostatin infusions and corresponding plasma concentrations are shown in Figure 2. A significant inhibition of acid secretion is seen already during infusion of somatostatin in a dose of 100 ng/kg/h with corresponding mean plasma concentration of 13.4±2.1 pmol/l. During infusion of the highest dose of somatostatin resulting in mean plasma concentrations of 66.5±12.0 pmol/l the gastric acid secretion was nearly abolished.

Plasma insulin concentrations decreased with increasing doses of somatostatin and the same was true for pancreatic glucagon as shown in Figure 3. Significant decreases were observed with doses >100 ng/kg/h.

No significant alteration in serum gastrin was seen during the first three doses of somatostatin, but

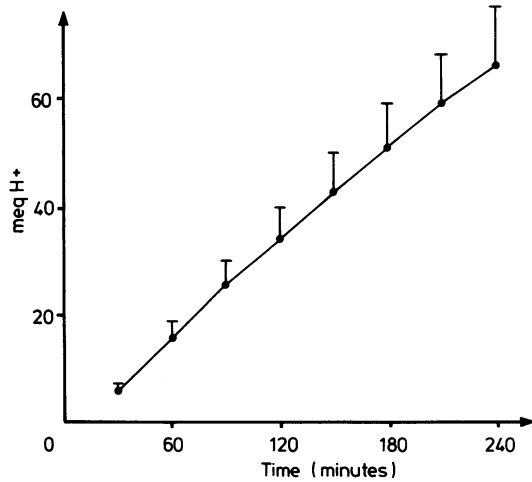


Fig. 1 Control study. Cumulated gastric acid secretion (meq H⁺) during intragastric titration with a peptone meal.

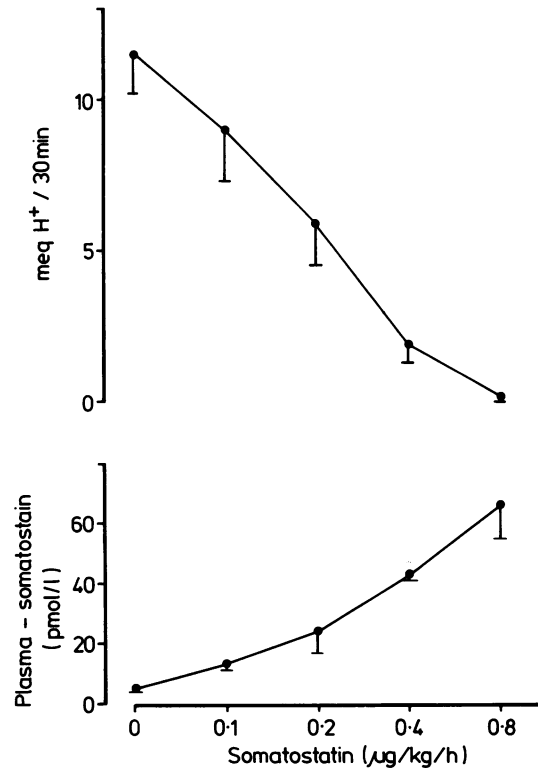


Fig. 2 Gastric acid secretion (meq H⁺/30 minutes) and corresponding plasma somatostatin concentrations during intragastric titration and iv infusion of somatostatin in increasing doses (0.1, 0.2, 0.4 and 0.8 µg/kg/h) in eight healthy subjects. Mean ± SEM.

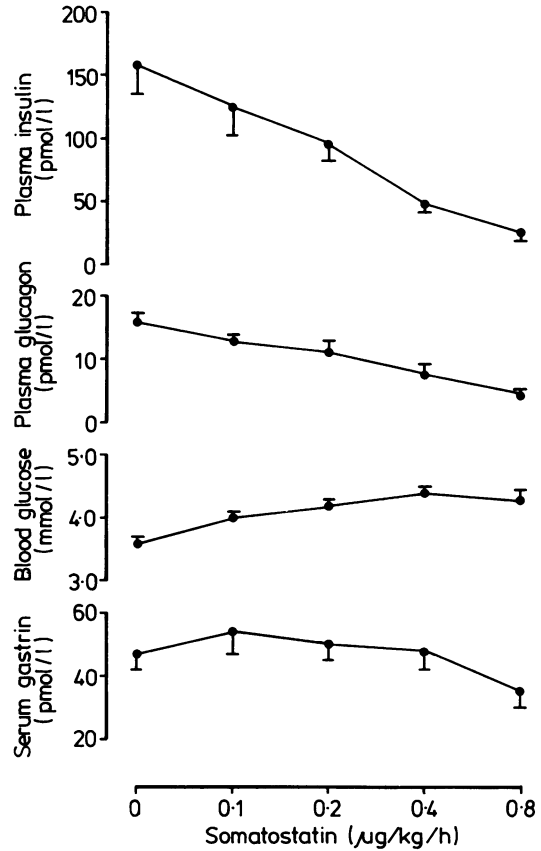


Fig. 3 Plasma insulin, plasma glucagon, blood glucose and serum gastrin during intragastric titration and iv infusion of somatostatin in increasing doses. Mean ± SEM of the mean values from the last 30 min of each infusion period or, for the control experiment, the mean value from the second and third hour of intragastric titration.

during the highest dose of somatostatin a significant decrease ($p < 0.05$) was noted.

Blood glucose increased significantly ($p < 0.01$) during all somatostatin doses.

Discussion

The study confirms that exogenous somatostatin is a potent inhibitor of gastric acid secretion in man,¹⁵⁻¹⁹ and shows that somatostatin inhibits acid secretion in a dose dependent manner. The doses used in the present study are lower than those of previous studies. The minimum dose required for significant inhibition was 100 ng/kg/h, resulting in a plasma concentration of 13.4 pmol/l. The increase, which is less than 10 pmol/l, may be considered physiological

because similar increases have been observed in relation to fasting, stress, meal ingestion, hypoglycaemia,²⁹⁻³⁰ (Holst *et al*, unpublished studies of plasma somatostatin responses to starvation, exercise, and mixed meals). The reported increases have been in the order of 10–30 pmol/l, calculated as somatostatin 1–14; in this laboratory, the meal induced increases in normal subjects average 21 pmol/l. It has been reported that part of the total concentration of somatostatin like immunoreactivity in peripheral plasma is owing to the presence of the 28-amino acid peptide somatostatin 1–28.³¹ Possibly, meal induced increases include this molecular form of somatostatin, too.³² Somatostatin 1–28, however, is also a potent inhibitor of acid secretion.^{33 34} Our exclusive use of somatostatin 1–14 for infusion should therefore give quantitatively valid results.

Previous findings indicate that somatostatin inhibits gastrin release in animals⁸⁻¹⁰ and in man^{14 15 17 19} and it has been suggested that the inhibitory effect of somatostatin on gastric acid secretion is caused by inhibition of gastrin release. Jansen and Lamers,¹⁹ however, found that inhibition of gastrin release by somatostatin could not fully account for the inhibition of bombesin stimulated gastric acid secretion, and Vatn *et al*¹⁶ found no changes in basal plasma gastrin during somatostatin infusion. In the present study there was no correlation between acid inhibition and serum gastrin. Thus low doses of somatostatin inhibits gastric acid secretion without affecting circulating gastrin, suggesting another mode of action, perhaps directly on the parietal cell.³⁵

The secretion of the pancreatic hormones insulin and glucagon, estimated on the basis of their peripheral plasma concentration, showed the same sensitivity to somatostatin as gastric acid secretion. Like in the gastric mucosa, somatostatin secreting cells are found locally in the pancreatic islets where they are believed to exert a paracrine control of islet function.¹ But our results show that circulating somatostatin may very well influence pancreatic endocrine secretion in an endocrine manner. In a recent study²⁰ the effects of low doses of somatostatin on the endocrine pancreas were less pronounced than those observed here. Undoubtedly the slight stimulation of the endocrine pancreas caused by the peptone meal administered in the present study facilitated the demonstration of the inhibitory effect of somatostatin.

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