Effect of Low-Dose Somatostatin Infusion on Pancreatic and Gastric Endocrine Function in Lean and Obese Nondiabetic Human Subjects

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SUMMARY

The present study was designed to compare, in lean and obese nondiabetic subjects, basal and postprandial levels of peripheral venous plasma insulin, glucagon, gastrin, pancreatic polypeptide (PP), glucose, triglycerides, and somatostatin-like immunoreactivity (SLI) during the infusion of synthetic somatostatin-14 or saline. Thirty-five minutes before the ingestion of the test meal, an infusion of synthetic somatostatin-14 was started at a rate of 0.5 ng/kg · min and was increased to 1.0 ng/kg · min 30 min after consumption of the meal and lasted for another 90 min. During the infusion of saline, basal peripheral vein levels of insulin, gastrin, and triglycerides were elevated in obese subjects, whereas basal plasma SLI levels were significantly lower compared with the lean controls. Basal glucagon and PP levels were similar in both groups. After the ingestion of the meal, augmented concentrations of insulin and gastrin were observed in the obese subjects, whereas postprandial SLI and PP levels were reduced. Chromatography of fasting plasma revealed all measurable SLI to be confined to the void volume fractions of a Bio-Gel P-10 column. The rise in SLI after the meal was due to an increase of SLI co-eluting with somatostatin-28 and somatostatin-14. During the infusion of somatostatin, only basal insulin levels were significantly lower in the obese subjects, whereas no change of any basal hormone level was observed in the lean group. During the infusion of somatostatin, SLI levels were elevated by 20–30 pg/ml in both groups compared with the saline controls. During the infusion rate of 0.5 ng/kg · min, only postprandial PP levels were reduced significantly in the obese group, while all the other parameters were unaffected in both groups. At 1.0 ng/kg · min, postprandial plasma insulin, PP, and gastrin levels were reduced significantly in the obese group, and a transient decrease of glucagon was observed in both groups in comparison with the respective saline control experiments. These data demonstrate an augmented inhibitory effect of intravenously infused synthetic somatostatin on basal and postprandial insulin and postprandial gastrin and PP release in obese subjects. This increased responsiveness to somatostatin suggests that reduced postprandial immunoreactive SLI levels in the obese group might represent true biologically relevant hyposomatostatinemia, facilitating the hypersecretion of some but certainly not all gastric and pancreatic endocrine factors in obesity. DIABETES 1985; 34:595–601.

Somatostatin, which is present in large quantities in the gastrointestinal tract and pancreas,[1-6] has been demonstrated to exert potent inhibitory effects on numerous gastrointestinal and pancreatic exo- and endocrine functions when infused in high, presumably pharmacologic doses (for review see ref. 7). The release of somatostatin-like immunoreactivity from stomach and pancreas after the ingestion of carbohydrate, fat, protein, and mixed meals and its postprandial rise in the peripheral circulation[8-14] support the hypothesis that peripherally circulating somatostatin acts as a true hormone.[15] Evidence for the hormonal role of somatostatin has initially been demonstrated in dogs, in which it retards nutrient entry and attenuates postprandial release of insulin, gastrin, pancreatic polypeptide, and enteroglucagon.[16-18] Subsequent studies have shown that in several species including man very low and presumably physiologic doses of somatostatin have an inhibitory effect on gastric and pancreatic exo- and endocrine functions, and gallbladder and gastric emptying.[19-26]

In various animal models of obesity associated with hyperinsulinemia (as in the *ob/ob* mouse), pancreatic somatostatin content is reduced,[27-29] whereas in the obese Zucker rat increased pancreatic somatostatin content has been demonstrated.[30,31] We have recently shown that obese Zucker rats display a greater sensitivity to the insulin-inhibitory action

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of low-dose somatostatin when compared with their lean littermates.[32] The present study was designed to determine the effects of low-dose somatostatin infusion on basal and postprandial hormone release in obese nondiabetic subjects in comparison to a normal-weight control group.

MATERIALS AND METHODS

The studies were performed in 10 normal subjects (7 males and 3 females), aged 20–49 yr, who were within 10% of their ideal body weight (54–80 kg, mean 70.7 kg) and in 17 obese subjects (7 males, 10 females), aged 17–52 yr, body wt 90–148 kg (mean 113.5 kg), which is on an average 79% over ideal body weight. Pathologic glucose metabolism was excluded in all subjects by an oral glucose tolerance test (100 g glucose). All subjects gave their informed consent.

In randomized order, either saline or synthetic somatostatin-14 (Serono, Freiburg, FRG) was infused via a forearm vein at a rate of 0.5 ng/kg · min starting 35 min before the ingestion of the test meal; 30 min thereafter the infusion rate was increased to 1.0 ng/kg · min until 120 min. All infusion solutions contained 0.5% human serum albumin, which prevents adsorption of somatostatin to the glassware and the tubing system employed. The test meal consisted of 200 g ground beef, 30 g bread, and 20 g sucrose dissolved in 200 ml water (total of 690 kcal, 60% fat, 22% protein, and 18% carbohydrate) and was ingested within 10 min.

Blood samples were obtained from a contralateral forearm vein via an indwelling catheter and collected into tubes containing 3 mg EDTA and 1000 KIU Trasylol. All samples were kept chilled in an ice bath until centrifugation at 2000 rpm for 15 min at 4°C. The separated plasma was stored at −20°C until time of assay.

Plasma insulin,[33] glucagon,[34] gastrin,[35] and triglyceride levels[36] were determined as described elsewhere. Plasma somatostatin-like immunoreactivity was determined by a modification of a previously described method[37] employing ^{11}Tyr-somatostatin as tracer, antibody 80 C (generously provided by Dr. R. H. Unger, Dallas, Texas), and a preincubation of sample (100 μl) and antibody (100 μl) in a total volume of 600 μl/tube for 48 h, after which time period incubation was continued with tracer for another 24 h at 4°C. Separation of bound from free somatostatin was performed with dextran-coated charcoal. All samples were analyzed in the same assay. The intraassay coefficient of variation was 5 ± 0.8% for concentrations of plasma SLI between 60 and 200 pg/ml. Recovery of synthetic somatostatin-14 and -28 added at concentrations of 25, 50, 75, 100, 150, and 200 pg/ml to plasma of lean and obese subjects was 94 ± 6.5% (lean) and 96 ± 5.7% (obese), respectively. The recovery was largely identical up to triglyceride concentrations of 3.5 mmol/L. The lower sensitivity of the assay was 20 pg/ml. The ID_{50} was 130 pg/ml. This method resulted in higher basal SLI levels compared with extraction procedures; however, postprandial increments in response to carbohydrate and fat test meals[38] were comparable to those observed after extraction of plasma samples.[14] Antibody 30K for glucagon measurements was also generously provided by Dr. R. H. Unger. Pancreatic polypeptide was determined as described elsewhere.[39] Standard human pancreatic polypeptide (hPP) and rabbit anti-hPP-serum were a generous gift from Dr. R. E. Chance of Eli Lilly and Company, Indianapolis, Indiana. Glucose was measured by the glucose-oxidase method using a Technicon autoanalyzer (Tarrytown, New York). Three-milliliter aliquots of plasma were subjected to gel chromatography at room temperature on a Bio-Gel P-10 column (1.2 × 50 cm) using 0.1 M NH_4HCO_3 buffer (pH 8.8) for elution as described previously.[40] The samples of four lean and four obese subjects obtained at time points 0, 10, and 90 min after ingestion of the meal were chromatographed. For statistical comparison, analysis of variance was employed and P-values of 0.05 or less were considered significant. Incremental values were calculated as the sum of the differences between each time point and the mean of the three baseline values.

RESULTS

Effect of somatostatin in normal subjects. In the control experiments, plasma SLI levels rose significantly within 10 min of the ingestion of the meal from a mean baseline of 118 ± 9 pg/ml to 114 ± 12 pg/ml ($P < 0.02$) and reached a maximum of 165 ± 18 pg/ml at 70 and 90 min (Figure 1). At all time points except for the 30- and 40-min values, plasma SLI levels were significantly elevated above basal. During

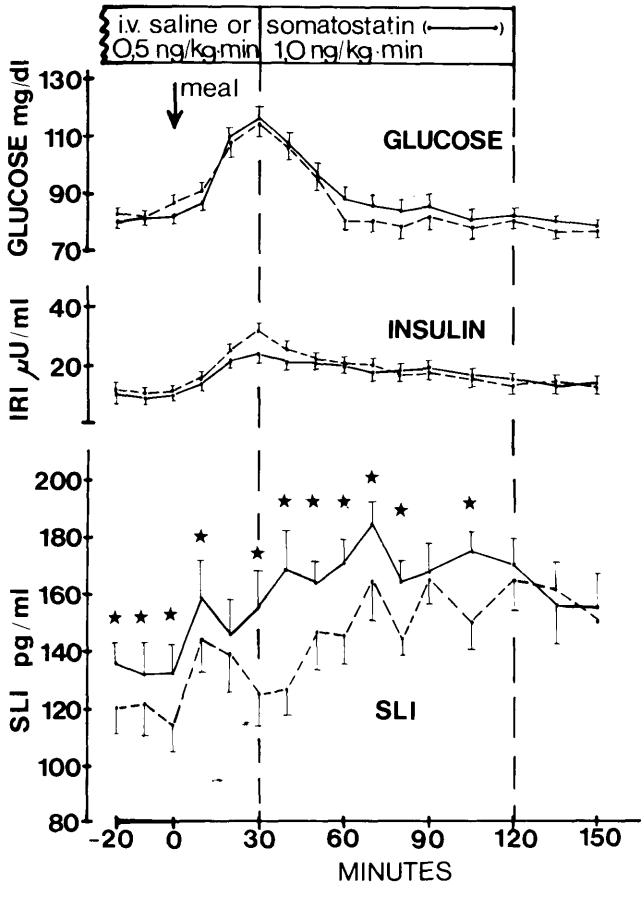

FIGURE 1. Effect of intravenously infused synthetic somatostatin-14 (●——●), which started 35 min before the ingestion of the test meal (M) at a dose of 0.5 ng/kg · min and was continued 30 min thereafter with a dose of 1.0 ng/kg · min, or saline (●------●), which was given alternatively throughout the entire experimental period, on basal and postprandial peripheral venous plasma levels of somatostatin-like immunoreactivity (SLI), insulin (IRI), and glucose in a group of 10 lean subjects. Mean ± SEM; ★ indicates significant difference of $P < 0.05$ versus saline controls.

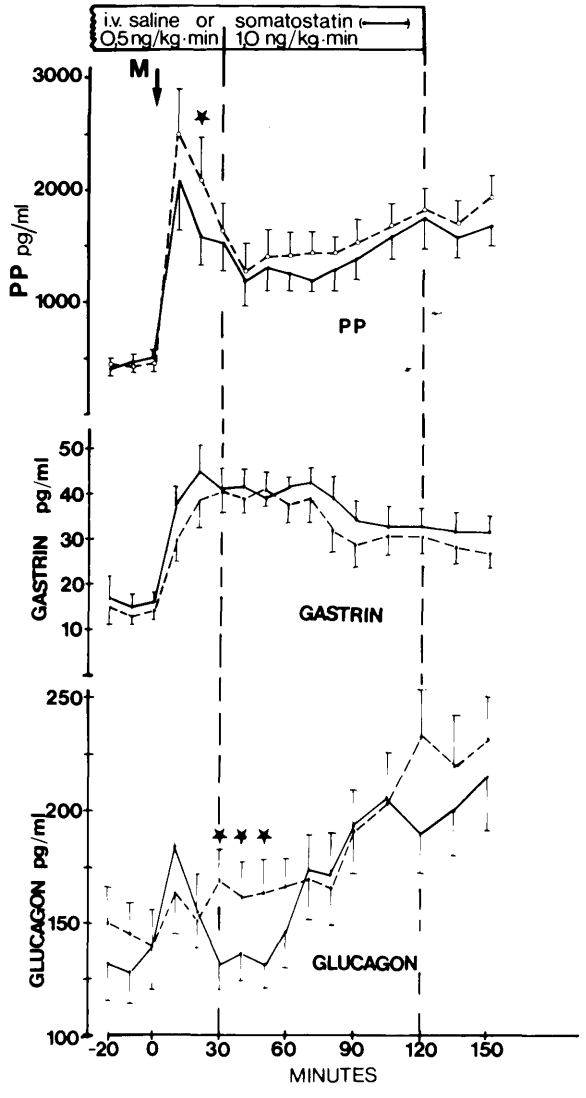

FIGURE 2. Effect of intravenously infused synthetic somatostatin-14 (●——●), which started 35 min before the ingestion of the test meal (M) at a dose of 0.5 ng/kg · min and was continued 30 min thereafter with a dose of 1.0 ng/kg · min, or saline (●------●), which was given alternatively throughout the entire experimental period, on basal and postprandial peripheral venous plasma levels of glucagon (IRG), pancreatic polypeptide (PP), and gastrin in a group of 10 lean subjects. Mean ± SEM; ★ indicates significant difference of $P < 0.05$ versus saline controls.

the infusion of somatostatin, basal SLI levels were 134 ± 11 pg/ml and in the postprandial state they remained elevated by approximately 20 pg/ml above those of the saline controls. The incremental SLI value above basal for the 120-min postprandial period was 301 ± 22 pg/ml during saline and 341 ± 19 pg/ml during somatostatin infusion (NS), indicating a fairly parallel shift of plasma SLI values to a higher level during the infusion of somatostatin. Basal and postprandial SLI levels were significantly above those of the saline controls at most time points during the infusion period, decreasing after the end of the study to control values (Figure 1).

As shown in Figures 1, 2, and 3, the somatostatin infusion had no effect on basal plasma insulin, glucagon, gastrin, pancreatic polypeptide (PP), glucose, or triglyceride levels compared with the saline controls. Postprandially, there was only a transient decrease of plasma glucagon levels, while all other parameters remained unchanged during somatostatin infusion when compared with the controls.

Effect of somatostatin in obese subjects. In the obese group, the mean basal plasma SLI level was 91 ± 8 pg/ml, which was significantly below that of the normal controls (118 ± 9 pg/ml, $P < 0.05$). After the ingestion of the meal, SLI levels rose significantly at only three time points to 106 ± 9 pg/ml at 60, 70, and 120 min ($P < 0.02$) (Figure 4). The incremental SLI level in the obese group during saline infusion was 118 ± 12 pg/ml, significantly below the lean control group (301 ± 22 pg/ml, $P < 0.001$). During the infusion of somatostatin, mean basal SLI was 106 ± 8 pg/ml and remained elevated by approximately 20–30 pg/ml above the saline control experiments after the ingestion of the meal (Figure 4). The incremental SLI level during somatostatin infusion was 128 ± 14, still significantly below the respective level in the lean group (341 ± 19 pg/ml, $P < 0.001$).

During the saline control study, basal plasma insulin averaged 19 ± 3 μU/ml, which was significantly elevated compared with the lean subjects (11 ± 1.4 μU/ml, $P < 0.02$). The postprandial rise of plasma insulin to a maximum of 54 ± 6 μU/ml at 20 min was also significantly greater compared with the lean group. The incremental plasma insulin level was 295 ± 7 μU/ml in the obese subjects and 99 ± 5 μU/ml in the lean subjects ($P < 0.001$). During the infusion of somatostatin, basal insulin was reduced by 6 μU/ml to 13 ± 2 μU/ml ($P < 0.05$). Postprandial insulin during the first 30 min after the meal was not different from the saline controls (40 ± 3 μU/ml versus 41 ± 3.5 μU/ml). During the increased somatostatin infusion rate of 1 ng/kg · min, postprandial insulin levels were reduced by 8–14 μU/ml compared with the saline controls. The incremental insulin levels for the time period between 30 and 120 min was 263 ± 14 μU/ml in the saline experiments and 192 ± 12 μU/ml during somatostatin ($P < 0.005$) (Figure 4).

Basal plasma glucagon levels were not significantly different in the obese compared with the lean group, nor was

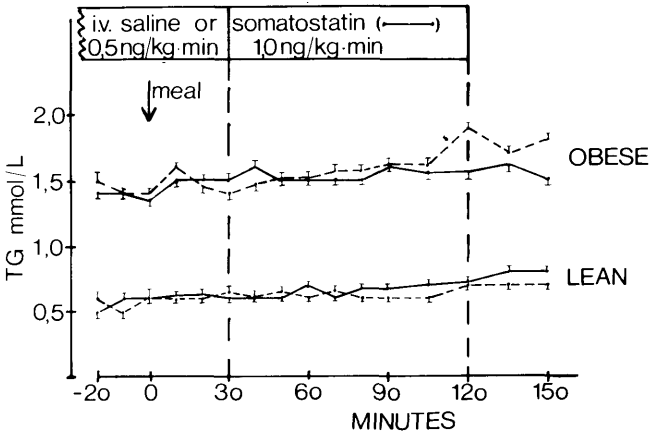

FIGURE 3. Effect of intravenously infused synthetic somatostatin-14 (●——●), which started 35 min before the ingestion of the test meal (M) at a dose of 0.5 ng/kg · min and was continued 30 min thereafter with a dose of 1.0 ng/kg · min, or saline (●------●), which was given alternatively throughout the entire experimental period, on basal and postprandial peripheral venous plasma levels of triglycerides (TG) in a group of 10 lean and 17 obese subjects. Mean ± SEM.

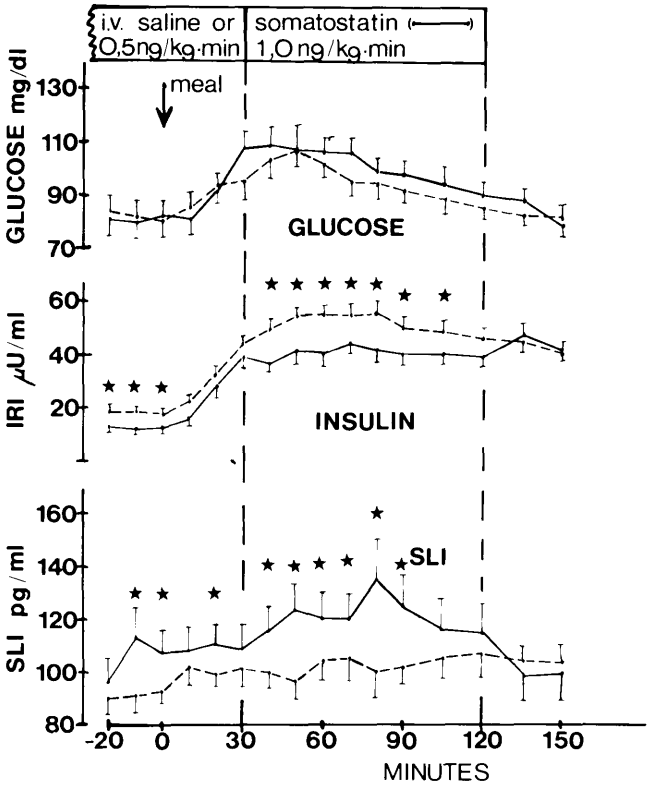

FIGURE 4. Effect of intravenously infused synthetic somatostatin-14 (●——●), which started 35 min before the ingestion of the test meal (M) at a dose of 0.5 ng/kg · min and which was continued 30 min thereafter with a dose of 1.0 ng/kg · min, or saline (●------●), which was given alternatively throughout the entire experimental period, on basal and postprandial peripheral venous plasma levels of somatostatin-like immunoreactivity (SLI), insulin (IRI), and glucose in a group of 17 obese subjects. Mean ± SEM; ★ indicates significant difference of P < 0.05 versus saline controls.

the postprandial rise in these two groups during the infusion of saline (Figures 2 and 5). During the infusion of somatostatin, however, the postprandial rise of plasma glucagon levels during the first 30 min after the meal was not different from the saline controls, whereas a transient decrease was observed during the infusion of somatostatin at 1 ng/kg · min (Figure 5).

Basal plasma gastrin levels in the obese subjects were significantly higher (33 ± 4 pg/ml) compared with the lean controls (14 ± 3 pg/ml, $P < 0.001$). The postprandial rise was also greater in the obese group (389 ± 10 pg/ml versus 238 ± 8 pg/ml, $P < 0.001$). During the infusion of somatostatin, there was a statistically significant difference between the saline controls and the obese group between 60 and 120 min ($P < 0.01$). The incremental level was 202 ± 8 versus 150 ± 6 pg/ml (Figure 5).

Basal plasma pancreatic polypeptide levels in the obese subjects were 420 ± 54 pg/ml, not significantly different from 460 ± 33 pg/ml in the lean group. The initial postprandial rise was also identical in both groups; however, after 30 min the lean subjects reached a plateau of 1500 pg/ml, whereas in the obese group, PP levels were between 800 and 900 pg/ml (Figures 2 and 5). The incremental postprandial PP level in the obese group was 9050 ± 350 pg/ml, significantly below the value of 13,832 ± 570 pg/ml in the lean controls ($P < 0.01$). During the infusion of somatostatin, there was a substantial inhibition of postprandial PP levels during the entire experimental period with a rebound after the end of somatostatin infusion (Figure 5). The incremental PP level during somatostatin was 3500 ± 130 pg/ml ($P < 0.001$).

Basal plasma triglycerides were significantly elevated in the obese group compared with the lean group (1.5 ± 0.2 mmol/L versus 0.6 ± 0.05 mmol/L, $P < 0.005$). The infusion of somatostatin had no effect on triglyceride levels in the obese or lean subjects (Figure 3). Basal and postprandial plasma glucose levels in the obese group were not different from the lean controls and glucose levels were not altered during the infusion of somatostatin.

Elution profiles of SLI in basal and postprandial peripheral vein plasma samples. Gel filtration of 3-ml samples of fasting plasma from four lean and four obese subjects revealed a peak of SLI in the void volume in all samples (Figures

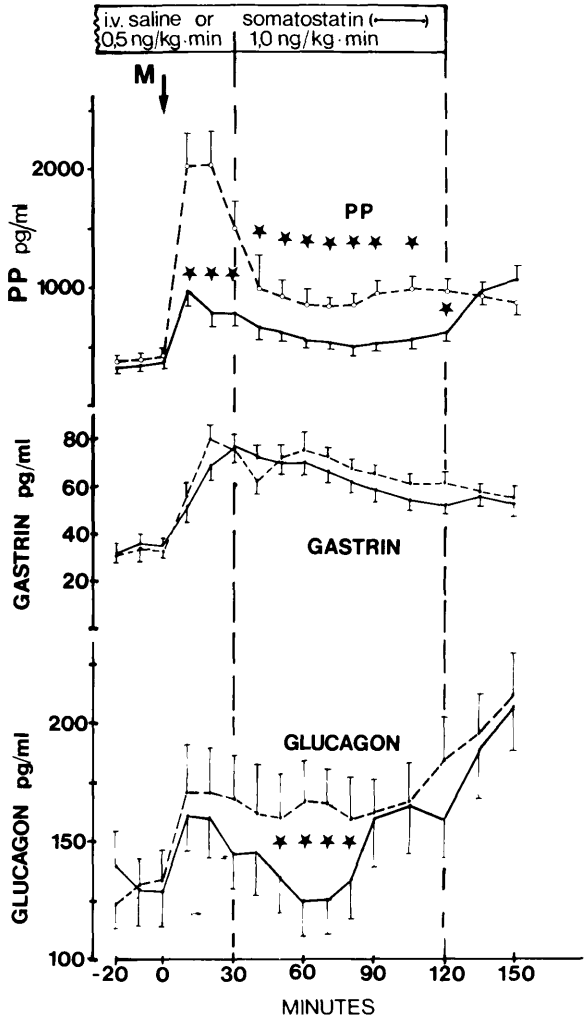

FIGURE 5. Effect of intravenously infused synthetic somatostatin-14 (●——●), which started 35 min before the ingestion of the test meal (M) at a dose of 0.5 ng/kg · min and was continued 30 min thereafter with a dose of 1.0 ng/kg · min, or saline (●------●), which was given alternatively throughout the entire experimental period, on basal and postprandial peripheral venous plasma levels of glucagon (IRG), pancreatic polypeptide (PP), and gastrin in a group of 17 obese subjects. Mean ± SEM; ★ indicates significant difference of P < 0.05 versus saline controls.

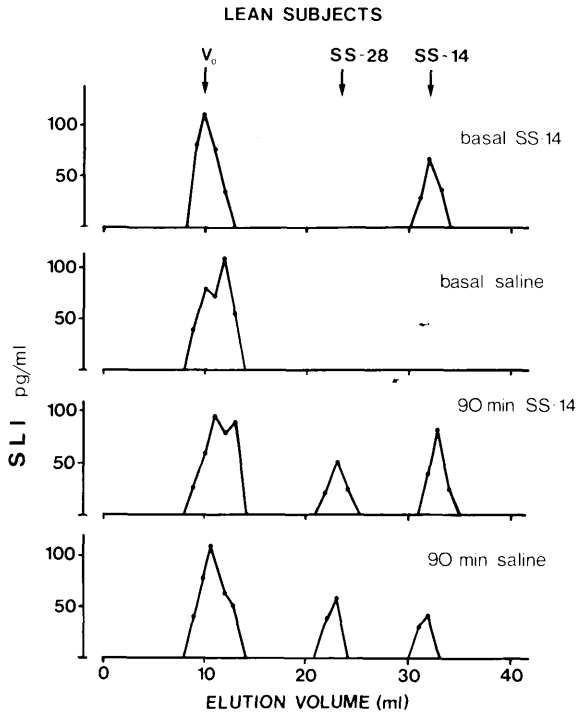

FIGURE 6. Elution profiles of SLI in basal and postprandial (90 min after ingestion of the meal) peripheral vein plasma samples of a lean subject during an infusion of saline or synthetic somatostatin-14 (SS-14). Three-milliliter aliquots were chromatographed on a Bio-Gel-P-10 column at pH 8.8 and collected in 1-ml fractions. V_o, void volume; SS-28, somatostatin-28; SS-14, somatostatin-14.

6 and 7). In none of these samples was a measurable amount of SLI detected in the fractions co-eluting with somatostatin-14 or somatostatin-28. In basal samples taken during the infusion of somatostatin-14, a peak co-eluting with SS-14 could be detected.

Elution profiles of 3-ml samples collected 90 min after ingestion of the meal revealed a SLI peak in the void volume and, in addition, two SLI peaks were detectable that co-eluted with SS-28 and SS-14, respectively. Representative examples of a sample from a lean and an obese subject are depicted in Figures 6 and 7. The elution profiles of samples collected 10 min after ingestion of the test meal were essentially identical to those collected after 90 min.

DISCUSSION

The present data demonstrate that, in a group of obese, nondiabetic subjects, basal and postprandial plasma SLI and postprandial PP levels were significantly lower when compared with a group of normal-weight control subjects. This was associated with an elevation of basal and postprandial plasma insulin, gastrin, and triglyceride levels.

No difference between obese and lean subjects was observed for basal and postprandial plasma glucagon and glucose concentrations.

The infusion of synthetic somatostatin-14 elevated circulating peripheral plasma SLI levels by 20–30 pg/ml above control values. Toward the end of the infusion period, this difference was not maintained completely, an effect that has already been observed in dog experiments.[16] A similar tendency toward a decrease in SLI levels during prolonged physiologic infusion rates of somatostatin-14 in the basal state has been shown by Souquet et al.[41] This infusion of somatostatin elicited an inhibitory effect on basal plasma insulin in the obese group, while basal levels of gastrin, glucagon, PP, glucose, and triglycerides were unaffected. In the lean group, somatostatin had no effect on any hormone or metabolite in the basal state at the dose employed.

The same infusion rate of 0.5 ng/kg · min reduced postprandial PP levels in the obese group. The increase of the somatostatin infusion rate to 1.0 ng/kg · min attenuated the rise of postprandial insulin in the obese group, significantly associated with a transient decrease in plasma glucagon levels and a decease in plasma gastrin and PP levels. In the lean group only was a transient decrease of glucagon levels observed.

Thus, the infusion of somatostatin demonstrates an increased sensitivity to physiologic elevations of circulating SLI levels in obese subjects compared with lean controls. Whether the preprandial infusion of somatostatin increases the sensitivity to somatostatin in the obese but not in the lean subjects cannot be determined from the present data.

Gel chromatography demonstrates that, in the basal state, endogenous SLI can be demonstrated only in the void-volume fraction, which is similar to previous findings in dogs.[10] Since the biologic activity of this large-molecular-weight material is unknown, the significance of lower basal SLI levels in the obese subjects remains unknown at this time. It is noteworthy, however, that injection of neutralizing somato-

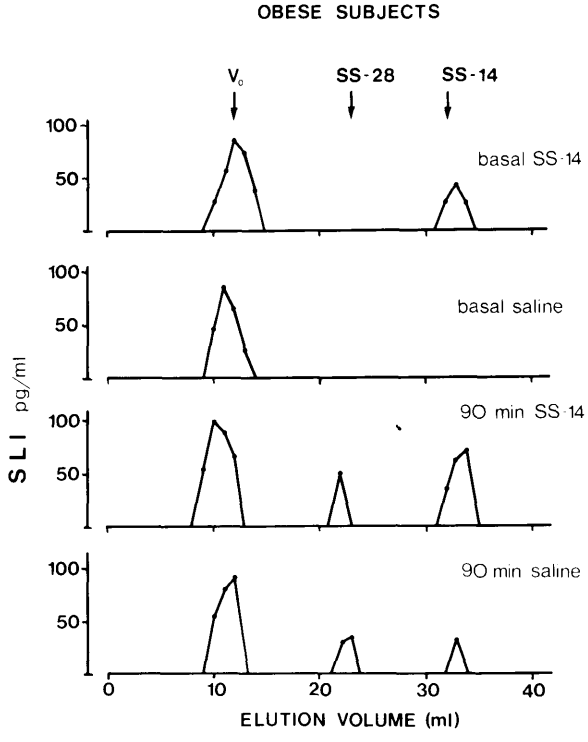

FIGURE 7. Elution profiles of SLI in basal and postprandial (90 min after ingestion of the meal) peripheral vein plasma samples of an obese subject during an infusion of saline or synthetic somatostatin-14 (SS-14). Three-milliliter aliquots were chromatographed on a Bio-Gel-P-10 column at pH 8.8 and collected in 1-ml fractions. V_o, void volume; SS-28, somatostatin-28; SS-14, somatostatin-14.

statin antiserum in the basal state results in an increase of basal enteroglucagon levels in dogs,[17] indicating that the large-molecular-weight fraction of SLI might also have some biologic activity.

In the postprandial state, SLI fractions co-eluting with somatostatin-14 and somatostatin-28 can be demonstrated, which is in agreement with previously reported data.[14,42]

In the present study, there was no effect on circulating triglycerides; however, this might be due to the rather short experimental period at the end of which an increase in postprandial triglyceride levels was not detectable.

Previous findings in animals have indicated that acute hyposomatostatinemia results in augmented postprandial gastrin, PP, and insulin levels.[18] This raises the possibility that reduced SLI levels in the obese group might in part be responsible for the observed hypergastrinemia and hyperinsulinemia. On the other hand, it has to be considered that, in spite of reduced somatostatin levels and an augmented inhibition by i.v. somatostatin, the pancreatic polypeptide response to the meal was lower than normal. A somatostatin-suppressive action of insulin has been previously shown[43,48] and, accordingly, reduced SLI levels in the obese are possibly the consequence of the existing hyperinsulinemia. Thus, an exact cause-and-effect relationship with regard to pathogenetic mechanisms is difficult to establish.

In conclusion, the present findings demonstrate that in obese subjects a reduced postprandial plasma SLI and PP response exists together with elevated gastrin and insulin levels, and, furthermore, in obese subjects synthetic somatostatin exerts an augmented biologic response. This indicates that some but certainly not all alterations of the endocrine response to a meal might, at least in part, be the result of an impaired SLI response in obese subjects. Whether the reduced SLI levels are primarily responsible for the observed alterations or whether reduced SLI is secondary to primary hyperinsulinemia cannot be determined from the present experiments and remains to be established in further studies.

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