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Research Article

The nature and extent of somatostatin-induced inhibition of pancreatic endocrine secretion were studied by administration of a number of stimuli of either glucagon or insulin to over night fasted baboons with and without an infusion of linear somatostatin. The stimuli for acute-phase insulin release were intravenous pulses of glucose, tolbutamide, isoproterenol, and secretin. When given 15 min after the start of a somatostatin infusion, these agents were essentially unable to stimulate insulin secretion. Chronic insulin secretion was stimulated by infusions of either glucose or glucagon. Within 10 min of the start of a super-imposed infusion of somatostatin, insulin levels fell to less than 40 percent of prestimulus control and remained suppressed for the duration of the somatostatin infusion. Stimulation of glucagon secretion by insulin-induced hypoglycemia was also blocked by somatostatin. Plasma glucose decreased during somatostatin infusions except when superimposed upon an infusion of glucagon. Somatostatin had no effect on glucose production in a rat liver slice preparation. We conclude: (a) Somatostatin is a potent and so far universally effective inhibitor of both acute and chronic phases of stimulated insulin and glucagon secretion (b) The inhibitory effect is quickly reversible and the pattern of recovery of secretion is appropriate to prevailing signals; (c) Present evidence suggests that the effect of somatostatin on blood glucose is mediated through its effect on blood […]

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Somatostatin Blockade of Acute and Chronic Stimuli of the Endocrine Pancreas and the Consequences of this Blockade on Glucose Homeostasis

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ABSTRACT The nature and extent of somatostatin-induced inhibition of pancreatic endocrine secretion were studied by administration of a number of stimuli of either glucagon or insulin to overnight fasted baboons with and without an infusion of linear somatostatin. The stimuli for acute-phase insulin release were intravenous pulses of glucose, tolbutamide, isoproterenol, and secretin. When given 15 min after the start of a somatostatin infusion, these agents were essentially unable to stimulate insulin secretion. Chronic insulin secretion was stimulated by infusions of either glucose or glucagon. Within 10 min of the start of a superimposed infusion of somatostatin, insulin levels fell to less than 40% of prestimulus control and remained suppressed for the duration of the somatostatin infusion. Stimulation of glucagon secretion by insulin-induced hypoglycemia was also blocked by somatostatin.

Plasma glucose decreased during somatostatin infusions except when superimposed upon an infusion of glucagon. Somatostatin had no effect on glucose production in a rat liver slice preparation.

We conclude: (*a*) Somatostatin is a potent and so far universally effective inhibitor of both acute and chronic phases of stimulated insulin and glucagon secretion (*b*) The inhibitory effect is quickly reversible and the pattern of recovery of secretion is appropriate to prevailing signals; (*c*) Present evidence suggests that the effect of somatostatin on blood glucose is mediated through its effect on blood glucagon; (*d*) In the overnight-fasted baboon both in the basal state and 45 min into a 4-mg/kg·min glucose infusion, a somatostatin-induced fall in serum insulin levels appears to be unable to prevent a decrease in hepatic glucose production.

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INTRODUCTION

Somatostatin, a 14-amino acid peptide isolated from ovine hypothalami and subsequently synthesized, has been shown to have potent growth hormone release-inhibiting effects in both in vivo and in vitro systems (1–6). A second pituitary action, the inhibition of thyroid-releasing hormone induced thyroid-stimulating hormone release has also been demonstrated (6–8). A fall in plasma glucose was noted (9, 10) during infusions of somatostatin into overnight fasted baboons. Investigations into this phenomenon resulted in the determination that somatostatin inhibits basal pancreatic secretion of insulin and glucagon (9, 10). Similar phenomena have been reported in man (11, 12). This inhibition extends to arginine-stimulated secretion of insulin and glucagon (10, 12). The present paper describes our further observations on the ability of somatostatin to inhibit a variety of acute and chronic stimuli for secretion of insulin and glucagon by the endocrine pancreas. Tested stimuli of acute-phase insulin secretion include single intravenous injections of glucose, tolbutamide, secretin, and isoproterenol. Chronic

insulin secretion was stimulated by infusions of glucose and glucagon. Insulin hypoglycemia was the stimulus of glucagon secretion.

This paper also examines evidence that the somatostatin-induced fall in plasma glucose in the overnight fasted animal is secondary to the direct effect of somatostatin on pancreatic hormone secretion. More specifically, we will suggest that this fall in glucose levels is secondary to the fall in glucagon and that in the overnight fasted baboon, glucagon plays a major role in controlling minute by minute hepatic glucose production. The influence of basal insulin levels on the minute by minute control of hepatic glucose production is also discussed.

METHODS

The in vivo studies were carried out on conscious, adolescent male baboons (*Papio cynocephalus*) weighing 11–14 kg which had been adapted to living in primate chairs. Silastic catheters, permanently implanted in the vena cava through either jugular or femoral veins, were kept patent by a continuous infusion of normal saline and heparin (10 U of heparin/ml) at the rate of 40–50 ml/24 h. At least 7 days postoperative (catheter implantation) recovery time was allowed before initiation of studies. The animals were housed in one- or two-animal isolation booths, permitting control of environmental conditions. Blood was withdrawn from the catheters which extend outside the booths. Further experimental details may be found in previous publications (13, 14).

All studies were performed after an overnight fast (18 h). Plasma glucose was measured by the ferricyanide method on the Technicon Autoanalyzer (Technicon Instruments Corp., Tarrytown, N. Y.). Serum insulin was assayed by the double antibody method of Morgan and Lazarow (15). Glucagon was measured in extracted plasma (10) by a modification of the immunoassay method of Nonaka and Foà (16) as described by Ensinck, Shepard, Dudl, and Williams (17). ACTH was kindly measured by Dr. John Kendall (Veterans Administration Hospital, Portland, Ore.) by radioimmunoassay (18). Cortisol was measured by a competitive protein-binding method (19). Synthetic linear somatostatin was kindly supplied by Dr. Roger Guillemin of the Salk Institute. Pure, natural secretin was purchased from the Karolinska Institute, Stockholm, Sweden. The tolbutamide (Orinase) was obtained from The Upjohn Company (Kalamazoo, Mich.), isoproterenol HCl from Winthrop Laboratories (New York), glucagon from Eli Lilly and Company (Indianapolis, Ind.).

Two general types of in vivo studies were performed: (*a*) Acute insulin responses were obtained by giving the animal single intravenous injections of glucose, secretin, isoproterenol, and tolbutamide. Glucagon responses were studied during insulin hypoglycemia. For all of these stimuli the injections were delivered as a pulse over 10 s, followed by saline wash sufficient to purge the dead space of the catheter. The five acute studies were variations on the same protocol. Two pulses of the secretagogue were given. One of these pulses was superimposed on a somatostatin infusion. According to the variations, the acute studies can be further subdivided into three groups.

(*i*) The glucose, secretin, and isoproterenol studies were performed in the following manner: Each of four animals to be studied received two pulses from the same stimulus in a single morning. One of the two pulses was given 15 min after a 30-min somatostatin infusion was begun. The other was given alone. With each stimulus studied, half of the animals were given the first pulse during somatostatin and the second pulse alone; the order was reversed for the other two.

Order was not found to make a difference in the outcome of the studies. The interval between the pulses was 75 min for glucose, 120 min for secretin, and 90 min for isoproterenol. The doses were: glucose, 500 mg; secretin, 1.0 U/kg; isoproterenol, 1 μg.

(*ii*) The tolbutamide study followed the format of the four acute studies just described with two exceptions: The interval between pulses was at least 24 h, and there was no effort to randomize order of pulses. Four animals were used. The dose of tolbutamide was 200 mg/animal.

(*iii*) In the insulin hypoglycemia study, 0.15 U/kg of insulin was given with and without somatostatin on 2 separate days. When given with somatostatin, the insulin was injected coincident with the beginning of a 2-h somatostatin infusion. No attempt at randomization of order of pulses was made. Five animals were employed.

(*b*) Chronic endocrine pancreatic function was evaluated by superimposition of a 30-min somatostatin infusion upon a 60-min infusion of glucagon (0.2 μg/kg·min) or a 105-min infusion of glucose (4 mg/kg·min). Control studies consisted of identical infusions of glucagon or glucose without superimposed somatostatin. Four animals were used in each study.

The dose of somatostatin used in all the in vivo studies presented in this paper was 0.8 μg/kg·min with no loading dose. This dose was selected because it was found to be the lowest dose that caused maximum suppression of basal insulin and glucagon levels. Table I summarizes our dose-response data. Subsequent to obtaining these dose-response data, the use of a loading dose was discontinued because additional studies demonstrated that the 0.8 μg/kg·min dose suppressed insulin and glucagon secretion equally with or without the loading dose.

The in vitro studies were performed in Dr. Mayer Davidson's Laboratory, University of California at Los Angeles. A full description of the methods has recently been published (20). In brief, female Sprague-Dawley rats weighing 150–180 g were sacrificed after either a 20-h fast or after being fed. A segment of liver was quickly removed, slices were prepared, and then incubated in one of two solutions: (*a*) regular Krebs-Ringer bicarbonate (KRB) [1] buffer with 150 mM Na^+ and 5 mM K^+ or (*b*) modified KRB containing 25 mM Na^+ and 130 mM K^+. The latter solution is used to stabilize intracellular glycogen and allow hormonal influences on glycogenolysis to become demonstrable. Glucose production was determined by measuring the change in concentration of glucose by the ferricyanide method (21) in the medium over 2 h of incubation. The effect of somatostatin (10^{-7} M) on basal- and glucagon- (10 μg/ml) stimulated glycogenolysis was assessed with the modified KRB buffer. The effect of somatostatin (10^{-7} M) on gluconeogenesis from glycerol (10 mM) and alanine (10 mM) was assessed with the regular KRB buffer. 10 rats, 5 rats/day on 2 separate days, were used to assess each pathway and

[1] *Abbreviation used in this paper:* KRB, Krebs-Ringer bicarbonate.

TABLE I

The Effect of Various Doses of Somatostatin upon Fasting Plasma Concentrations of Glucose, Insulin, Glucagon, and Growth Hormone

	Percent of mean control ±SEM (*n*) at 30 min						
Loading dose, μg/kg	0.45	0.91	2.27	4.54	9.08	25.00	90.80
Infusion dose, μg/kg·min	0.015	0.030	0.080	0.150	0.300	0.830	3.000
Glucose (91±1.6 mg/100 ml = 100%)	103±2 (4)	95±2 (4)	94±3 (4)	81±3 (7)	74±2 (6)	70±5 (4)	71±2 (6)
Insulin (73.5±7.4 μU/ml = 100%)	60±6 (4)	54±12 (4)	44±16 (4)	37±7 (7)	24±4 (6)	11±7 (4)	4±3 (4)
Glucagon (187.6±19.5 pg/ml = 100%)	89±9 (4)	67±14 (4)	63±16 (3)	42±18 (5)	13±13 (3)	0 (4)	0 (3)
Growth hormone (7.6±1.4 ng/ml = 100%)	20±10 (3)	42±13 (4)	57±22 (3)	21±6 (3)	43±9 (6)	47±8 (4)	68±23 (5)

Samples were obtained before and 30 min after the start of somatostatin infusion at the indicated doses. The concentration of each substance is expressed as a percent of its preinfusion mean control value. The mean control values did not vary significantly from day to day. The average of all the control values for each parameter ±SEM is in parentheses under that parameter

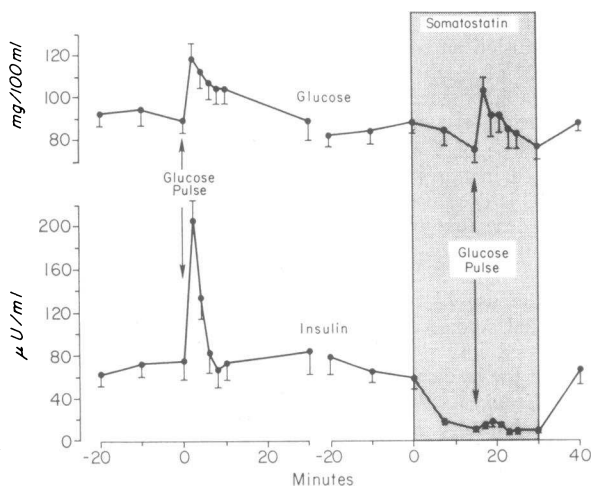

FIGURE 1 Glucose pulse alone and during somatostatin infusion. The left panel presents data obtained when the stimulus was given alone; the right panel, when the stimulus was given 15 min after beginning a somatostatin infusion. The dose of glucose, 500 mg/animal, was chosen so that a uniphasic insulin response would result. Somatostatin 0.8 μg/kg·min markedly inhibited this response ($n = 4$) computed as the area under the curve from 0 to 10 min post-stimulus and above the base line existant at the time of stimulus. These areas differed significantly ($P < 0.01$) before and after somatostatin when compared by the paired t test. The fall in serum glucose and insulin (the right panel) from 0 to 15 min of the somatostatin infusion was compared with the −20–0 change in serum glucose and insulin under basal conditions (the left panel); the results of the four acute pulse studies (Figs. 1–4) were pooled ($n = 16$). In the nonpaired t test the somatostatin-induced fall of basal glucose was significant ($P < 0.01$) as was the somatostatin-induced fall of basal insulin ($P < 0.01$).

all experimental points in each animal were performed in triplicate.

RESULTS

Glucose, secretin, and isoproterenol pulses alone and during somatostatin infusion (Figs. 1–3). All three stimuli resulted in a uniphasic insulin secretory response and this response was almost totally abolished during

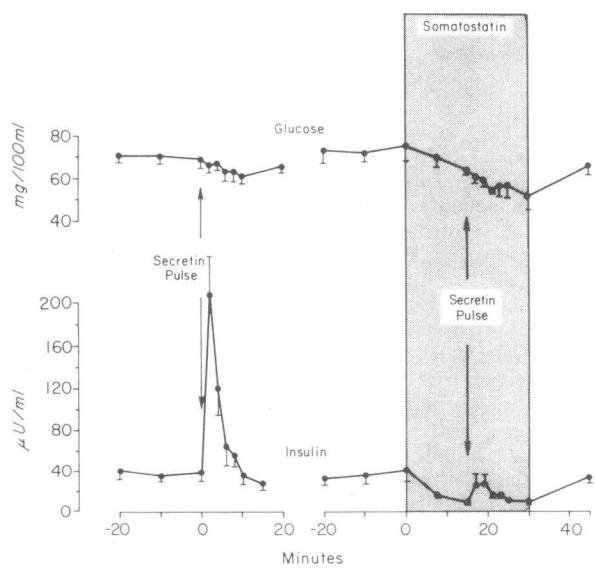

FIGURE 2 Secretin pulse alone and during somatostatin infusion. Format as for Fig. 1. The dose of secretin was 1.0 U/kg. Somatostatin markedly inhibited the insulin response ($n = 4$). The responses, compared as in Fig. 1, differed significantly ($P < 0.01$).

infusion of somatostatin. Before the pulse, during infusion of somatostatin, a moderate fall in plasma glucose was evident at 15 min and basal insulin fell to 20% of control. After the somatostatin infusion was stopped, glucose and insulin returned to control levels within 10 min.

Tolbutamide alone and during somatostatin infusion (*Fig. 4*). Tolbutamide alone results in an acute insulin spike as well as a more sustained secretion. A concomitant lowering of plasma glucose occurred. The release of insulin by tolbutamide was greatly inhibited during the somatostatin infusion. 20 min after ending the somatostatin infusion, the plasma insulin was elevated, probably reflecting the effect of tolbutamide still circulating (assuming a similar half-life for tolbutamide in baboons as in humans).

Glucose infusion alone and with superimposition of a somatostatin infusion. (*Fig. 5*). The infusion of glucose as expected, caused a rise in serum glucose levels. Glucagon was depressed and insulin rose. These trends were abruptly altered by somatostatin. The glucose concentration decreased. Glucagon and insulin concentrations fell dramatically. Upon termination of the somatostatin infusion, glucose and insulin concentrations quickly returned to their elevated levels whereas the glucagon concentration returned to the glucose suppressed presomatostatin level. Upon termination of the glucose infusion, the fall in plasma glucose concentration was accompanied by a fall in insulin and a slight rise in glucagon concentration. Thus, at the end of the somatostatin infusion, the secretion of glucagon and insulin were as expected for the prevailing plasma glucose concentration.

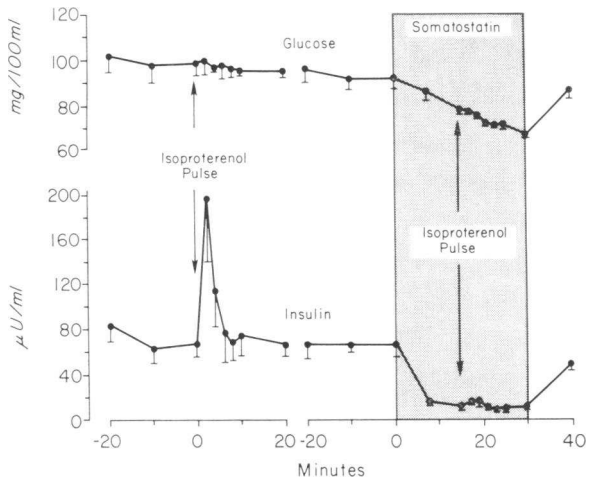

FIGURE 3 Isoproterenol pulse alone and during somatostatin infusion. Format as for Fig. 1. The dose of isoproterenol was 1.0 μg/animal. Somatostatin inhibited the insulin response ($n = 4$). With the method of comparison used in Figs. 1 and 2 statistical significance ($P < 0.05$) was not obtained in this study. However, in each of the four animals the response was markedly inhibited by somatostatin, and significance is obtained if the *total* areas under the 0–10 min curves (base line = 0 μU/ml insulin) are compared. Thus, the total output of insulin, as reflected in peripheral insulin levels, in the 10 min after the stimulus differs significantly before and after somatostatin.

Glucagon infusion alone and with superimposition of a somatostatin infusion (*Fig. 6*). The glucagon in-

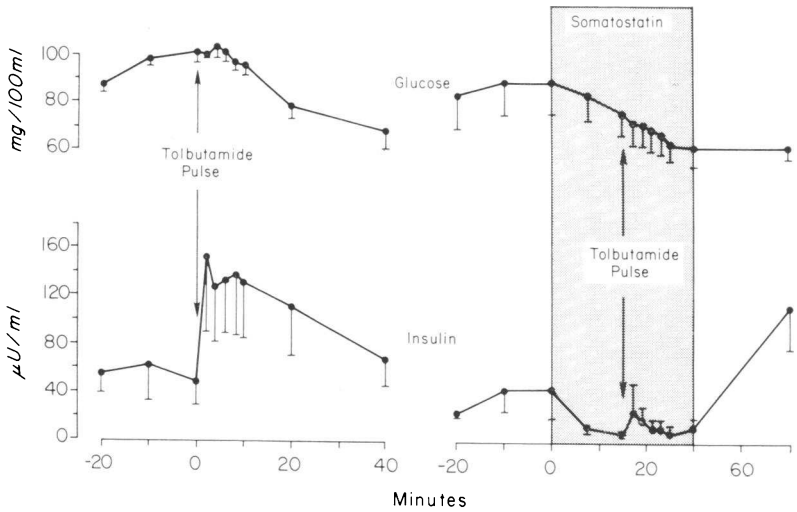

FIGURE 4 Tolbutamide alone and during somatostatin infusion. Format as for Fig. 1. The dose of tolbutamide was 500 mg/animal. Somatostatin markedly inhibited the tolbutamide-induced insulin response ($n = 4$). The responses, compared as in Fig. 1 differed significantly ($P < 0.05$).

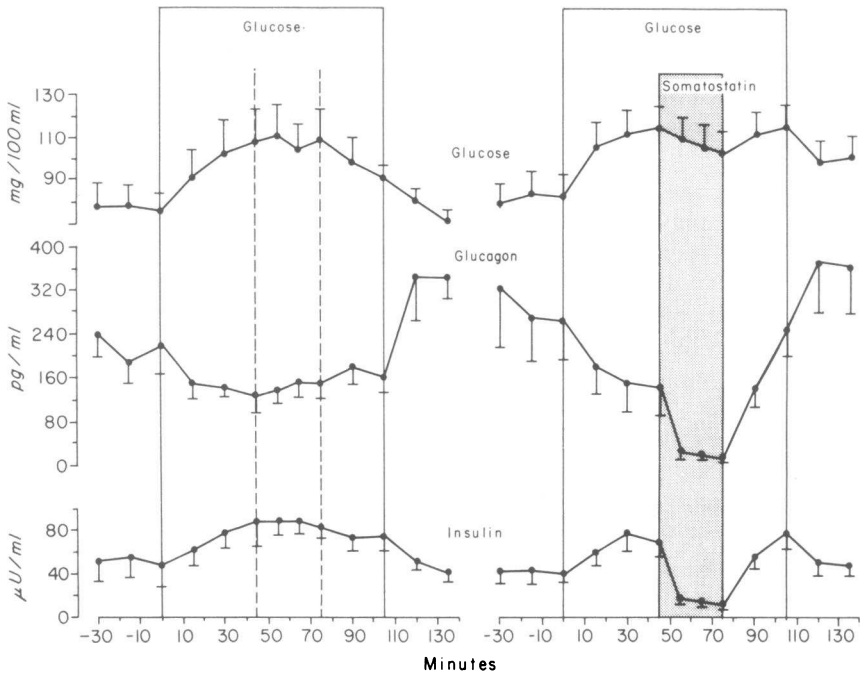

FIGURE 5 Glucose infusion, 4 mg/kg·min, alone and with superimposition of a somatostatin infusion. The left panel presents data obtained when the glucose was given alone; the right panel, with the superimposition of a 30-min somatostatin infusion. Glucose alone suppressed glucagon and elevated insulin levels. Somatostatin markedly suppressed glucagon and insulin levels and was associated with decreasing glucose values ($n = 4$). A point by point comparison by nonpaired t test was made between the two panels. The somatostatin-induced fall in both glucagon and insulin at 55, 65, and 75 min was significant ($P < 0.01$).

fusion caused a rise in serum glucose and insulin concentrations. No effect of somatostatin on the glucagon-induced glucose rise is apparent. However, marked inhibition of insulin secretion by somatostatin occurred. Upon termination of the somatostatin infusion, insulin rose to presomatostatin levels, and glucose fell slightly. Upon termination of the glucagon infusion, glucose and insulin concentrations declined appropriately.

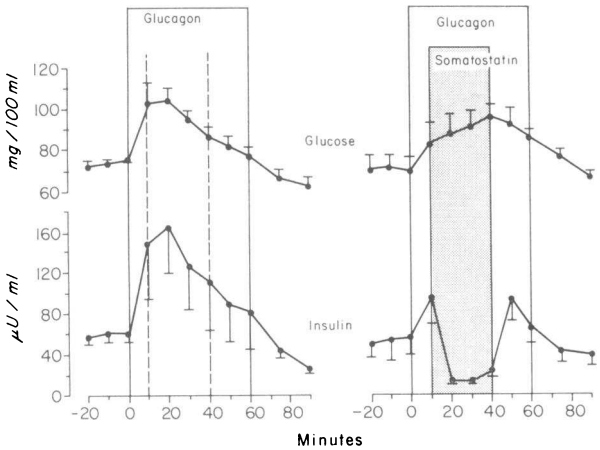

FIGURE 6 Glucagon infusion, 0.2 μg/kg·min, alone and with superimposition of a somatostatin infusion. Format as for Fig. 5. At 20 and 30 min after starting glucagon, somatostatin markedly suppressed the insulin response to glucagon ($P < 0.05$, $n = 4$). In the presence of glucagon, infusion of somatostatin was not associated with a fall in plasma glucose.

Insulin hypoglycemia alone and during somatostatin infusion (*Fig. 7*). Insulin-induced hypoglycemia resulted in a prompt increase in glucagon secretion with peak values being obtained within 20–30 min. ACTH and cortisol secretory responses were slightly delayed with cortisol concentrations being elevated for over 2 h. The hypoglycemia obtained during the somatostatin infusion was prolonged. Though there was partial escape during the 2nd h of somatostatin infusion, the glucagon response to hypoglycemia was markedly inhibited. Probably in response to the more exaggerated and prolonged hypoglycemia during somatostatin, ACTH concentrations were markedly elevated for the duration of the experiment. Cortisol secretion was correspondingly greater and more prolonged during somatostatin infusion. Thus, ACTH and cortisol secretion are apparently not inhibited by somatostatin infusion.

In vitro glucose production. The results of the in vitro studies are given in Table II. Somatostatin at 10^{-7} M had no effect on basal glycogenolysis or on glycogenolysis stimulated by glucagon. Furthermore somatostatin was without effect on gluconeogenesis with either glycerol or L-alanine as the substrate.

DISCUSSION

Somatostatin is a potent and so far universally effective inhibitor of both acute and chronic phases of insulin and glucagon secretion. It differs in many respects from other known inhibitors of insulin release. It is a naturally occurring substance in the mammalian organism (2) and of the known inhibitors shares this attribute only with the catecholamines (22), serotonin (23), prostaglandins (24), glucosamine (25), and possibly the ammonium ion (26). Among this group somatostatin is the only peptide inhibitor and it is the most potent in vivo.

Among pharmacologic inhibitors of insulin secretion, propranolol, mannoheptulose, and 2-deoxy-glucose are not able to inhibit as many diverse stimuli for insulin release as somatostatin (25, 27–29). Diazoxide and diphenylhydantoin are widely effective inhibitors of insulin secretion (25, 30), but their in vivo effectiveness does not match that of somatostatin (31, 32).

Until now, glucose has been the most potent and best established inhibitor of glucagon (33), although secretin (34) and free fatty acids (35) have also been reported to block glucagon secretion. Somatostatin differs from glucose as an inhibitor of glucagon secretion in that: (*a*) It almost totally blocks basal release of glucagon (10); (*b*) It is able to markedly inhibit glucagon secretion stimulated by arginine and insulin hypoglycemia; (*c*) Finally, somatostatin appears to be the only known biologically derived substance which simultaneously inhibits both glucagon and insulin release.

At this time one can only speculate on the mechanism of somatostatin's pancreatic effect. As a polypeptide, somatostatin probably acts on the cell membrane. Its specificity, affecting release of many, but not all, hormones (1, 4, 5, 8), suggests the presence of specific receptor sites on the membrane. The ubiquity of its effect in the beta cell indicates that its action is on a step leading to insulin secretion that is common to all the stimuli tested. The rapidity with which the beta and alpha cells respond to prevailing signals once somatostatin infusion is stopped indicates that the effects seen are not secondary to a deleterious influence on cell metabolism.

During somatostatin infusion alone, a fall in glucose was always noted. Through the use of [^{14}C]glucose infusions, we have previously demonstrated that this fall in basal glucose is due to decreased glucose production (10). The decreased hepatic glucose production does not appear to be secondary to a direct effect of somatostatin on the liver, because in the rat liver slice preparation, somatostatin was without effect on glucagon-stimulated glycogenolysis or gluconeogenesis from glycerol or from alanine and the infusion of somatostatin into isolated fed rat livers is without effect on glucose production (36).

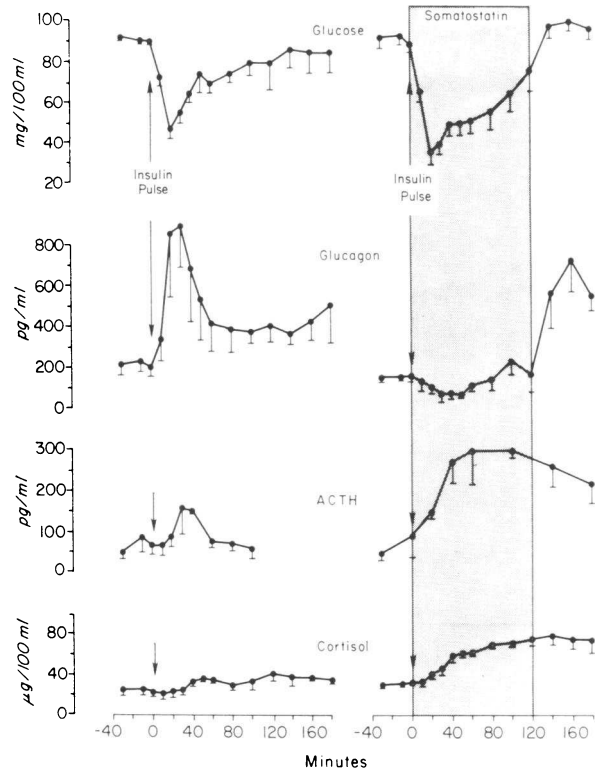

FIGURE 7 Insulin hypoglycemia alone and during somatostatin infusion. Format as for Fig. 1. The dose of insulin was 0.15 U/kg. Somatostatin blocked the glucagon response to insulin. ACTH and cortisol were not inhibited ($n = 5$). If statistical analysis is performed as for Figs. 5 and 6, significance at $P < 0.05$ is attained for the falling glucagon values at 20, 30, 40, 50, 60, and 80 min, for the rising cortisol values at 20 through 160 min and for the rising ACTH value at 100 min ($P < 0.001$).

We have previously suggested that the decreased hepatic glucose production is due to inhibition of glucagon by somatostatin (10). This hypothesis is supported by the inability of somatostatin to decrease serum glucose levels during a glucagon infusion (Fig. 6). In the overnight fasted animal a consistent fall in glucose secondary to a fall in glucagon implies that in the basal state, minute by minute hepatic glucose production is maintained by the basal glucagon concentration.

TABLE II

The Effect of Somatostatin on Glucagon-Stimulated Glycogenolysis and on Gluconeogenesis from Glycerol and from L-Alanine in Rat Liver Slices

1	2	3	4	5	6
(A) Glucose production from glycogen			Buffer—high K^+ (125 mM) KRB, liver slices from 10 fed rats, results are presented as μg/glucose produced/100 mg tissue/2 h, mean ±SEM		
Basal	Glucagon*	Δ	Somatostatin‡	Glucagon* and somatostatin‡	Δ
810±25	1,168±43	358±45	878±40	1,172±54	294±31
(B) Gluconeogenesis from glycerol			Buffer—regular K^+ (5 mM) KRB, liver slices from 10 fasted rats, results are presented as μg/glucose produced/100 mg tissue/2 h, mean ±SEM		
Basal	Glycerol§	Δ	Somatostatin‡	Glycerol§ and somatostatin‡	Δ
402±18	1,067±26	665±18	413±20	1,090±33	667±26
(C) Gluconeogenesis from L-alanine			Buffer—regular K^+ (5 mM) KRB, liver slices from 10 fasted rats, results are presented as μg/glucose produced/100 mg tissue/2 h, mean ±SEM		
Basal	L-Alanine§	Δ	Somatostatin‡	L-Alanine§ and somatostatin‡	Δ
470±24	550±28	80±15	474±34	544±26	70±22

KRB = Krebs-Ringer bicarbonate. The high K^+ KRB is necessary to demonstrate influences on glycogenolysis. By paired *t* test there are no significant differences between columns 1 and 4, 2 and 5, or 3 and 6 in either part A, part B, or part C. Significant difference = $P < 0.05$.

* Glucagon concentration = 10 μg/ml.

‡ Somatostatin concentration = 10^{-7} M.

§ Substrate concentration = 10 mM.

Basal insulin production in the overnight fasted animal is dramatically diminished by somatostatin infusion. The conclusion is derived from results attained in species as diverse as man and the cat and in systems including the isolated perfused rat pancreas (11, 37) and arteriovenous sampling across the dog pancreas (36, 38). This decrease in insulin production is unable to prevent the somatostatin-induced fall in hepatic glucose production. If, as we postulate, somatostatin's signal to the liver is a decline in portal vein glucagon levels, these data suggest that the effect of lowered glucagon on hepatic glucose production is not effectively counteracted by the fall in insulin. Questions are thus raised as to the relative contributions of basal glucagon and insulin in the short-term regulation of basal hepatic glucose production. Furthermore, at a point 45 min after beginning a 4-mg/kg·min glucose infusion (Fig. 5), a superimposed somatostatin infusion was also associated with a falling plasma glucose. Though statistical significance of this decrease in glucose cannot be demonstrated, the abrupt change in slope (over three time points) of the glucose curve under the influence of somatostatin suggests that this change is real. If so, it appears that even after maintenance of insulin levels higher than basal for 45 min, an abrupt fall in insulin is unable to prevent a decrease in hepatic glucose output. Again, the falling glucose concentrations are associated with a sharp fall in serum glucagon.

At this time, it is unclear whether somatostatin plays a physiological role in regulating the endocrine pancreas. Physiological or even pathophysiological counterparts to the almost complete endocrine pancreatic blockade seen with the 0.8-μg/kg·min somatostatin infusion are not known; and, thus, it is unlikely that the alpha and beta cells of the pancreas are exposed endogenously to the concentration of somatostatin that this large dose engenders. Partial inhibition of insulin or glucagon secretion may occur under numerous circumstances, however. The characteristics of somatostatin blockade—its speed of onset, the ease with which it is reversed, the lack of toxicity—are characteristics that would serve well a physiologically active substance. Endogenous somatostatin might then exert a modulatory influence upon the stimulated or unstimulated endocrine pancreas (10). The data presented in this paper are consistent with the possibility that somatostatin might be part of a control system to which the

alpha and beta cells respond. What is not clear is whether endogenous somatostatin actually reaches the pancreas.

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