Influence of Somatostatin on Splanchnic Glucose Metabolism in Postabsorptive and 60-Hour Fasted Humans

JOHN WAHREN, SUAD EFENDIĆ, ROLF LUFT, LARS HAGENFELDT, OLA BJÖRKMAN, and PHILIP FELIG

From the Department of Clinical Physiology, Serafimer Hospital, Stockholm, Sweden, the Departments of Endocrinology and Clinical Chemistry, Karolinska Hospital, Stockholm, Sweden, and the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06510

ABSTRACT Cyclic somatostatin was administered intravenously (10 μg/min for 60 min) to 10 healthy overnight fasted (postabsorptive) subjects and to 5 healthy 60-h fasted subjects. In both groups, arterial insulin and glucagon fell 50% and splanchnic release of these hormones was inhibited. In the overnight fasted subjects splanchnic glucose output fell 70%, splanchnic uptake of lactate and pyruvate was unchanged, alanine uptake fell by 25%, and glycerol uptake rose more than twofold in parallel with an increase in arterial glycerol.

In the 60-h fasted group splanchnic glucose output was less than 40% of that observed in the overnight fasted subjects. Somatostatin led to a further decrease (−70%) in glucose production. Splanchnic uptake of lactate and pyruvate fell by 30–40%, amino acid uptake was unchanged, while uptake of glycerol rose fivefold. Total uptake of glucose precursors thus exceeded the simultaneous glucose output by more than 200%. Splanchnic uptake of FFA rose fourfold during somatostatin while output of beta-hydroxybutyrate increased by 75%.

Estimated hepatic blood flow fell 25–35% and returned to base line as soon as the somatostatin infusion ended.

It is concluded that (*a*) somatostatin-induced hypoglucagonemia results in inhibition of splanchnic glucose output in glycogen-depleted, 60-h fasted subjects as well as in postabsorptive subjects, indicating an effect of glucagon on hepatic gluconeogenesis as well as glycogenolysis; (*b*) the glucagon-sensitive step(s) in gluconeogenesis affected by somatostatin involves primarily intra-hepatic disposal rather than net hepatic uptake of glucose precursors; (*c*) splanchnic uptake of fatty acids and ketone output are increased in the face of combined insulin and glucagon deficiency; and (*d*) diminished splanchnic blood flow may contribute to some of the effects of somatostatin on splanchnic metabolism.

INTRODUCTION

Somatostatin, a tetradecapeptide, originally isolated from the hypothalamus (1) and also subsequently identified in the D cells of the islets of Langerhans (2), has been demonstrated to inhibit the secretion of growth hormone, insulin, and glucagon in both in vivo and in vitro systems (1, 3–11). Administration of somatostatin is accompanied by a fall in blood glucose in man and animals (8, 12, 13), the nature of which is incompletely understood. Studies with isotopically labeled glucose in baboons (4) and isotopically labeled glucose plus hepatic vein catheterization in dogs (14) have suggested that the lowering of blood glucose levels during somatostatin infusion is primarily a consequence of diminished glucose production rather than of increased peripheral utilization. Since no information is available on the influence of somatostatin on hepatic glucose metabolism in man, the present study was undertaken to examine in healthy, postabsorptive subjects the effects of this hormone

Dr. Felig is the recipient of a Research Career Devleopment Award (AM 70219) from the National Institutes of Health.

Reprints may be obtained from Dr. Felig, Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn. 06510.

Received for publication 9 August 1976 and in revised form 11 October 1976.

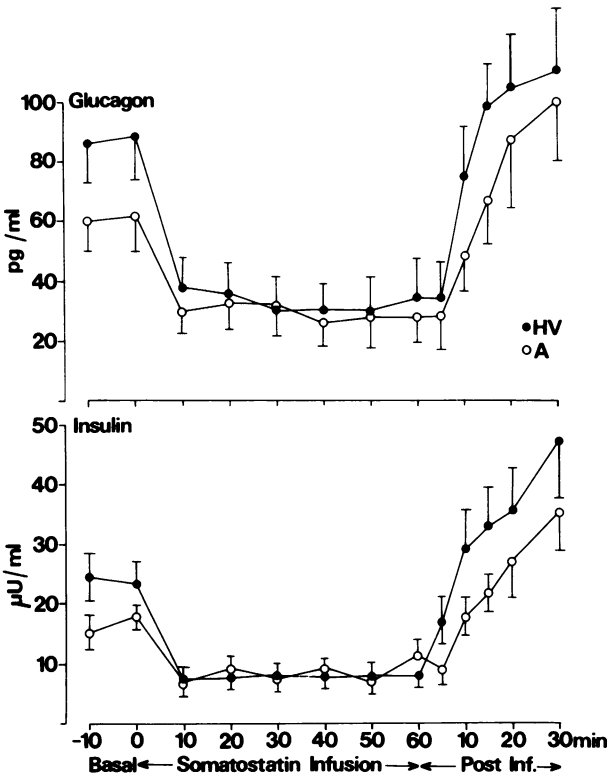

FIGURE 1 Arterial (A) (○ —— ○) and hepatic venous (HV) (● —— ●) concentrations of glucagon and insulin in the basal state, during and after somatostatin infusion (10 μg/min) in postabsorptive subjects. Mean values±SE are indicated.

on splanchnic glucose output and uptake of glucose precursors.

In the postabsorptive, overnight-fasted individual approximately 75% of hepatic glucose output is derived from hepatic glycogenolysis, while the remainder reflects de novo glucose synthesis by hepatic gluconeogenesis (15, 16). Thus an effect of somatostatin on splanchnic glucose output in overnight fasted subjects may reflect an alteration of hepatic glycogenolysis or gluconeogenesis or both. Furthermore, an effect on gluconeogenesis could involve alterations in the uptake and (or) intrahepatic disposal of glucose precursors. To examine more selectively the influence of somatostatin on hepatic gluconeogenesis, healthy subjects who had fasted for 60 h were studied. In this situation glucose production from the liver is primarily dependent on gluconeogenesis, inasmuch as the hepatic glycogen stores are virtually completely exhausted (16). Thus, any effect of somatostatin on hepatic glucose output in the 60-h fasted state should reflect a change in hepatic gluconeogenesis. Furthermore, by measuring net splanchnic exchange of glucose precursors in these subjects information can be obtained on the relative sensitivity to glucagon lack of the processes involved in hepatic uptake and intrahepatic disposal of gluconeogenic substrates.

METHODS

Two groups of subjects were studied, one in the overnight (12–14 h) fasted state (postabsorptive subjects) and the other after 60–64 h of fasting. The former group was made up of 10 healthy, nonobese, male subjects 23–42 yr of age. Their mean body weight was 72 kg (range 67–80 kg). The latter group consisted of five healthy, nonobese, female subjects, who fasted for 60–64 hours before the study. Their age was 24–37 yr and their mean body weight was 61 kg (53–69 kg). The subjects in both groups were all within 10% of ideal body weight (Metropolitan Life Insurance Tables). All subjects were informed of the nature, purpose, and possible risks involved in the study before giving their consent to participate.

Procedure. The subjects were studied in the morning after 12–14 h overnight fast. Catheters were inserted percutaneously into a peripheral vein, a brachial artery and into a right-sided hepatic vein under fluoroscopic control. Blood samples for determination of substrate and hormone concentrations were drawn from the arterial and hepatic venous catheters in the basal state as well as during and after the intravenous infusion of sterile, pyrogen-free cyclic somatostatin (10 μg/min) (Supplied by A. B. Kabi, Stockholm, Sweden, and by Wyeth Laboratories, Radnor, Pa.). The infusion was administered for 60 min and blood sampling continued for 30 min after the end of the somatostatin infusion. Hepatic blood flow was estimated with the continuous infusion technique (17) and indocyanine green dye (18). In six subjects, the study was repeated on another occasion, at which time saline instead of somatostatin was infused intravenously; catheterization and blood sampling procedures were identical, except that no post-infusion samples were drawn after saline infusion.

In the second group of subjects, studied after 60–64 h of fasting, the catheterization procedure, blood sampling, and somatostatin administration were the same as described above.

Analytical methods. Glucose was analyzed in whole blood by the glucose oxidase reaction (19). Lactate (20), pyruvate (21), glycerol (22), and 3-hydroxy-butyrate (23) were all determined enzymatically in whole blood. Individual acidic and neutral amino acids were measured in plasma by the automated ion-exchange chromatographic method (24). Plasma glucagon (25) and insulin were determined by radioimmunoassay, with talc to separate bound and free insulin (26). Plasma free fatty acids were measured by gas chromatography, with heptadecanoic acid as an internal standard (27). Blood urea concentration was determined using a colorimetric method (28).

Data in the text, tables, and figures are given as mean ±SE. Standard statistical methods (29) were employed, with the paired *t* test when applicable.

RESULTS

Postabsorptive subjects. Fig. 1 shows the concentrations of glucagon and insulin in arterial and hepatic venous plasma. A consistently greater concentration (30–55%) of both hormones was observed in samples

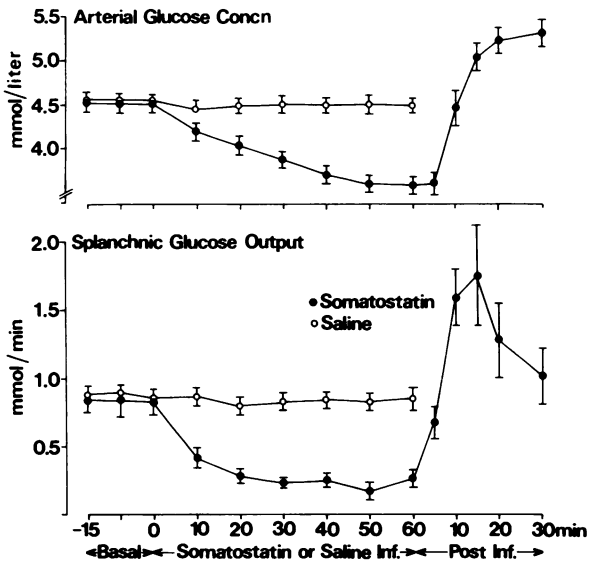

FIGURE 2 Arterial glucose concentration and splanchnic glucose output in the basal state and during infusion of somatostatin (● —— ●) at 10 μg/min or infusion of saline (○ —— ○) in postabsorptive subjects. Mean values±SE are indicated.

from the hepatic vein as compared to arterial samples ($P < 0.02$–0.01). Somatostatin infusion was accompanied by a prompt fall in arterial as well as hepatic venous glucagon concentrations. A new, relatively stable level was established at approximately 50% of the initial arterial glucagon concentration. An hepatic venous-arterial concentration gradient for glucagon was not detectable during the infusion. Similarly, the arterial insulin level fell by 40–50% during somatostatin infusion. A new level was reached and arterial and hepatic venous insulin concentrations became similar. In contrast, a rapid rise in hormone concentrations was observed immediately after the end of the somatostatin infusion, the hepatic venous concentrations rising to significantly higher levels than the arterial (Fig. 1). At 30 min after the end of the somatostatin infusion, both the glucagon ($P < 0.05$) and the insulin ($P < 0.01$) concentrations were still significantly greater than the corresponding basal values.

As expected (4, 12), the arterial glucose concentration fell in response to somatostatin infusion (Fig. 2, Table I). The glucose concentration declined from a basal level of 4.50±0.05 mmol/liter at a gradually diminishing rate during the infusion period, the drop after 60 min amounting to 20% ($P < 0.001$). A prompt increase in blood glucose was observed when the infusion ended, the initial basal level being reached after only 10 min; after 30 min blood glucose showed a 20% increment above preinfusion basal levels ($P < 0.001$). The arterial concentrations of FFA and glycerol rose by 130–170% during somatostatin infusion, while the arterial levels of lactate and pyruvate were unchanged (Table I). The arterial levels of plasma amino acids were not significantly altered during somatostatin infusion, except in the case of glutamine, which showed a 10% rise ($P < 0.01$, Table II).

TABLE I

*Arterial Concentrations and Splanchnic Exchange of Substrates in the Basal State during and after Somatostatin Infusion in Postabsorptive Subjects**

	Basal	Somatostatin infusion, 10 μg/min		Postinfusion
		30 min	60 min	30 min
Arterial concentrations				
Glucose, *mmol/liter*	4.50±0.05	3.87±0.10‡	3.58±0.10‡	5.33±0.15‡
Lactate, *mmol/liter*	0.44±0.02	0.45±0.02	0.43±0.02	0.48±0.04
Pyruvate, *μmol/liter*	44±3	36±1	36±2	30±6
Glycerol, *μmol/liter*	47±3	88±8‡	111±12‖	72±6‡
FFA, *μmol/liter*	398±39	723±68‡	1,075±88‡	1,019±76‡
Splanchnic blood flow, *ml/min*	1,240±70	910±30‖	910±25‖	1,230±80
Splanchnic exchange				
Glucose, *mmol/min*	−0.82±0.06	−0.24±0.03‡	−0.27±0.07‡	−1.02±0.20§
Lactate, *mmol/min*	0.13±0.02	0.19±0.02	0.18±0.02	0.26±0.02‖
Pyruvate, *μmol/min*	6±4	12±2	14±2	18±3§
Glycerol, *μmol/min*	30±3	56±5‡	74±9‡	55±9§
FFA, *μmol/min*	74±13	140±12‖	258±58‖	182±11‡

* Data are given as mean±SE. Values for the basal state represent the mean of two–four observations in each subject.

‡ Significantly different from the corresponding value in the basal state, $P < 0.001$.

§ Significantly different from the corresponding value in the basal state, $P < 0.05$.

‖ Significantly different from the corresponding value in the basal state, $P < 0.01$.

TABLE II

Arterial Concentrations and Splanchnic Exchange of Amino Acids in the Basal State, during and after Somatostatin Infusion in Postabsorptive Subjects

	Arterial concentrations			Splanchnic exchange		
	Basal	60-min Somatostatin infusion	30-min Post-infusion	Basal	60-min Somatostatin infusion	30-min Post-infusion
	μmol/liter ±SE			*μmol/min ±SE*		
Taurine	49±3	49±2	41±3	4.1±2.6	0.6±1.4	0.2±1.5
Threonine	113±11	117±9	115±9	10.6±2.7	7.7±1.2	10.8±4.6
Serine	121±7	122±8	120±7	18.4±3.4	8.8±1.6*	16.0±5.0
Glutamine	575±35	635±24*	629±22	68.1±14.4	53.6±6.4	80.5±17.6
Proline	141±12	135±11	141±12	9.8±2.9	2.2±1.2‡	7.1±4.9
Glycine	177±15	195±16	188±16	11.8±4.2	1.2±3.2‡	12.0±8.9
Alanine	202±21	195±18	185±15	64.5±8.4	47.7±10.0‡	68.0±12.7
α-NH_2-butyrate	27±2	29±3	29±3	0.6±1.0	−1.5±1.1	−0.1±3.0
Valine	206±9	214±11	221±11	5.1±5.7	0.7±0.7	7.0±8.5
½ Cystine	114±14	93±5	102±10	16.6±5.4	2.5±2.4‡	13.8±7.1
Methionine	25±1	22±1	25±2	3.5±0.6	0.8±0.6	3.6±1.3
Isoleucine	63±3	67±3	68±2	2.1±2.0	−2.9±1.3	0.1±2.8
Leucine	135±18	133±8	141±7	16.3±11.6	−4.0±2.3	0.8±6.2
Tyrosine	46±3	47±3	47±3	6.7±0.8	5.1±0.9	7.5±1.8
Phenylalanine	47±2	50±2	49±2	3.7±1.3	1.7±0.6‡	5.1±1.9

* Significantly different from the corresponding value in the basal state, $P < 0.01$.

‡ Significantly different from the corresponding value in the basal state, $P < 0.05$.

A consistent reduction in estimated hepatic blood flow was seen in each subject during somatostatin infusion (Table I). The fall in blood flow had already occurred after 10 min of somatostatin infusion and the new level at 65–75% of the initial flow was maintained throughout the rest of the infusion period. After the infusion, the blood flow returned to the previous basal level within 10 min and no rebound effect was observed.

Splanchnic glucose output was 0.82±0.06 mmol/min in the basal state and fell during somatostatin infusion (Table I). This was a consequence of reduced hepatic venous-arterial glucose differences ($P < 0.02$–0.01) as well as diminished hepatic blood flow. The fall in glucose output was most marked during the first 10–20 min of the infusion, whereupon the glucose output tended to reach a new level at 20–30% of the initial value. As soon as the somatostatin infusion ended, glucose output from the splanchnic area rose rapidly; the basal level was exceeded and a peak value 120% greater than the basal was observed at 15 min after termination of the somatostatin infusion (Fig. 2).

A consistent net uptake of lactate and pyruvate by the splanchnic bed was observed in the basal state (Table I). No significant alteration in splanchnic exchange was seen during the somatostatin infusion. However, an increased uptake of both substrates was noted at 30 min after the end of infusion. In the case of glycerol and FFA, splanchnic uptake increased markedly during the somatostatin infusion (Table I). The augmented uptake of FFA was a consequence of both a rise in arterial concentration and an increase in splanchnic fractional uptake. The latter rose from 0.19±0.03 in the basal state to 0.33±0.04 during somatostatin infusion ($P < 0.001$). Splanchnic uptake of amino acids fell during somatostatin infusion (Table II) in the case of alanine (25%, $P < 0.05$), serine (50%, $P < 0.01$), proline, glycine, cystine, and phenylalanine (55–85%, $P < 0.05$).

60-h fasted subjects. Insulin and glucagon concentrations in arterial and hepatic venous plasma in the 60-h fasted subjects are shown in Fig. 3. This group demonstrated higher levels of arterial glucagon (+45%, $P < 0.02$) and lower concentrations of arterial insulin (−55%, $P < 0.005$) than the overnight fasted subjects. Like the latter group, the 60-h fasted subjects had a positive hepatic venous-arterial concentration difference for glucagon ($P < 0.01$) as well as for insulin ($P < 0.02$) during the preinfusion control period. During somatostatin infusion the arterial levels of glucagon and insulin fell 40–50% while the hepatic venous concentrations no longer differed statistically from the arterial levels. Relatively stable arterial concentrations were reached for both hormones after 10–20 min and were maintained until the end of the infusion period.

The fasted subjects demonstrated decreased arterial

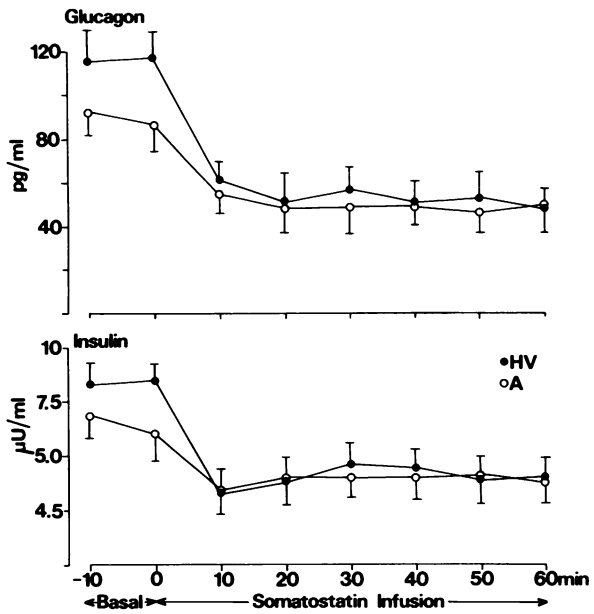

FIGURE 3 Arterial (A) (○ —— ○) and hepatic venous (HV) (● —— ●) concentrations of glucagon and insulin before, during, and after somatostatin infusion (10 μg/min) in 60-h fasted subjects. Mean values±SE are indicated.

glucose levels (as compared to postabsorptive subjects) before somatostatin administration (3.27±0.14 mmol/liter vs. 4.5±0.05, $P < 0.01$). During the first 40 min of the somatostatin infusion the arterial glucose concentration showed a further, progressive decline and then remained relatively stable at approximately 2.5 mmol/liter for the final 20 min (Fig. 4). None of the subjects developed clinical symptoms of hypoglycemia.

The arterial concentrations of glycerol and FFA rose two to threefold during the somatostatin infusion (Table III). A small (10%) but significant rise in the arterial level of 3-hydroxybutyrate was also seen at the end of the infusion period ($P < 0.01$). The arterial levels of lactate and pyruvate did not change significantly during the somatostatin infusion. The arterial levels of amino acids were also stable during the infusion (Table IV).

As in the overnight fasted group, the estimated hepatic blood flow fell during somatostatin infusion in the 60 h fasted subjects. The basal value was 1,400±65 ml/min and a 25% reduction occurred during somatostatin administration ($P < 0.01$). The glucose output from the splanchnic area amounted to 0.30±0.04 mmol/min after 60 h of fasting, a rate of production that is approximately 35% of that for overnight fasted subjects ($P < 0.01$) (Table I). Somatostatin infusion induced a prompt reduction of glucose output (Fig. 4) to a new level at approximately 30% of the initial value. This level was maintained for the rest of the infusion period.

Splanchnic uptake of both lactate ($P < 0.01$) and pyruvate ($P < 0.05$) was increased two- to fourfold after 60 h of fasting compared with the postabsorptive state (Table III). This was primarily a consequence of an increased fractional extraction, since the arterial levels were similar under both conditions. During the infusion of somatostatin, lactate uptake by the splanchnic area fell 30% ($P < 0.01$) and pyruvate uptake fell 40% (Table III). In keeping with the marked increments in arterial concentrations of glycerol and FFA, four- to five-fold elevations in the splanchnic uptake of these substrates were observed. In addition, the splanchnic fractional uptake of FFA rose from 0.12±0.03 in the basal state to 0.21±0.04 ($P < 0.05$) at 30 min of the infusion and to 0.28±0.08 ($P < 0.02$) after 60 min of somatostatin infusion. Splanchnic production of 3-hydroxybutyrate rose 75% during the infusion of somatostatin (Table III).

Splanchnic exchange of amino acids in the 60-h fasted subjects did not change significantly during somatostatin administration (Table IV). Blood urea concentrations were also measured. The arterial level of urea was 5.4 mmol/liter in the basal state and was stable during the somatostatin infusion. Splanchnic urea output was 0.20±0.04 mmol/min in the basal state and 0.16±0.04 and 0.13±0.05 mmol/min at 30 and 60 min, respectively, of somatostatin infusion. However, these changes in urea production did not attain statistical significance.

DISCUSSION

The present findings demonstrate that administration of somatostatin in man is accompanied by a marked inhibition of splanchnic glucose output. When given

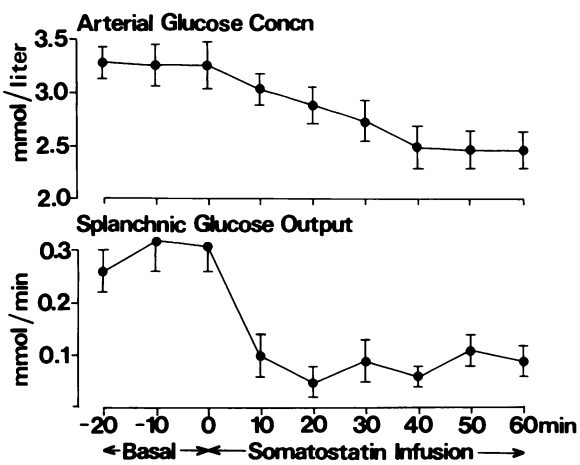

FIGURE 4 Arterial glucose concentration and splanchnic glucose output before, during, and after somatostatin infusion (10 μg/min) in 60-h fasted subjects. Mean values±SE are indicated.

TABLE III

*Arterial Concentrations and Splanchnic Exchange of Substrates in the Basal State, during, and after Somatostatin Infusion of 60-H Fasted Subjects**

	Basal	Somatostatin infusion 30 min	Somatostatin infusion 60 min
Arterial concentrations			
Glucose, *mmol/liter*	3.27±0.14	2.72±0.20‡	2.46±0.17‡
Lactate, *mmol/liter*	0.50±0.02	0.48±0.01	0.53±0.02
Pyruvate, *μmol/liter*	30±3	30±2	29±3
Glycerol, *μmol/liter*	92±9	127±15	329±54‡
FFA, *μmol/liter*	950±88	1,028±68	2,046±184‡
3-hydroxybutyrate, *mmol/liter*	3.35±0.43	3.25±0.64	3.67±0.68‡
Splanchnic exchange			
Glucose, *mmol/min*	−0.30±0.04	−0.09±0.04‖	−0.09±0.03‡
Lactate, *mmol/min*	0.28±0.03	0.20±0.03‖	0.20±0.04‡
Pyruvate, *μmol/min*	24±2	18±3	14±1§
Glycerol, *μmol/min*	61±9	95±12	300±52‡
FFA, *μmol/min*	93±20	149±31	395±52§
3-hydroxybutyrate, *mmol/min*	−0.48±0.05	−0.48±0.05	−0.85±0.17

* Data are given as mean±SE. Values for the basal state represent the mean of two–four observations in each subject.

‡ Significantly different from the corresponding value for the basal state, $P < 0.01$.

§ Significantly different from the corresponding value for the basal state, $P < 0.001$.

‖ Significantly different from the corresponding value for the basal state, $P < 0.05$.

to subjects in the overnight fasted state, somatostatin resulted in a 70–80% reduction of glucose release (Fig. 2). These observations in human subjects confirm and extend previous findings in animal studies with isotopically labeled glucose (13, 14, 30). In view of the magnitude of the changes in glucose output in the present study (70–80% reduction) and inasmuch as glycogenolysis accounts for the major part (75%) of the liver's glucose production in the basal state (15, 16), it is likely that the fall in glucose production reflects primarily a decreased rate of hepatic glycogenolysis. Hepatic gluconeogenesis may have fallen in these subjects as well but this cannot be determined from the present results. In this context it is noteworthy that the total splanchnic uptake of glucose precursors in the postabsorptive subjects did not fall during somatostatin infusion (Tables I and II).

With regard to the mechanism responsible for the altered hepatic glucose production, a direct effect of somatostatin has been suggested (9). However, somatostatin does not interfere with glucagon-induced hyperglycemia in man (10, 31). Furthermore, in vitro studies have indicated that somatostatin does not by itself inhibit hepatic glucose metabolism (13, 32). Thus the observed redution in glucose output is probably a consequence of somatostatin-induced hormonal changes. Glucagon release from the splanchnic area ceased entirely and the arterial glucagon concentration fell promptly when somatostatin was infused (Fig. 1). In view of the known stimulatory effect of glucagon on hepatic glucose production, it is likely that the acutely induced hypoglucagonemia was a major factor in the inhibition of splanchnic glucose output during somatostatin infusion. This is also suggested by the finding that at the termination

TABLE IV

Arterial Concentrations and Splanchnic Exchange of Amino Acids in the Basal State and during Somatostatin Infusion in 60-H Fasted Subjects

	Arterial concentrations			Splanchnic exchange		
		Somatostatin infusion			Somatostatin infusion	
	Basal	30 min	60 min	Basal	30 min	60 min
	μmol/liter±*SE*			*μmol/min*±*SE*		
Taurine	47±3	43±4	46±4	−2.8±2.5	0.2±0.7	−1.0±0.4
Threonine	57±4	57±7	61±6	14.4±1.4	10.8±2.6	11.3±1.7
Serine	57±5	59±4	60±3	14.4±2.0	11.8±1.6	14.0±2.9
Glutamine	504±7	544±22	578±32	33.6±10.6	25.8±6.3	33.5±9.7
Proline	104±18	135±32	133±22	−4.7±14.7	1.0±22.2	4.5±10.6
Glycine	155±36	178±35	180±30	−0.2±5.6	7.0±4.4	18.3±7.7
Alanine	100±15	102±17	99±14	62.0±3.0	56.4±7.6	53.3±10.2
α-NH_2-butyrate	58±4	66±6	66±8	2.2±2.2	1.2±3.0	5.8±3.4
Valine	412±58	398±55	410±50	3.2±13.8	−1.6±10.1	1.5±4.8
½ Cystine	95±10	84±7	85±6	14.8±7.3	1.6±5.6	4.8±4.0
Methionine	12±1	15±2	14±2	3.7±1.2	0.7±3.4	3.7±0.3
Isoleucine	125±21	122±18	127±17	0.2±2.9	1.0±2.6	−0.3±0.9
Leucine	239±39	233±35	246±30	−0.2±4.9	1.0±1.7	0.5±1.4
Tyrosine	40±4	36±6	39±4	7.2±1.5	8.8±1.4	7.5±1.0
Phenylalanine	41±1	42±4	43±2	7.4±4.3	6.8±1.6	4.8±0.8

of somatostatin infusion, when glucagon concentrations rose and exceeded the basal level, splanchnic glucose output responded similarly and surpassed its basal level.

Fig. 2 demonstrates that the splanchnic glucose output reached a relatively stable level of approximately 0.25 mmol/min during the last 30 min of the infusion period. In addition, the arterial glucose concentration also tended to stabilize towards the end of the infusion, in keeping with previous observations for longer periods of administration (7, 33). In this circumstance (as in the basal state) the rate of peripheral glucose utilization may be estimated as equivalent to the splanchnic glucose output. These observations thus indicate that peripheral glucose uptake was substantially reduced at the end of the infusion of somatostatin (0.25 mmol/min) as compared to the basal state (0.8 mmol/min). This decline coupled with the fall in the insulin suggests a diminution in insulin-dependent glucose uptake. In addition, the possibility of a reduction in cerebral utilization of glucose secondary to an increased availability of alternative substrates (e.g. FFA) cannot be excluded.

Splanchnic glucose output in the 60-h fasted group during the preinfusion control period was less than 40% of that for overnight fasted (postabsorptive) subjects (Tables I and III). Although the subjects in the 60-h fasted group were women while those in the postabsorptive group were men, it is unlikely that the difference in sex was responsible for the lower glucose production observed after the 60-h fast. The total splanchnic uptake of glucose precursors after the 60-h fast could account for more than 80% of the glucose production (Table V), in good agreement with earlier observations in 3-day fasted subjects (34). In view of the large precursor uptake and the fact that the liver glycogen stores are known to be almost entirely depleted after this period of fasting (16), it appears reasonable to assume that the glucose output in this situation derived primarily from gluconeogenesis. The finding that somatostatin infusion in 60-h fasted subjects was accompanied by a substantially reduced rate of glucose output from the splanchnic area thus provides evidence for a somatostatin-induced inhibition of gluconeogenesis. Presumably this effect of somatostatin is a consequence of the fall in plasma glucagon. Although a direct effect of somatostatin on gluconeogenesis has been suggested (9), other studies have failed to confirm those observations with either glycerol or alanine as the substrate (13).

The present findings thus indicate a role for glucagon (at least transiently), in the regulation of gluconeogenesis as well as glycogenolysis during starvation. Of particular interest in this regard is the observation that despite the marked decline in splanchnic glucose output, there was only a moderate drop in the splanchnic uptake of lactate and pyruvate (−30%), no change in amino acid uptake, and a fivefold increment in glycerol uptake during somatostatin infusion. As a consequence, the total splanchnic uptake of glucose precursors exceeded the simultaneous glucose output by as much as 200% (Table V). The results thus suggest that the glucagon-sensitive steps involved in gluconeogenesis are not at the locus of hepatic uptake but involve intrahepatic disposal of glucose precursors. A similar conclusion has been previously reached on the basis of evidence of an intrahepatic stimulatory effect of glucagon on gluconeogenesis in studies involving infusion of glucagon to high physiological levels in normal man (35).

TABLE V

Splanchnic Uptake of Glucogenic Precursors and Glucose Output in 60-h Fasted Subjects before and during Somatostatin (SRIF) Infusion

	Before SRIF	During SRIF infusion
Splanchnic uptake of*		
Lactate, *μmol/min*	140	100
Pyruvate, *μmol/min*	12	7
Glycerol, *μmol/min*	31	150
Amino acids, *μmol/min*	63	65
Total	246	322
Splanchnic glucose output, *μmol/min*	300	90

* Data are given as glucose equivalents.

As expected, the arterial levels of free fatty acids and 3-hydroxybutyrate were elevated in the 60-h fasted subjects. After somatostatin administration hepatic uptake of FFA and ketone output rose. These findings indicate that increased substrate (FFA) availability results in some augmentation of ketogenesis in the absence of basal glucagon secretion.

Somatostatin infusion also resulted in a rise in the splanchnic fractional uptake of FFA in the postabsorptive as well as the 60-h fasted subjects. This could be the result of either a decrease in FFA release from extrahepatic splanchnic tissues or an augmentation of hepatic uptake of arterial FFA. In view of the elevation in arterial FFA and glycerol concentrations indicating an overall increase in lipolysis, a diminution in extrahepatic splanchnic release of FFA seems unlikely. A direct hormonal effect on hepatic uptake of FFA has not to our knowledge been previously described. The present results suggest the possibility that hypoinsulinemia and (or) hypoglucagonemia may stimulate hepatic FFA uptake.

In both the postabsorptive and the 60-h fasted individuals, somatostatin induced a prompt reduction of the estimated hepatic blood flow. Noteworthy in

this context is the report that the administration of somatostatin was followed by cessation of gastrointestinal bleeding in a patient with peptic ulcer (36). With the technique employed for flow measurement in the present study it is not possible to distinguish between changes in arterial hepatic as opposed to portal venous blood flow. Thus the distribution of blood flow in the splanchnic area during somatostatin administration remains to be determined. However, since the splanchnic metabolite changes in the 60-h fasted individuals largely parallel the changes in blood flow, the effects of somatostatin on splanchnic blood flow may be central to the mechanism of action of this agent on glucose homeostasis in starvation.

It should be noted that the current investigation involved infusions of somatostatin lasting no more than 60 min. Recent studies have demonstrated the progressive development of fasting hyperglycemia in normal subjects infused with somatostatin for periods extending beyond 2–4 h (37, 38). Thus the effects of hypoglucagonemia on splanchnic glucose balance observed in the current study may not apply to more prolonged periods of somatostatin administration.

ACKNOWLEDGMENTS

We wish to express our appreciation to A. B. Kabi, Stockholm, Sweden and to Dr. Virginia Upton, Wyeth Laboratories, Radnor, Pa. for their generosity in supplying somatostatin.

The study was supported by grants from the Swedish Medical Research Council (19X-34-11, 19X-3108, 19X-722), Nordisk Insulinfond, and the National Institutes of Health (AM 13526).

REFERENCES

1. Braneau, P., W. Vale, R. Burgus, N. Ling, M. Butcher, J. Rivier, and R. Guillemin. 1973. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. *Science (Wash. D. C.).* **179:** 77–79.
2. Hökfelt, T., S. Efendić, C. Hellerström, O. Johansson, R. Luft, and A. Arimura. 1975. Cellular localization of somatostatin in endocrine-like cells and neurons of the rat with special references to the A_1-cells of the pancreatic islets and to the hypothalamus. *Acta Endocrinol.* **80**(Suppl. 200): 41 pp.
3. Hall, R., G. M. Besser, A. V. Schally, D. H. Coy, D. Evered, D. J. Goldie, A. J. Kastin, A. S. McNeilly, C. H. Mortimer, C. Phenekos, W. M. G. Tunbridge, and D. Weightman. 1973. Action of growth-hormone-release inhibitory hormone in healthy men and in acromegaly. *Lancet.* **2:** 581–584.
4. Koerker, D. J., W. Ruch, E. Chideckel, J. Palmer, C. J. Goodner, J. Ensinck, and C. C. Gale. 1974. Somatostatin: Hypothalamic inhibitor of the endocrine pancreas. *Science (Wash. D. C.).* **184:** 482–484.
5. Alberti, K. G. M. M., N. J. Christensen, S. E. Christensen, Aa. P. Hansen, J. Iversen, K. Lundbaek, K. Seyer-Hansen, and H. Ørskov. 1973. Inhibition of insulin secretion by somatostatin. *Lancet.* **2:** 1299–1301.
6. Efendić, S., R. Luft, and V. Grill. 1974. Effect of somatostatin on glucosse induced insulin release in isolated perfused rat pancreas and isolated rat pancreatic islets. *FEBS (Fed. Eur. Biochem. Soc.) Lett.* **42:** 169–172.
7. Sakurai, H., R. Dobbs, and R. H. Unger. 1974. Somatostatin-induced changes in insulin and glucagon secretion in normal and diabetic dogs. *J. Clin. Invest.* **54:** 1395–1402.
8. DeVane, G. W., T. M. Siler, and S. S. C. Yen. 1974. Acute suppression of insulin and glucose levels by synthetic somatostatin in normal human subjects. *J. Clin. Endocrinol. Metab.* **38:** 913–915.
9. Oliver, J. R., and S. R. Wagle. 1974. Studies on the inhibition of insulin release, glycongenolysis and gluconeogenesis by somatostatin in the rat islets of Langerhans and isolated hepatocytes. *Biochem. Biophys. Res. Commun.* **62:** 772–777.
10. Efendic, S., R. Luft, and A. Claro. 1976. Studies on the mechanism of somatostatin action on insulin release in man. II. Comparison of the effects of somatostatin on insulin release induced by glucose, glucagon and tolbutamide. *Acta Endocrinol.* **81:** 743–752.
11. Efendic, S., A. Claro, and R. Luft. 1976. Studies on the mechanism of somatostatin action on insulin release. III. Effect of somatostatin on arginine induced release of insulin and glucagon in man and perfused rat pancreas. *Acta Endocrinol.* **81:** 753–761.
12. Gerich, J. E., M. Lorenzi, S. Hane, G. Gustafson, R. Guillemin, and P. H. Forsham. 1975. Evidence for a physiological role of pancreatic glucagon in human glucose homeostasis: Studies with somatostatin. *Metab. Clin. Exp.* **24:** 175–182.
13. Chideckel, E. W., J. Palmer, D. J. Koerker, J. Ensinck, M. B. Davidson, and C. J. Goodner. 1975. Somatostatin blockade of acute and chronic stimuli of the endocrine pancreas and the consequences of this blockade on glucose homesotasis. *J. Clin. Invest.* **55:** 754–762.
14. Jennings, A. S., A. D. Cherrington, J. L. Chiasson, J. E. Liljenquist, and W. W. Lacy. 1975. The fine regulation of basal hepatic glucose production. *Clin. Res.* **23:** 323A. (Abstr.)
15. Wahren, J., P. Felig, G. Ahlborg, and L. Jorfeldt. 1971. Glucose metabolism during leg exercise in man. *J. Clin. Invest.* **50:** 2715–2725.
16. Nilsson, L. H:son, P. Fürst, and E. Hultman. 1973. Carbohydrate metabolism of the liver in normal man under varying dietary conditions. *Scand. J. Clin. Lab. Invest.* **32:** 331–337.
17. Bradley, S. E., E. J. Ingelfinger, G. P. Bradley, and J. J. Curry. 1945. The estimation of hepatic blood flow in man. *J. Clin. Invest.* **24:** 890–897.
18. Rowell, L. B., J. R. Blackmon, and R. A. Bruce. 1964. Indocyanine green clearance and estimated hepatic blood flow during mild to maximal exercise in upright man. *J. Clin. Invest.* **43:** 1677–1690.
19. Huggett, A. S. G., and D. A. Nixon. 1957. Use of glucose oxidase, perioxidase, and o-dianisidine in determination of blood and urinary glucose. *Lancet.* **2:** 368–370.
20. Wahren, J. 1966. Quantitative aspects of blood flow and oxygen uptake in the human forearm during rhythmic exercise. *Acta Physiol. Scand.* **67**(Suppl. 269): 1–93.
21. Bücher, R., R. Czok, W. Lamprecht, and E. Latzko. 1962. Pyruvat. *In* Methoden der Enzymatischen Analyse. H. U. Bergmeyer, editor. Verlag-Chemie, Weinheim, W. Germany. 253.
22. Wieland, O. 1962. Glycerin. *In* Methoden der Enzymatischen Analyse. H. U. Bergmeyer, editor. Verlag-Chemie, Weinheim, W. Germany. 211.
23. Williamson, D. H., J. Mellanby, and H. A. Krebs. 1962. Enzymatic determination of D(-)-β-hydroxybutyric acid and acetoacetic acid in blood. *Biochem. J.* **82:** 90–96.

24. Spackman, D. H., W. H. Stein, and S. Moore. 1958. Automatic recording apparatus for use in the chromatography of amino acids. *Anal. Chem.* **30**: 1190–1206.
25. Aguilar-Parada, E., A. M. Eisentraut, and R. H. Unger. 1969. Pancreatic glucagon secretion in normal and diabetic subjects. *Am. J. Med. Sci.* **257**: 415–419.
26. Rosselin, G., R. Assan, R. S. Yalow, and S. A. Berson. 1966. Separation of antibody-bound and unbound peptide hormones labelled with iodine-131 by talcum powder and precipitated silica. *Nature (Lond.).* **212**: 355–357.
27. Hagenfeldt, L. 1966. A gas chromatographic method for the determination of individual free fatty acids in plasma. *Clin. Chim. Acta.* **13**: 266–268.
28. Fawcett, J. K., and J. E. Scott. 1960. A rapid and precise method for the determination of urea. *J. Clin. Pathol. (Lond.).* **13**: 156–159.
29. Snedecor, G. W., and W. G. Cochran. 1967. Statistical Methods. Iowa State University Press, Ames, Iowa. 6th edition. 593 pp.
30. Altszuler, N., B. Gottlieb, and J. Hampshire. 1976. Interaction of somatostatin, glucagon and insulin on hepatic glucose output in the normal dog. *Diabetes.* **25**: 116–121.
31. Gerich, J. E., M. Lorenzi, V. Schneider, and P. H. Forsham. 1974. Effect of somatostatin on plasma glucose and insulin responses to glucagon and tolbutamide in man. *J. Clin. Endocrinol. Metab.* **39**: 1057–1060.
32. Sakurai, H., and R. Unger. 1976. Effects of somaostatin (SRIF) on insulin (I) and glucagon (G) and I/G ratio in normal and diabetic dogs. *Diabetes.* **23**(Suppl. 1): 365. (Abstr.).
33. Gerich, J. E., M. Lorenzi, D. M. Bier, E. Tsalikian, V. Schneider, J. H. Karam, and P. H. Forsham. 1976. Effects of physiological levels of glucagon and growth hormone on human carbohydrate and lipid metabolism. Studies involving administration of exogenous hormone during suppression of endogenous hormone secretion with somatostatin. *J. Clin. Invest.* **57**: 875–884.
34. Garber, A. J., P. H. Menzel, G. Boden, and O. E. Owen. 1974. Hepatic ketogenesis and gluconeogenesis in humans. *J. Clin. Invest.* **54**: 981–989.
35. Chiasson, J. L., J. E. Liljenquist, B. C. Sinclair-Smith, and W. W. Lacy. 1975. Gluconeogenesis from alanine in normal postabsorptive man. Intrahepatic stimulatory effect of glucagon. *Diabetes.* **24**: 574–584.
36. Mattes, P., S. Raptis, Th. Heil, H. Rasche, and R. Scheck. 1975. Extended somatostatin treatment of a patient with bleeding ulcer. *Horm. Metab. Res.* **7**: 508–511.
37. Sherwin, R. S., J. Wahren, and P. Felig. 1976. Evanescent effects of hyper- and hypoglucagonemia on blood glucose homeostasis. *Metab. Clin. Exp.* **25**: 1381–1383.
38. Sherwin, R. S., R. Hendler, R. A. DeFronzo, J. Wahren, and P. Felig. 1977. Glucose homeostasis during prolonged suppression of insulin and glucagon secretion by somatostatin. *Proc. Natl. Acad. Sci. U.S.A.* In press.