

Antidiabetic Action of Somatostatin— Assessed by the Artificial Pancreas

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SUMMARY

By means of a glucose-controlled insulin- and glucose-infusion system (GCIGIS) we examined the effect of somatostatin on insulin and glucose requirements following meals or oral glucose loads in juvenile diabetics.

In six of seven patients the insulin requirement with somatostatin was remarkably reduced to between 38 per cent and 79 per cent of that of otherwise identical control experiments. No reduction could be found in the seventh case, fed only 575 kcal. In all cases we observed an increase in dextrose demanded from the GCIGIS ranging between 28 per cent and 192 per cent of the control amounts. In addition, a lowering and smoothing of postprandial blood glucose curves caused by somatostatin application was a general finding.

It seems to us most likely that the well-known suppression of the secretion of growth hormone and glucagon, both insulin antagonists, is responsible for the antidiabetic action of somatostatin. *DIABETES* 24:988-96, November, 1975.

The unique capacity of the hypothalamic hormone somatostatin to inhibit the secretion of the pituitary hormones (studies in humans,¹⁻⁷ studies in animals⁸⁻¹¹) as well as of insulin and glucagon (studies in humans,^{6,7,12,13} studies in animals^{14,15}) has been well documented. Moreover, observations in vitro that somatostatin inhibits release of glucagon as well as of growth hormone,^{12,16-22} both of which counteract the action of insulin, have raised new optimism

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as regards its use in insulin-deficient juvenile diabetics as an adjunct to insulin therapy. The artificial pancreas has provided a unique means of assessing the profound action of somatostatin on pre- and postprandial insulin and glucose requirements. Not only did the application of the apparatus facilitate an unbiased view of the magnitude of the antidiabetic action of the hypothalamic hormone on the basis of only a few experiments; it also permitted a direct insight into the mechanism of this action.

MATERIALS AND METHODS

Artificial Pancreas or Glucose-controlled Insulin- and Glucose-infusion System (GCIGIS)

The artificial pancreas or the *glucose-controlled insulin- and glucose-infusion system* (GCIGIS) used herewith has been described elsewhere.^{23,24} The program was instituted following the pioneer work of Kadish,²⁵⁻²⁷ Kadish and Litle,²⁸ Shames,²⁹ Kline et al.,³⁰ and Srinivasan et al.³¹ considering certain more recent modifications.³²⁻³⁶ The modifications consist of measuring the blood sugar values per se as well as the rate of changes in blood glucose concentrations as the factor determining reactive insulin releases. An extrapolated "predicted" glucose value is computed in order to reduce the delay caused by enzymatic blood glucose determination. An initial peak of insulin infusion is generated as soon as the increase in blood glucose is detected. Thus, the rate of increase is reduced. On the other hand, as soon as a decrease in blood glucose appears, the insulin infusion rate is depressed disproportionately and, if required, glucose is infused.

The system consists of (a) a Technicon AutoAnalyzer measuring blood glucose levels continuously, (b) a microcomputer (Life Science Instruments, Miles Laboratories, Elkhart, Indiana) programmed for the optimal adaptation of the diabetics to the artificial endocrine pancreas by determining the rates of insulin

and glucose infusion and management of dose adjustments, (c) a specially designed pump system (Life Science Instruments, Miles Laboratories, Elkhart, Indiana) and (d) a Teletype (Teleprint), printing out in real time blood glucose levels, rate of insulin and glucose infusion, and a running total of insulin infused during the course of the experiment.

Somatostatin

Synthetic cyclic somatostatin, kindly provided by Serono Pharmaceutical Preparations GmbH,‡ was given as a priming intravenous bolus followed by a secondary infusion (table 1).

Patients

The patients were seven insulin-dependent juvenile diabetics or diabetic children (table 1) from whose parents informed consent, if necessary, was obtained prior to the study. The clinical and biochemical status was established by extensive observations in the hospital or in a home for diabetic children affiliated with the university. The details of three patients are given as examples.

1. *Patient M. C.* A twenty-three-year-old medical student suffering from diabetes for four years was treated with one dose of 28 U. of insulin in the morning (20 U. of Monotard and 8 U. of Actrapid Regular Novo), on which regimen the daily blood glucose levels fluctuated between 60 and 320 mg./100 ml. Liability to hypoglycemic reactions was present predominantly in the morning hours. Urinary glucose was positive in nearly all samples; acetone was not excreted. Diabetic microangiopathy was absent.

2. *Patient K. J.* A fourteen-year-old boy suffered from diabetes mellitus for eleven years. Sudden onset of diabetic coma. Insulin treatment consisted of 28 U. of Novo Rapitard in the morning and 16 U. of Novo Rapitard in the evening. Daily variations of blood glucose levels were between 100 and 400 mg./100 ml.; glucose excretion amounted to 10-50 gm. per day. Multiple microaneurysms were present in both eyes.

3. *Patient R. G.* Also a fourteen-year-old boy, whose diabetes mellitus was discovered one year ago. Insulin dose consisted of injection of 30 U. Depot Insulin Hoechst in the morning and of 20 U. Depot Insulin Hoechst in the evening. Frequent hypoglycemia was noted; coma and ketoacidosis were never observed. No signs of diabetic microangiopathy were established by ophthalmoscopy.

‡ We are indebted to Dr. Romandini, of Serono, Freiburg, Germany, for a generous supply of somatostatin.

Meals

The day before the control experiment the patients received their usual morning insulin dose and diet. In the evening they were attached to the artificial beta cell. After a steady-state period lasting at least three hours, with blood glucose levels between 80 and 90 mg./100 ml. and constant rates of insulin and dextrose infusion (insulin infusion: 5-15 mU./min.; dextrose infusion: 5-10 mg./min.), at about noon the experiments were started. The patients were fed meals composed of 40 per cent carbohydrate, 20 per cent protein, and 40 per cent fat. In two cases 100 gm. glucose was given as a challenge instead of standard meals (table 2).

On the day following the control experiment somatostatin was applied under otherwise identical conditions before food and glucose consumption. Somatostatin was given as an intravenous bolus of 250 μ g., followed by a continuous intravenous infusion of 250 μ g. per hour.

Control of Side Effects During Somatostatin Infusion

At the time of our experiments we were unaware of possible hemorrhagic complications following long-term treatment with somatostatin. Nevertheless, we examined side effects of our short-term somatostatin experiments on enzyme patterns of liver and heart, on renal function, and on blood count. These parameters were analyzed just before and one day as well as two weeks after somatostatin application.

During the infusion of somatostatin, heart action and vascular system were controlled by continuously monitoring the electrocardiogram and regular measurement of blood pressure and pulse rate. The patients were asked to report any discomfort that occurred during and after the experiment.

RESULTS

Figure 1 (patient M. C.) illustrates, first of all, the marked reduction in total insulin (from 22.8 U. to 4.9 U.) required for the second part of the eight hours of somatostatin infusion. Secondly, a considerable lower and smoother blood sugar curve was observed with somatostatin in spite of food intake of 800 kcal. Moreover, the exogenous glucose demanded by the apparatus was significantly higher with somatostatin than without it.

Figure 2 (patient K. J.) demonstrates in a similar fashion the marked reduction in the insulin dose needed to maintain normal blood glucose during five hours of the total eight hours of the experiment (from 22.16 U. to 5.9 U.) effected by somatostatin. Also in

TABLE 1

Clinical and experimental data of seven juvenile diabetics (ages 14 to 27) treated with somatostatin: The diabetic condition of the patients was discovered between one and nineteen years ago and treated with intermediate-acting and regular insulin; the daily dose ranged between 28 and 64 U. Diabetic microangiopathy was present in three cases.

Patients (sex)	M.C. (F)	K.J. (M)	R.G. (M)	B.A. (M)	S.K. (M)	W.E. (F)	SCH.H. (F)
Age in years	23	14	14	27	14	26	17
Duration of diab. mell. in years	4	11	1	2	12	19	3
Diabetic microangiopathy of the retina*	Stage 0	Stage 0-1	Stage 0	Stage 0	Stage 2	Stage 2	Stage 0
Treatment (units of insulin)	20 U. Mon + 8 U. Actr (M.)	28 U. Rap (M.) 16 U. Rap (E.)	30 U. Dep CS (M.) 20 U. Dep CS (E.)	34 U. NPH + 18 U. reg (M.) 18 U. NPH + 16 U. Reg (E.)	24 U. NPH + 16 U. Reg (M.) 14 U. NPH (E.)	12 U. Reg (M.) 8 U. Reg (N.) 16 U. NPH (E.)	44 U. Dep CR (M.) 20 U. Dep CR (E.)
Loads (food or glucose)	800 kcal.	800 kcal.	375 kcal.	1,000 kcal.	100 gm. glucose	800 kcal.	100 gm. glucose
Dose of somatostatin:							
1. I. V. bolus	250 µg.	250 µg.	250 µg.	250 µg.	250 µg.	100 µg.	50 µg.
2. Rate and duration of infusion	250 µg./hr. for 8 hr.	250 µg./hr. for 4 hr.	250 µg./hr. for 7 hr.	250 µg./hr. for 5 hr.	250 µg./hr. for 5 hr.	100 µg./hr. for 5 hr.	50 µg./hr. for 5 hr.
Control experiment:							
1. Insulin requirement	22.8 U.	22.16 U.	6.94 U.	40.95 U.	74.3 U.	76.5 U.	32.8 U.
2. Dextrose demand	1,177 mg.	471 mg.	1,084 mg.	856 mg.	310 mg.	508 mg.	197 mg.
Experiment with somatostatin:							
1. Insulin requirement	4.9 U.	5.9 U.	6.59 U.	21.9 U.	46.1 U.	17.08 U.	9.5 U.
2. Dextrose demand	2,245 mg.	1,011 mg.	2,950 mg.	1,097 mg.	904 mg.	937 mg.	3,218 mg.
Reduction of insulin requirement compared with control experiment	- 78.5%	- 73.4%	No reduction	- 46.5%	- 37.95%	- 77.7%	- 71%
Increase in dextrose demand compared with control experiment	+ 90.7%	+ 114.6%	+ 172%	+ 28.1%	+ 191.6%	+ 84.4%	+ 63%

*According to classification of Oakley et al.⁵⁵

Abbreviations: Mon = Novo Monotard
 Dep CS = Chromatographed Depot Insulin Hoechst (Pork)
 Dep CR = Chromatographed Depot Insulin Hoechst (Beef)
 NPH = Insulin Retard LEO NPH
 Actr = Novo MC Actrapid
 Reg = Insulin LEO
 Rap = Novo Rapitard
 (M.) = Morning dose
 (N.) = dose at Noon
 (E.) = Evening dose

TABLE 2

Compositions of Meals		
Kcal.	carbohydrates	protein fat
M.C.	800	40% = 79 gm. 20% = 39 gm. 40% = 35 gm.
K.J.	800	40% = 79 gm. 20% = 39 gm. 40% = 35 gm.
R.G.	375	40% = 38 gm. 20% = 19 gm. 40% = 20 gm.
B.A.	1,000	40% = 100 gm. 20% = 50 gm. 40% = 44 gm.
S.K.	100 gm. glucose	
W.E.	800	40% = 79 gm. 20% = 39 gm. 40% = 35 gm.
Sch. E.	100 gm. glucose	

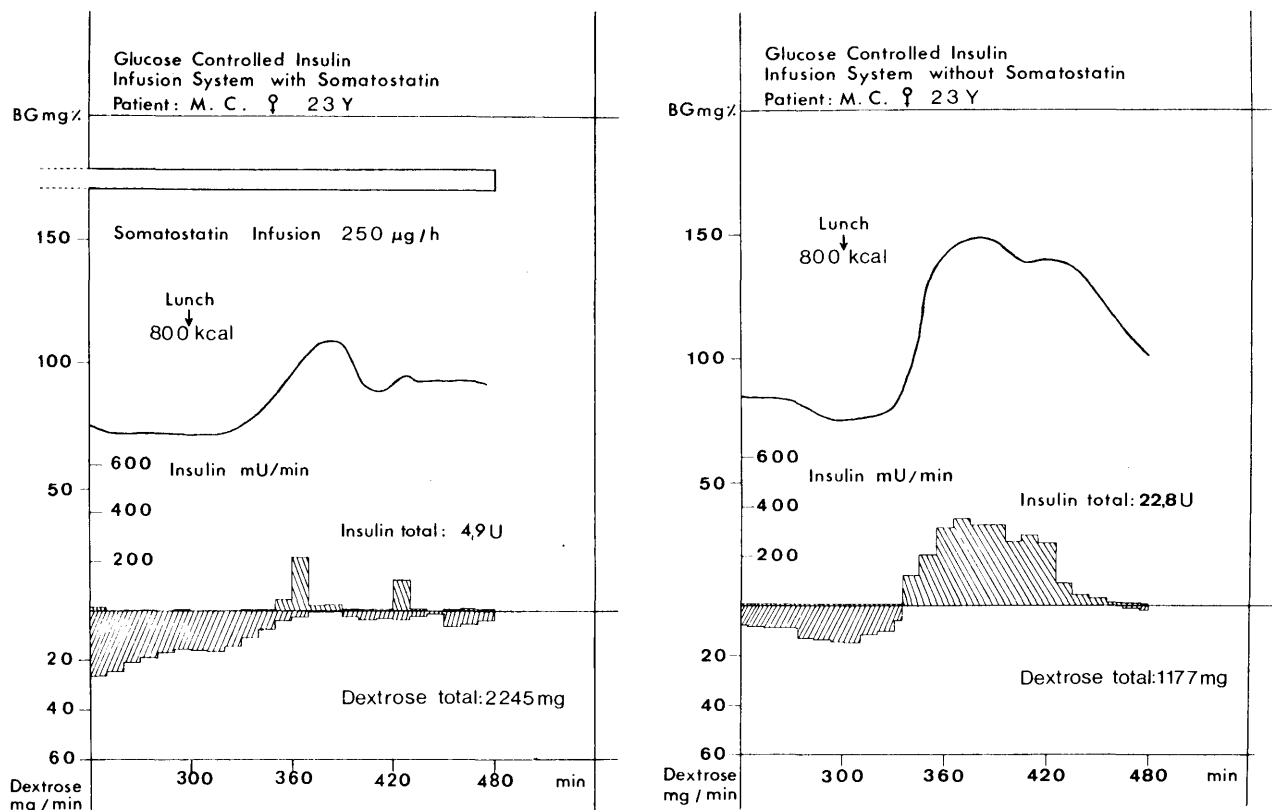


FIG. 1. Continuous blood glucose analysis and glucose-controlled infusion of glucose and insulin by GCIGIS in a juvenile diabetic female during lunch consisting of 800 kcal. with (left) and without (right) a somatostatin infusion of 250 µg. per hour. Somatostatin induces a distinct reduction of insulin requirement.

this case, during the infusion of the somatostatin, plasma glucose levels remained in a much lower range than without administration of the hypothalamic hormone, nearly abolishing the rise in the glucose levels noted following food administration in the control experiment. Indeed, the blood glucose levels during the infusion of the inhibitor remained in the 100-mg./100 ml. range. Furthermore, in this case also, plasma glucose levels were kept constant only by the higher supply of exogenous glucose from the GCIGIS (from 471 mg. glucose before to 1,011 mg. during somatostatin administration).

In figure 3 (patient R. G.) is shown how an intravenous injection and a seven-hour-infusion of somatostatin did not cause marked reduction of insulin requirements following a meal of 375 kcal., 6.94 U. and 6.81 U. of insulin, respectively, being infused. Once again, somatostatin abolished postprandial hyperglycemia, maintaining blood glucose levels in the range of and below 100 mg./100 ml. during most of the experiment. However, in association with a fall of blood glucose to nearly hypoglycemic values of about 60 mg./100 ml., five times more exogenous

glucose was required during somatostatin infusion than in the control experiment (an increase from 1,084 mg. glucose to 5,425 mg.).

In table 1 the findings obtained in all of the seven patients are summarized. In our first five experiments we used the high rate of 250 µg. per hour for somatostatin infusion. When we infused only either 100 µg. per hour or 50 µg. per hour somatostatin showed the same effect: Except in patient R. G. we found reduction of insulin requirement by GCIGIS ranging from 37.95 per cent to 78.5 per cent, whereas we found increased rates of dextrose needed in all seven cases, ranging from 28.1 per cent (B. A.) to 191.6 per cent (S. K.). When glucose (100 gm.) was used as a challenge a less remarkable reduction of insulin requirement (37.95 per cent) was found in patient S. K., but the relatively highest demand of dextrose occurred. Patient Sch. H. showed the expected reduced insulin requirement (71 per cent) and increased demand for dextrose (63 per cent).

In all cases neither the laboratory parameters examined nor heart action or pulse rate were influenced by infusion of somatostatin. Immediately after appli-

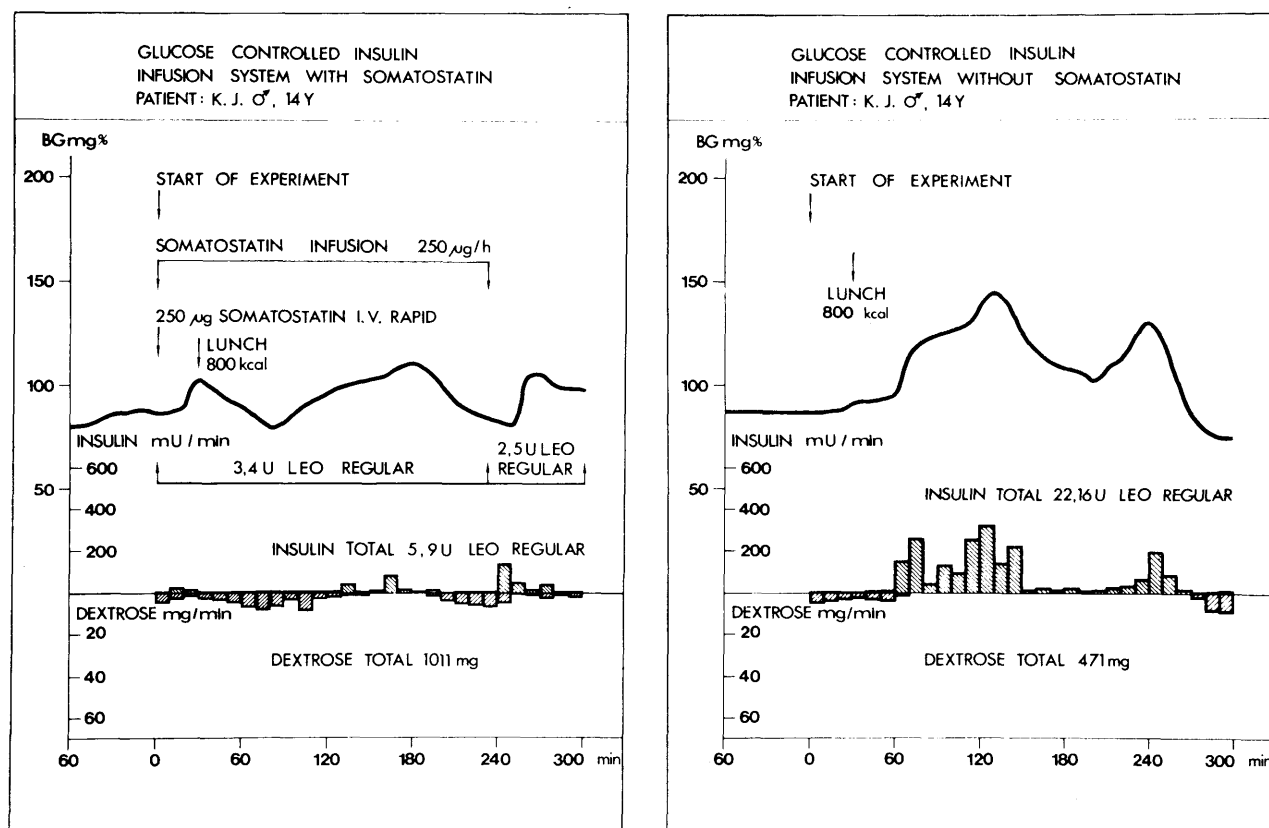


FIG. 2. Continuous blood glucose analysis and glucose-controlled infusion of glucose and insulin by GCIGIS in a diabetic child during a lunch consisting of 800 kcal. with (left) and without (right) a somatostatin infusion of 250 μ g. per hour. Somatostatin induces a distinct reduction of insulin requirement.

cation of the somatostatin bolus the patients complained of flush lasting for thirty to sixty seconds and nausea for three to five minutes. No other clinical symptoms were observed.

DISCUSSION

Somatostatin, a hypothalamic inhibitor, given as an intravenous infusion together with exogenous insulin and glucose—the latter two provided automatically by a glucose-controlled insulin- and glucose-infusion system (GCIGIS)—reduced the postprandial insulin requirements in six of seven juvenile diabetics fed meals of 800 kcal., 1,000 kcal., or 100 gm. glucose to between half and one fourth of the initial dose. After a third patient was fed a meal of 375 kcal., the insulin requirement remained essentially unaltered. However, antidiabetic activity of somatostatin was shown again by a fivefold higher glucose demand from the apparatus.

Since our device is entirely regulated by the blood glucose levels, somatostatin primarily must have decreased the actual insulin demand by means of the

lower blood sugar concentrations. As a matter of fact, not only did the steady-state blood sugar values fall following administration of the somatostatin in two of three cases but also the blood sugar rises following meals were nearly abolished in comparison with those of controls. It has been stated that somatostatin causes a fall in fasting blood sugar levels in diabetics, healthy humans, acromegalics, and baboons^{7,15,37,39} as well as improving glucose uptake in juvenile diabetics.^{15,37,40} On the other hand, Alberti et al.¹² and Mortimer et al.⁶ observed impaired glucose uptake in healthy humans following intravenous or oral glucose. The interesting feature of our experimental design is to be seen in the fact that, despite combined application of somatostatin and insulin at any phase of the experiment, the singular action of the intravenous insulin was shown by the single insulin peaks above the baseline level (figures 1a-3a). Moreover, it was not the insulin secretion derived and calculated in a more or less complicated and uncertain manner from the peripheral immunoinsulin levels but the direct amount of the immediately biologically active quantity that was assessed by our system.

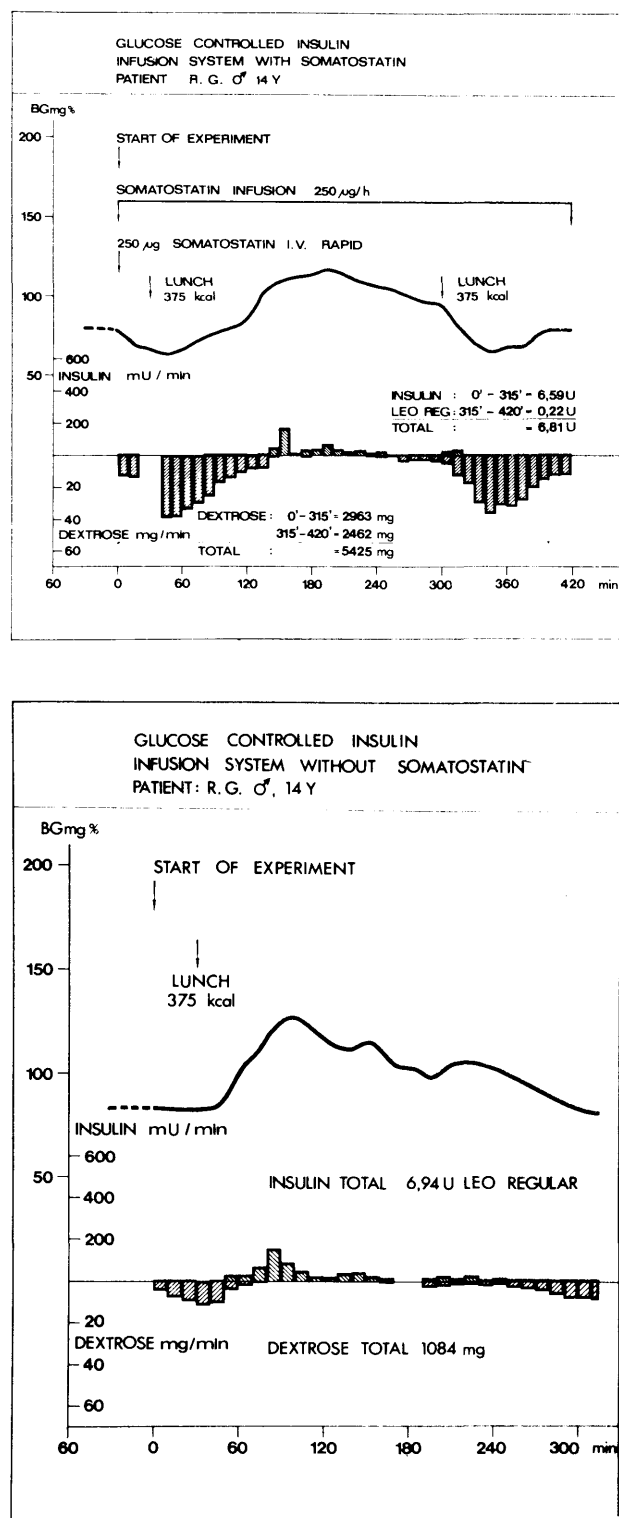


FIG. 3. Continuous blood glucose analysis and glucose controlled infusion of glucose and insulin by GCIGIS in a diabetic child during a lunch consisting of 375 kcal. with (top) and without (bottom) a somatostatin infusion of 250 µg. per hour. No reduction of insulin requirement.

Various explanations for the antidiabetic action of somatostatin might be offered: First of all, somatostatin improves peripheral glucose uptake or inhibits glucose production. Koerker et al.¹⁵ and Goodner et al.⁴¹ concluded from *in vivo* studies that the peripheral utilization of glucose in the presence of somatostatin is unaltered. These results were confirmed by experiments *in vitro* examining the glucose uptake by the rat hemidiaphragm.^{42,43} Mortimer et al.⁶ assumed no direct effect of somatostatin on lipolysis since they observed an obvious correlation between plasma levels of insulin and N.E.F.A., whereas Yen et al.⁷ did not exclude the possibility that somatostatin might have an effect on blood glucose concentration and lipolysis that cannot be attributed to insulin action. According to Koerker et al.,⁴³ Lavis was unable to show effects of somatostatin on lipolysis in isolated adipocytes. In *in-vitro* experiments Sakurai et al.⁴⁴ and Koerker et al.⁴³ found no direct effect on gluconeogenesis and glycogenolysis of liver tissue. On the other hand, glycogenolysis of hepatocytes was found to be inhibited by somatostatin if stimulated by glucagon and to be unaffected if stimulated by epinephrine.⁴⁵

Secondly, somatostatin enhances insulin action, as both reduction in exogenous insulin demands and lowering of blood glucose levels before and after meals were observed when insulin and somatostatin infusion were combined. However, for extended periods of time, marked falls in blood glucose concentrations were established without concomitant insulin infusion (figures 1a-5a). Likewise, nocturnal hypoglycemia in diabetic children (without any intervention on the part of the pituitary or application of somatostatin) were observed on several occasions in our laboratory without any contribution from the exogenous insulin supply from GCIGIS. They were readily prevented by sufficient supply of glucose from the apparatus.^{46,47} Perhaps these changes in glucose utilization might be better explained in these cases by the influence that circadian variations of secretions of metabolically active diabetogenic hormones may also exert on the metabolism of diabetic individuals.⁴⁸⁻⁵¹

This leads us to, thirdly: Somatostatin suppresses the secretion of some of the major hormones exhibiting insulin-antagonistic actions, especially growth hormone and glucagon, since no inhibiting effect of somatostatin on ACTH, corticosteroid, and adrenal catecholamine secretion is known.^{1,15} At present it is difficult to decide to which of the two candidates discussed above, i.e. STH and glucagon, major significance might be ascribed. *In vivo* inhibition of growth hormone secretion in healthy, diabetic, or ac-

romegalic humans^{1-3,6,7,37} as well as of pancreatic and gastroduodenal glucagon release has been established.^{6,37,38,52,53} Furthermore, direct inhibition of growth hormone release in vitro from human and rat pituitary tissue⁹ and of glucagon release from the perfused rat pancreas have been reported.^{17,18}

The lack of the normal amount of the diabetogenic hormones in the peripheral tissues, including the liver, might shift the balance between the forces favorably influencing glucose utilization and their counterparts antagonistic to this action in such a fashion that considerable fall of plasma glucose results. As a matter of fact, the pattern of plasma glucose on the one hand and the demands of insulin and/or glucose from the GCIGIS observed under the influence of somatostatin on the other accord to a large extent with our observations in diabetics subjected to therapeutic hypophysectomy.

However, the decrease in blood glucose levels following somatostatin in a hypophysectomized patient observed by Gerich et al.³⁷ and Pfeiffer et al.⁵⁶ as well as the fall in plasma glucose and in exogenous insulin requirements in a totally pancreatectomized human subject, as also established by means of the artificial pancreas,^{54,56} should stimulate us to examine further whether inhibition of pancreatic and possibly also of gastroduodenal glucagon or of growth hormone secretion can be regarded as *the* most important factor for demonstration of antidiabetic somatostatin action.

In any case, the clear-cut determination of the action of somatostatin in reducing insulin requirements and smoothing the blood sugar curve is giving new hope of perhaps dealing successfully with one of the most urgent problems of diabetology, the development of microangiopathy.

Recently serum growth hormone and glucagon determinations were completed, in part in collaboration with Dr. Lefebvre from Liège, on the serum samples of some of the patients reported herein. Depressions of growth hormone were established uniformly as well as less remarkable decreases in the glucagon levels, the latter in the pancreatectomized patient, too.⁵⁶ Therefore, the question raised above remains open to answer.

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