24-Hour Studies of the Effects of Somatostatin on the Levels of Plasma Growth Hormone, Glucagon, and Glucose in Normal Subjects and Juvenile Diabetics

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SUMMARY

Somatostatin was infused in various doses into normal subjects and juvenile diabetics for a 24-hour period preceded by a 24-hour control period and followed by another three-hour control period. Saline was infused during the first control period. Meals were served during the two 24-hour periods. Blood samples were taken hourly.

Five normal males received a total dose of 4 mg. somatostatin. Four male diabetics received 2 mg., four received 4 mg., and four 6 mg. In the diabetics, somatostatin suppressed plasma growth hormone, glucagon, and glucose throughout the infusion. All parameters rebounded at cessation of infusion. In the normals, somatostatin suppressed plasma growth hormone, glucagon, and insulin but increased plasma glucose.

It is concluded that the plasma glucose suppression in the diabetics is mainly due to the suppression of the diabetogenic hormones growth hormone and glucagon. A minor effect of decreased and/or delayed absorption of carbohydrates cannot be excluded in these experiments. The elevated plasma glucose levels in normals must be due to the suppressive effects of somatostatin on insulin secretion. DIABETES 27:300-06, March, 1978.

Somatostatin strongly inhibits a large number of endocrine and exocrine functions. Moreover, when it is given intravenously its effects disappear immediately after the infusion is stopped. This potent compound cannot, therefore, be used as a drug in clinical practice today. Currently intensive research work is being carried out in various centers to produce one or more clinically acceptable preparations by chemical manipulation of the somatostatin molecule.

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In the future the various inhibitory properties of somatostatin may be applied in the treatment of various disease states. As suggested already in the publication about the discovery of somatostatin by Guillemin and co-workers,[1] one of the potential fields of clinical application is diabetes mellitus.

At the moment there are two schools of thought in the field of diabetes mellitus and somatostatin. As somatostatin is known to inhibit the hypersecretion of growth hormone and glucagon in diabetic patients, it is regarded by some workers primarily as an agent that may be used as a supplement to insulin in an endeavor to lower the blood sugar level of diabetic patients, providing a better control state and thereby probably inhibiting the development of diabetic vascular disease. To others it appears also as a possible direct antiangiopathic agent by virtue of its growth-hormone-depressing effect.

The effect of somatostatin on growth hormone and glucagon hypersecretion in juvenile diabetes has so far been tested in short-term experiments, over some hours, during fasting or in response to various stimuli.[2-12] In the present study the effect of somatostatin on plasma growth hormone, glucagon, and glucose was studied during a 24-hour period in normals and juvenile diabetics.

MATERIAL AND METHODS

The control subjects (table 1) consisted of five healthy young nonobese male medical students. The diabetics (table 2) consisted of 12 young nonobese male subjects with juvenile-type diabetes, one of them newly diagnosed. This patient was put on insulin

TABLE 1

Clinical data for all control subjects investigated

Case no.	Age (yr.)	Ideal body weight (%)	24-hr. plasma glucagon (pg./ml.) saline/somatostatin	24-hr. plasma insulin (μU./ml.) saline/somatostatin	24-hr. plasma glucose (mg./100 ml.) saline/somatostatin	24-hr. plasma growth hormone (ng./ml.) saline/somatostatin
1	23	94	28/13	19/9	103/144	2.6/0.8
2	22	87	26/14	14/6	105/157	2.8/0.8
3	24	93	33/14	29/13	104/130	3.6/1.2
4	23	101	8/6	13/7	89/98	4.8/0.9
5	24	91	28/13	8/4	90/117	4.2/1.4
Mean	23	93	25/12	17/7.8	98/129	3.6/1.0
S.E.M.	0.4	2.3	4.3/1.5	3.5/1.5	3.5/10	0.4/0.1

All 24-hour values are average values of the 24 determinations.

treatment after the experiment. The duration of diabetes of the others varied between one and nine years. They received insulin in one or two daily doses. None of them had signs or symptoms of diabetic angiopathy.

All subjects arrived at the department shortly before 7:30 on the day of the experiment after 12 hours' fasting. Indwelling catheters were inserted bilaterally in antecubital veins for blood sampling and infusion of saline and somatostatin. The experiment started at 8:00. Blood was drawn hourly during the following 51 hours. Occlusion of the catheters was prevented by filling the catheters with saline after every blood drawing. Before sampling, the first 2 ml. of blood was drawn out by a syringe and discarded. Saline (500 ml.) was infused during the first 24 hours. Cyclical somatostatin (dissolved in 500 ml. saline) was infused during the following 24 hours. During the last three hours no infusions were given. The five control subjects received a total dose of 4 mg. somatostatin. Four diabetics received 2 mg. somatostatin, four received 4 mg., and four received 6 mg.

During the study the subjects were confined to bed. During the daytime they were talking, reading, listening to the radio; they were allowed to sleep only during the night. They all followed the dietary program outlined in table 3.

Five-milliliter blood samples for growth hormone, insulin, and glucose determinations were drawn every hour. An additional 4 ml. was drawn every fourth

TABLE 2

Clinical data for all diabetic subjects investigated

Case no.	Age (yr.)	Ideal body weight (%)	Diabetes duration (yr.)	Insulin treatment (units) 8 a.m./5 p.m.	24-hr. plasma glucagon (pg./ml.) saline/somatostatin	24-hr. plasma glucose (mg./100 ml.) saline/somatostatin	24-hr. plasma growth hormone (ng./ml.) saline/somatostatin
Experiments with 2 mg. somatostatin							
6	30	87	1	20 NPH/0	35/28	227/196	2.7/1.7
7	17	89	5	34 NPH/8 NPH 4 reg/2 reg	18/18	268/183	8.9/4.1
8	24	97	6	28 NPH/0	61/67	135/103	6.7/2.6
9	39	99	8	36 NPH/0	35/27	258/207	2.8/1.1
Experiments with 4 mg. somatostatin							
10	28	108	7	20 NPH/0	13/28	182/203	2.6/1.9
11	24	92	0	0	26/15	251/236	5.0/2.8
12	40	99	9	16 NPH/6 NPH 6 reg	30/7	247/208	1.1/0.6
13	30	116	4	18 NPH/6 NPH	15/0	266/205	1.8/1.2
Experiments with 6 mg. somatostatin							
14	24	91	8	26 NPH/6 NPH 6 reg	12/17	247/80	2.4/1.4
15	17	101	6	20 NPH/6 NPH	58/40	216/146	10/3.9
16	22	88	3	16 NPH/4 NPH	47/28	246/286	5.8/1.7
17	35	93	6	24 NPH/12 NPH	42/8	307/145	1.9/0.7
Mean	27	96			33/24	238/183	4.3/2.0
S.E.M.	2.2	2.5			4.8/5.1	13/16	0.9/0.3

TABLE 3

Timetable for the 24-hour periods

8:00-8:30	Breakfast containing	
	protein	6 gm.
	carbohydrate	65 gm.
	lipid	17 gm.
	calories	453
12:00-12:30	Lunch containing	
	protein	24 gm.
	carbohydrate	44 gm.
	lipid	28 gm.
	calories	538
14:30-15:00	Coffee or tea and snack	
17:30-18:00	Dinner containing	
	protein	16 gm.
	carbohydrate	123 gm.
	lipid	28 gm.
	calories	830
21:30-22:00	Coffee or tea and snack	
23:00-7:00	Sleep period	

hour for glucagon determinations and collected in EDTA (final dilution 0.3 per cent) and Trasylol (final dilution 500 kallikrein inactivator units (KIU/ml.)). The samples were immediately chilled in ice water until they were spun at 4° C. within 10 minutes after sampling. Plasma growth hormone, pancreatic glucagon, and insulin were determined by radioimmunoassays using wick chromatography.[13] The growth hormone standard used was a Wilhelmi preparation. Pancreatic-glucagon-specific antibody was kindly provided by Lise Heding (Novo Research Laboratories, Copenhagen), whose procedure was used to extract glucagon from plasma. Novo pork glucagon and Novo human insulin were used for standards. Plasma glucose was measured by a glucose oxidase method.[14]

Paired Student's *t*-tests were used for statistical analysis of differences between saline and somatostatin experiments. Student's *t*-tests were used for determination of differences between normal subjects and diabetics. Dose-response relationships were tested by the Krushal and Wallis multisample test.[15] The correlation coefficient (r) was calculated between parameters. In the case of growth hormone, both numeric values and logarithmic transformed values were used in the calculations.

RESULTS

Normal Subjects

Figure 1 shows the average values of plasma pancreatic glucagon, insulin, glucose, and growth hormone in the five normal subjects during the complete 51-hour period of the experiment: 24 hours with saline infusion followed by 24-hour somatostatin infusion. The experiment ended with a three-hour period between 8 and 11 o'clock, in which no intravenous infusion was performed and no food was given.

Plasma pancreatic glucagon remained low and stable in both saline and somatostatin experiments. At cessation of somatostatin a large rebound occurred. The average 24-hour value was significantly suppressed by somatostatin (12 pg./ml., as against 25 pg./ml.; $p < 0.02$).

Plasma insulin rose after meals in both saline and somatostatin experiments. At cessation a large rebound occurred. The average 24-hour value was significantly suppressed by somatostatin (7.8 μU./ml., as against 17 μU./ml.; $p < 0.02$).

Plasma glucose rose after meals, but the rise was much more pronounced in somatostatin than in saline experiments. The average 24-hour value was higher in somatostatin than in saline experiments (129 mg./100 ml., as against 98 mg./100 ml.; $p < 0.02$). At cessation of somatostatin a slight fall in glucose occurred.

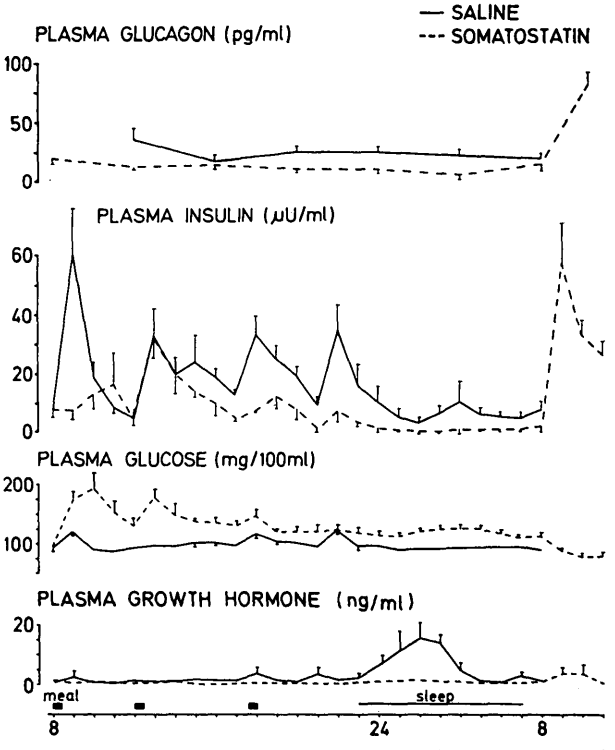

FIG. 1. Plasma pancreatic glucagon, insulin, glucose, and growth hormone during a 24-hour period in five normal male subjects. ——— saline infusion, ------ somatostatin (4 mg.) infusion (mean ± S.E.M.). In this as well as in the following figures the total experiment lasted for 51 hours: a 24-hour period with saline, followed immediately by 24 hours of somatostatin. During the final three-hour period no somatostatin or food was given.

Plasma growth hormone was low during most of the day in saline and somatostatin experiments. The "night peak" seen in the saline experiments did not occur in the somatostatin experiments. The average 24-hour value was significantly suppressed by somatostatin (1.0 ng./ml., as against 3.6 ng./ml.; $p < 0.01$).

Figure 2 shows the individual plasma growth hormone values in the five normal subjects. It can be seen that even the postprandial peaks were blocked by somatostatin. In none of these five control subjects did a spontaneous growth hormone peak break through the somatostatin infusion. At cessation of infusion a rebound occurred in two of the subjects.

Diabetics

Somatostatin (2, 4, and 6 mg.) induced similar changes in plasma pancreatic glucagon, glucose, and growth hormone in the diabetic patients studied.

Figure 3 shows the average value of the three parameters in the 12 diabetics during a 24-hour period with saline infusion, a 24-hour period with somatostatin infusion, and the final three-hour fasting period.

Plasma pancreatic glucagon behaved in diabetics as in normals, with low and stable values during infusions and rebound secretion at cessation of somatostatin. The average 24-hour value was significantly suppressed by somatostatin (24 pg./ml., as against 33 pg./ml.; $p < 0.05$).

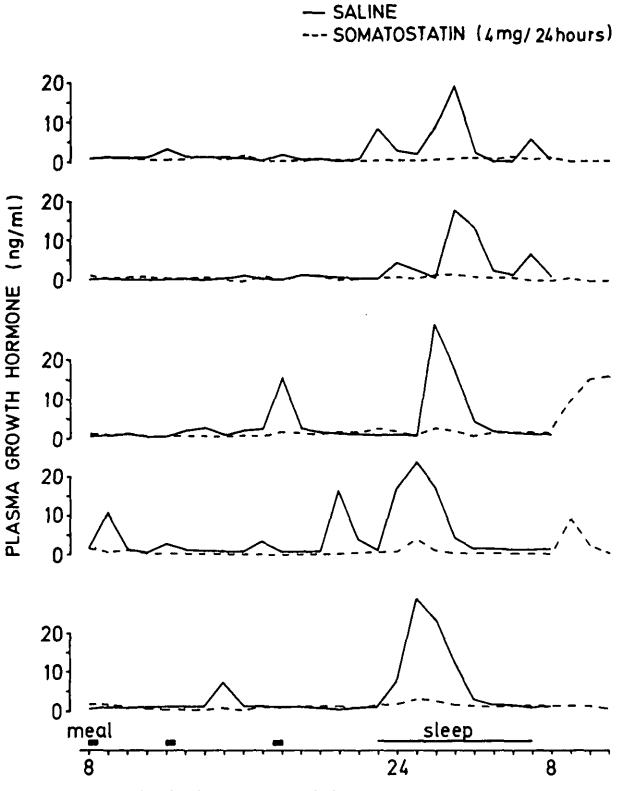

FIG. 2. Individual plasma growth-hormone values during a 24-hour period in five normal male subjects.

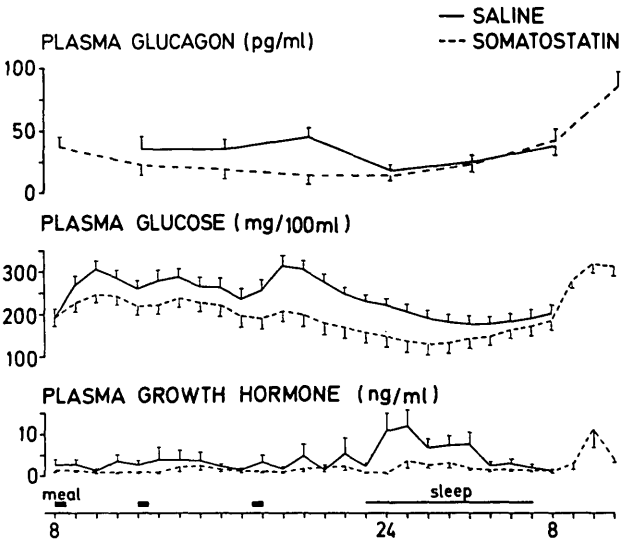

FIG. 3. Plasma pancreatic glucagon, glucose, and growth hormone during a 24-hour period in four juvenile diabetics receiving 2 mg. somatostatin, four receiving 4 mg., and four receiving 6 mg. Mean ± S.E.M.

Plasma glucose rose after meals, but in contrast to what was seen in normals the postprandial peaks were smaller in somatostatin than in saline experiments and cessation of somatostatin induced a glucose rebound.

The fasting value at the start of the first period (control period) was 189 ± 22 mg./100 ml. The fasting value at the start of the somatostatin period, 24 hours later, was 193 ± 19. However, the average 24-hour level was suppressed in somatostatin experiments (183 mg./100 ml., as against 238 mg./100 ml.; $p < 0.002$).

Plasma growth hormone fluctuated during daytime and showed a high "night peak" in saline experiments. The average 24-hour value was significantly suppressed by somatostatin (2.0 ng./ml., as against 4.2 ng./ml.; $p < 0.01$).

Figures 4, 5, and 6 show the individual plasma growth hormone values in the diabetics receiving 2, 4, and 6 mg. somatostatin. During saline experiments large postprandial peaks, night peaks, and spontaneous peaks could be seen in most patients.

In the somatostatin experiments some of these peaks broke through during the infusion; they did not, however, reach the same magnitude as in the saline experiments. Even after 6 mg. of somatostatin two larger peaks occurred. At cessation of infusion a

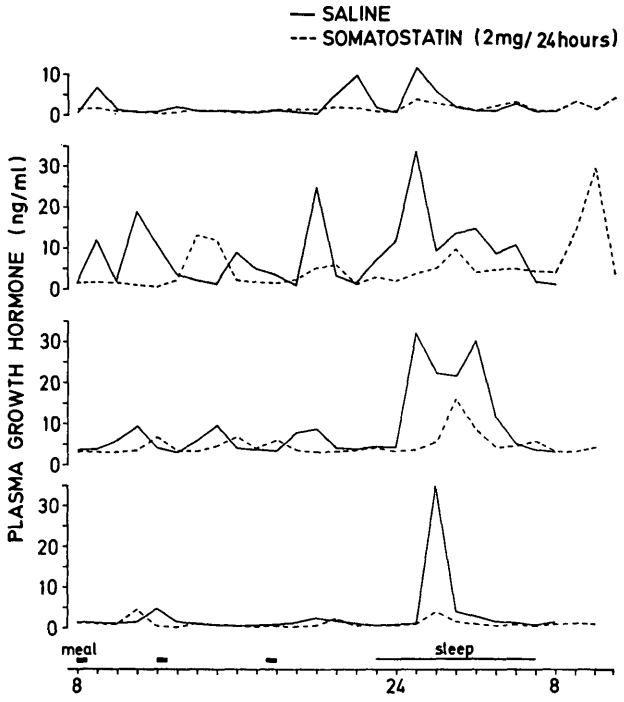

FIG. 4. Individual plasma growth-hormone values during a 24-hour period in four juvenile diabetics receiving 2 mg. somatostatin.

rebound phenomenon could be seen in half of the patients.

The 24-hour values from the saline experiments for the three parameters were tested for correlations. No positive correlations, however, could be found between growth hormone and glucose, between growth hormone and glucagon, or between glucose and glucagon.

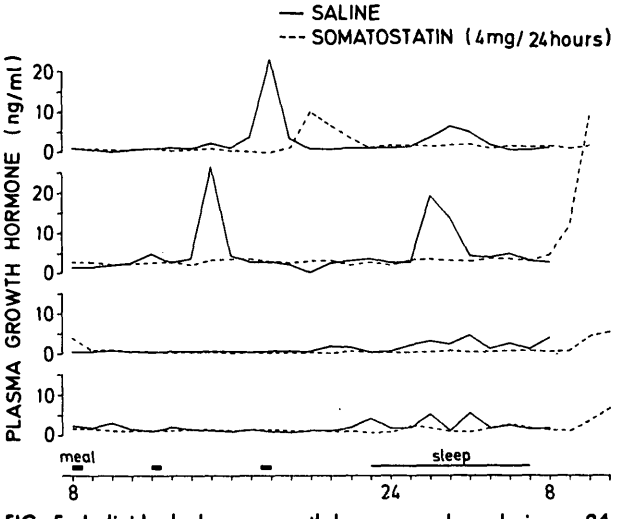

FIG. 5. Individual plasma growth-hormone values during a 24-hour period in four juvenile diabetics receiving 4 mg. somatostatin.

Diabetics Versus Normals

The 24-hour plasma glucose values of the saline experiments were much higher in diabetics than in normals (238 mg./100 ml., as against 98 mg./100 ml.; $p < 0.01$). The 24-hour plasma glucagon values from the saline experiments were higher in diabetics than in normals, but the difference was not statistically significant (33 pg./ml., as against 25 pg./ml.).

The average value of plasma growth hormone was 4.3 ng./ml. in the diabetic group, as against 3.6 in the group of normals. The early-night peak was unusually high in this group of normal persons. The mean of the plasma growth hormone levels from 4 to 23 o'clock was 3.6 ng./ml. in the diabetics and 1.8 in the nondiabetics. This difference is statistically significant (p 0.05).

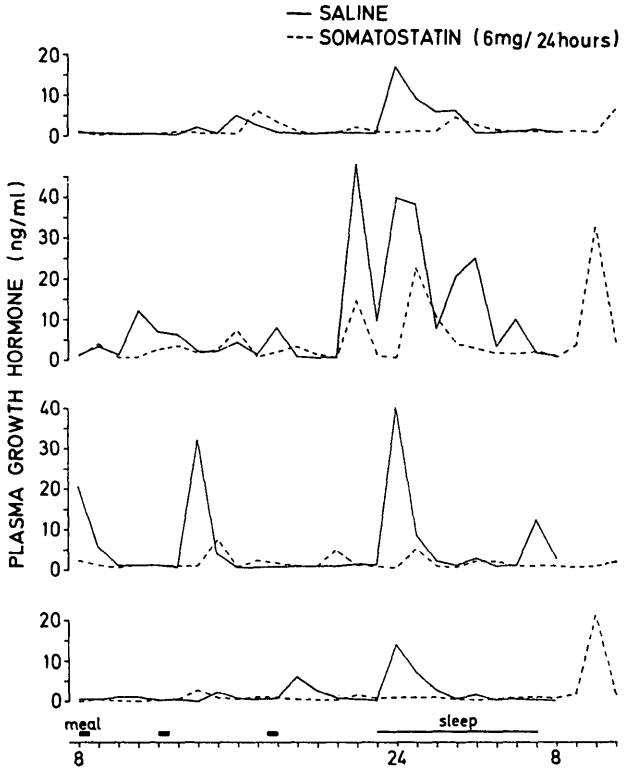

FIG. 6. Individual plasma growth-hormone values during a 24-hour period in four juvenile diabetics receiving 6 mg. somatostatin.

DISCUSSION

It has thus been shown that a continuous infusion of somatostatin to juvenile diabetic patients is able to inhibit the diurnal level of the two diabetogenic hormones, growth hormone and glucagon. These two hormones induce glycogenolysis, gluconeogenesis, and ketosis. The reduction of the plasma level of the

two hormones is probably of major importance for the lowering effect of somatostatin on the diurnal level of plasma glucose found in the juvenile-diabetic patients.

Our results confirm those obtained by Gerich et al.[7] in experiments directly aiming at the clinical situation in diabetes control. They showed that somatostatin given subcutaneously with insulin before meals was able to prevent the postprandial rise in plasma glucose and glucagon in juvenile diabetics. These results indicate that a suitable somatostatin analogue may in the future be used in the day-to-day control of diabetic patients.

The idea of using somatostatin to inhibit diabetic angiopathy is a consequence of the growth-hormone hypothesis according to which growth hormone is a causal factor in the development of diabetic vascular disease.[16-18] The growth-hormone hypothesis is based on two facts: (1) plasma growth hormone is high in diabetic patients;[19-22] (2) pituitary ablation followed by substitution with thyroid, steroid, and gonadal hormones inhibits the development of diabetic angiopathy, as shown in a controlled clinical trial and described with full documentation.[23] The effect of pituitary ablation in this trial was not due to a Houssay effect. The diabetes-control state of the hypophysectomized patients was not better than that of the nonhypophysectomized patients. The growth hormone hypothesis has found support in studies of growth-hormone-deficient dwarfs[24-26] as well as in studies of growth hormone secretion in diabetic patients with and without retinopathy.[27,28]

The effects of increased growth hormone and hyperglycemia are combined in the glucose–growth-hormone hypothesis,[29,30] according to which "growth hormone increases the synthesis of the peptide chain and perhaps enhances hydroxylase activity, while glucose increases the activity of the specific glucosyltransferases."[30]

In the group of normal subjects studied here the diurnal levels of growth hormone and glucagon were suppressed by somatostatin as in the diabetics. In contrast, plasma glucose, which was reduced in the diabetics, was elevated in the normals. This result in normal subjects can be due only to the concomitant suppression of insulin.

In juvenile-type diabetes, plasma insulin is low and does not rise in response to meals. Any possible small changes in endogenous insulin secretion induced by somatostatin in juvenile diabetics must be of minor importance for the diurnal plasma level of glucose in comparison to the changes in plasma growth hormone and glucagon.

The present study does not include patients with maturity-onset diabetes. In such patients, infusion of somatostatin may induce hyperglycemia, because they secrete insulin, as do normal subjects, in response to meals. If this turns out to be so, a somatostatin analogue inhibiting growth hormone and glucagon secretion but without effect on insulin secretion may be necessary for future application to the large group of diabetics suffering from maturity-onset diabetes.

The endocrine mechanisms explaining the effect of somatostatin on plasma glucose has been questioned by Wahren and Felig.[31,32] They reported that infusion of somatostatin in juvenile diabetics results in a 75-100 per cent reduction in the blood glucose rise after oral glucose administration but did not improve intravenous glucose tolerance. Somatostatin reduced blood xylose levels by 50-90 per cent after ingestion of this pentose and reduced splanchnic blood flow by 30 per cent. On the basis of these findings they concluded that the lowering effect on plasma glucose of somatostatin in juvenile diabetics is due primarily to decreased and/or delayed carbohydrate absorption rather than enhanced carbohydrate disposal.

It cannot be excluded from our present findings that decreased and/or delayed carbohydrate absorption may partially explain the lowering effect of somatostatin on glucose in the juvenile diabetics. However, this effect cannot be very pronounced, because our normal subjects responded to somatostatin infusion with immediate and high plasma glucose responses to meals, thus excluding a major reduction in intestinal absorption.

In this connection it is also of interest to observe the large rebounds seen in the diabetic patients during the final three-hour period, when no somatostatin was given and no food was offered. Plasma glucose rose abruptly, and so did plasma glucagon and also plasma growth hormone, although less constantly. In this situation, 10 hours after the last evening snack, the change in plasma glucose cannot be due to changes in intestinal absorption but must be explained on the basis of the changes of the two hormones measured.

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