Effects of the Somatostatin Analog, Octreotide, on Glucose Metabolism and Insulin Sensitivity in Insulin-Dependent Diabetes Mellitus

L. Ørskov, N. Møller, J.F. Bak, N. Pørksen, and O. Schmitz

To examine the effect of the somatostatin analog, octreotide, on insulin-mediated glucose uptake, seven insulin-dependent diabetic (IDDM) subjects were studied with and without 4 days of continuous subcutaneous octreotide administration (1 μg/kg/d). Insulin dosage was adjusted after frequent measurements of plasma glucose level. On the third day a hormonal and metabolic blood profile was obtained, and on the fourth day a euglycemic (5 mmol/L), hyperinsulinemic (1 mU/kg/min) clamp was performed in combination with calorimetry and a muscle biopsy. Mean plasma glucose levels on day 3 were similar (7.9 ± 0.9 *v* 9.0 ± 0.6 mmol/L). Growth hormone (GH) (0.39 ± 0.10 *v* 0.78 ± 0.23 μg/L, $P < .05$), insulin-like growth factor-I (IGF-I) (127 ± 17 *v* 157 ± 21 μg/L, $P < .05$), and nonesterified fatty acids (NEFA) (239 ± 25 *v* 405 ± 44 μmol/L, $P < .01$) were lower following octreotide administration. Insulin requirements were reduced during octreotide administration, resulting in significantly lower insulin levels (27.3 ± 2.7 *v* 39.9 ± 9.9 mU/L, $P < .5$). During the clamp, glucose and insulin levels were similar. Following octreotide, glucose disposal (7.33 ± 0.49 *v* 6.08 ± 0.55 mg/kg/min, $P < .05$) increased and hepatic glucose production (HGP) was more suppressed (−1.56 ± 0.07 *v* −0.63 ± 0.34 mg/kg/min, $P < .05$, 220 to 270 minutes). Oxidative glucose disposal (indirect calorimetry) was enhanced (3.09 ± 0.24 *v* 2.70 ± 0.37 mg/kg/min, $P = .08$), whereas glucose storage, as well as the fractional velocity for glycogen synthase activity, were unaltered during octreotide administration. Conversely, octreotide decreased lipid oxidation (0.12 ± 0.1 *v* 0.41 ± 0.15 mg/kg/min, $P < .05$). In conclusion, a low-dose octreotide infusion for 4 days to IDDM subjects leads to significantly increased insulin sensitivity.

ELEVATED growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels have been implicated in the pathogenesis of diabetic complications (metabolic instability, insulin resistance, the dawn phenomenon, diabetic nephropathy, and proliferative retinopathy).[1-4] Somatostatin has been shown to suppress GH and glucagon levels and to reduce hyperglycemia in insulin-dependent diabetic (IDDM) patients.[5]

Development of the somatostatin analog, SMS 201-995 (octreotide), which has a much longer half-life, is effective with subcutaneous administration, and possibly has a more selective GH-suppressive effect,[6] has increased attention to the possibility of using this hormone as adjuvant therapy in type I diabetes. The benefits of such an approach would theoretically be reduction of elevated GH and glucagon levels, leading to improved metabolic control and, in the long-term, a reduced number of microvascular complications.

Most previous studies have demonstrated insulin requirements to be decreased by up to 50% during octreotide administration,[7-11] whereas one study failed to show such an effect.[12] A reduction in insulin resistance and thereby in insulin levels could reduce the higher frequency of dyslipidemia, atherosclerosis, and hypertension that affect diabetic patients.[13-15]

The aim of the present study was therefore to examine the effect of continuous low-dose subcutaneous octreotide infusion on the hormonal milieu and insulin-mediated glucose uptake in type I diabetic patients.

SUBJECTS AND METHODS

Clinical Data

Seven insulin-dependent diabetic men recruited from our outpatient clinic participated. The mean age was 29.9 ± 3.7 years (range, 20 to 49), and mean body mass index was 24.4 ± 0.9 kg/m^2. Subjects had a mean diabetes duration of 11 ± 1.5 years (range, 4 to 13), and, apart from simplex retinopathy, no diabetic complications. Six participants were on a multiple-injection regimen, and one used an insulin pump.

The study protocol was in accordance with the Helsinki Declaration and was approved by the local ethics committee. All subjects gave informed consent.

Experimental Design

All subjects were examined twice, with approximately 1-month intervals, with and without 4 days of continuous subcutaneous octreotide (Sandostatin; Sandoz, Basel, Switzerland) administration (1 μg/kg/d). Octreotide dosage was gradually increased over the first 2 study days to minimize gastrointestinal side effects. During the first 3 days, insulin dosage was adjusted by frequent measurements of plasma glucose levels to prevent hypoglycemia and maintain a target glucose level between 5 and 15 mmol/L (Fig 1).

On the third day, participants were admitted to the hospital at 8 AM, an intravenous cannula was placed, and hormonal and metabolic profiles were obtained, with hourly measurement of plasma glucose and glucagon and serum insulin, GH, nonesterified fatty acids (NEFA), and blood metabolites for 7 hours. Patients were encouraged to remain ambulatory and received their usual diet.

Clamp (day 4)

On the fourth day, a euglycemic (5 mmol/L), hyperinsulinemic clamp was performed after an overnight fast. Two catheters were placed: one in a heated dorsal hand vein for sampling of arterial-

From the Department of Medicine C (Diabetes and Endocrinology), Århus Amtssygehus, and Department of Medicine M (Diabetes and Endocrinology), Århus Kommunehospital and Institute of Clinical Experimental Research, Århus University, Århus University Hospital, Århus, Denmark.

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Address reprint requests to L. Ørskov, MD, Department of Medicine and Endocrinology, Århus Amtssygehus, 8000 Århus C, Denmark.

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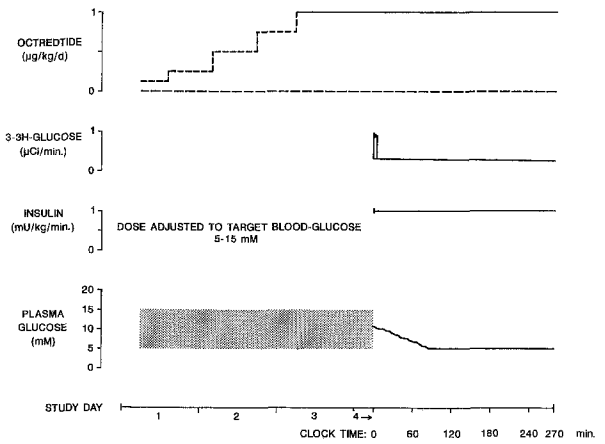

Fig 1. Seven IDDM patients were examined twice, before and after 3 days' octreotide administration, with approximately a 1-month interval. On the third day, a hormonal/metabolic blood profile was taken. On the fourth day, a hyperinsulinemic-euglycemic clamp was performed. −30 to 0 minutes was defined as the basal period, and 220 to 270 minutes as the steady-state period. A muscle biopsy was taken at the end of every study.

ized blood, and another in the contralateral antecubital vein for infusions. Insulin (Insulin Actrapid human; Novo-Nordisk, Bagsvard, Denmark) was infused at a rate of 1 mU/kg/min. Plasma glucose was allowed to decline slowly to 5 mmol/L and was subsequently clamped at this level by a variable glucose infusion. (3-^{3}H)-Glucose (Du Pont–New England Nuclear, Boston, MA) was infused in a primed (30 to 60 μCi, depending on plasma glucose concentration) continuous manner (0.30 μCi/min) to evaluate glucose turnover. As assessed by high-performance liquid chromatography, 3-^{3}H-glucose batches contained no contaminating radiochemicals.

Blood Sampling

Plasma glucose was measured every 5 minutes by a glucose analyzer (Beckman Instruments, Palo Alto, CA). Blood for determination of glucose (glucose specific activity) and insulin was drawn as shown in Fig 3. GH, glucagon, NEFA, and blood metabolite levels were measured in the basal (−30 to 0 minutes) and steady-state (220 to 270 minutes) period.

Indirect Calorimetry

Energy expenditure and respiratory exchange ratio were estimated at 220 to 250 minutes. A computerized, open-circuit system was used to measure gas exchange across a 25-L canopy (Deltatrac; Datex Instrumentarium, Helsinki, Finland). The monitor determines carbon dioxide production and oxygen consumption by multiplying dry-air flow through the canopy with alterations in gas concentration over the canopy. Estimated net glucose and lipid oxidation rates were calculated from the above measurements, and protein oxidation rates were estimated from urinary excretion rates of urea.[16] Net nonoxidative glucose disposal was determined in the steady-state period by subtracting oxidative glucose disposal from total glucose disposal (glucose infusion rate [GIR]).

Muscle Biopsy

At the end of each study (250 to 270 minutes), a biopsy was obtained from the vastus lateralis muscle.[17]

Analytical Methods

Plasma glucose level was measured in duplicate immediately after sampling (Beckman Instruments). Plasma glucagon and serum insulin were determined by radioimmunoassay as previously described, but with the modification that polyethylene glycol was used for separation before the determination and plasma glucagon was extracted with ethanol.[18] GH was measured using a immunofluorometric sandwich assay with two monoclonal antibodies (Delfia hGH; Wallac Oy, Turku, Finland). Serum total (extractable) IGF-I was determined after acid ethanol extraction to avoid interference from IGF binding proteins; serum extracts were assayed directly after dilution in assay buffer (final dilution, 1:1,000) according to Frystyk et al.[19] Serum NEFA levels were determined by a colorimetric method using a commercial kit (Wako Chemicals, Neuss, Germany). Blood 3-hydroxybutyrate (3-OHB), glycerol, lactate, and alanine were assayed by automated enzymatic fluorometric methods.[20]

Muscle Enzyme Analysis

Glycogen synthase activity was measured as described previously[21] using 0.13 mmol/L UDP-U-^{14}C-glucose (DuPont–New England Nuclear), 0.67% (wt/vol) glycogen, and 0 to 6.7 mmol/L glucose-6-phosphate (G-6-P) (final concentrations). In this context, 1 U glycogen synthase activity equals incorporation of 1 nmol UDP-glucose into glycogen per minute. Total glycogen synthase activity is defined as the activity in the presence of a saturating concentration (6.7 mmol/L) of G-6-P. Fractional velocities were calculated as glycogen synthase activity in the presence of 0.07 mmol/L G-6-P divided by glycogen synthase activity in the presence of 6.7 mmol/L G-6-P. The concentration of G-6-P producing half-maximal activity of glycogen synthase ($A_{0.5}$ for G-6-P) was calculated using a Hill plot.[22]

Calculations and Statistical Analysis

Rates of total glucose appearance and disappearance were determined from tritiated-glucose data in samples taken in the last 2.5 hours of the study. The values were calculated according to the non–steady-state equations of Steele[23] as modified by De Bodo et al.[24] A distribution volume of 220 mL/kg and a pool fraction of 0.65 were used. Hepatic glucose production (HGP) was calculated by subtracting GIR from rate of appearance. To circumvent the well-known problem of negative HGP rates at high glucose turnover rates,[25] using the constant tracer infusion technique,[26] GIRs, instead of rates of disappearance, were used to describe total glucose disposal.

All values are expressed as the mean ± SEM. Student's *t* test for paired data was used to assess differences between experiments basally and in the steady-state period. A one-tailed *t* test was used to test the hypothesis that GH, IGF-I, and glucagon levels are suppressed by octreotide.

RESULTS

Metabolic Profile (day 3)

Mean plasma glucose levels were similar (7.9 ± 0.9 *v* 9.0 ± 0.6 mmol/L, NS). GH (0.39 ± 0.10 *v* 0.78 ± 0.23 μg/L, $P < .05$) and IGF-I, measured at baseline on day 4 (127 ± 17 *v* 157 ± 21 ng/mL, $P < .05$), were significantly suppressed during octreotide infusion. The difference in mean glucagon levels did not reach statistical significance (47.5 ± 4.5 *v* 64.2 ± 12.0 ng/L).

Insulin requirements were reduced by approximately 30% following octreotide (33 ± 3.9 *v* 47 ± 4.5 IE/d, $P < .001$), as reflected by a significant reduction in the mean insulin level (27.3 ± 2.7 *v* 39.9 ± 9.9 mU/L, $P < .05$).

Mean NEFA (239 ± 25 *v* 405 ± 44 μmol/L, $P < .01$) and glycerol (21 ± 6 *v* 35 ± 4 μmol/L, $P < .05$) were lower, whereas there was no difference in 3-OHB levels.

Mean alanine levels were higher during octreotide administration (389 ± 29 *v* 292 ± 20 μmol/L, $P < .01$), whereas lactate levels were similar (Fig 2).

Euglycemic Clamp (day 4)

The mean octreotide level was 445 ± 104 ng/L.

There was no difference between plasma glucose levels, without or with octreotide infusion, basally (10.9 ± 1.6 *v* 13.5 ± 1.4 mmol/L, NS) or during the clamp (Fig 3). Likewise, basal insulin levels were not significantly lower during octreotide administration (9.2 ± 1.3 *v* 12.7 ± 2.6 mU/L, $P = .23$), and levels were also similar during the clamp (Fig 3).

The difference in basal GH levels was not significant (0.05 ± 0.02 *v* 0.17 ± 0.09 μg/L, with and without octreotide, NS). In the steady-state period, GH levels were lower following octreotide administration (0.26 ± 0.14 *v* 2.16 ± 1.48, $P < .05$).

Glucagon levels were similar basally and in the steady-state period.

Basal alanine levels tended to be higher (266 ± 23 *v* 220 ± 15 μmol/L, with and without octreotide, $P = .08$), and steady-state levels (225 ± 18 *v* 117 ± 14 μmol/L, with and without octreotide, $P = .05$) were higher during octreotide infusion, whereas no difference was detected between basal and steady-state values of lactate, NEFA, glycerol, or 3-OHB. Insulin infusion suppressed NEFA, glycerol, and 3-OHB levels to a similar degree (Table 1).

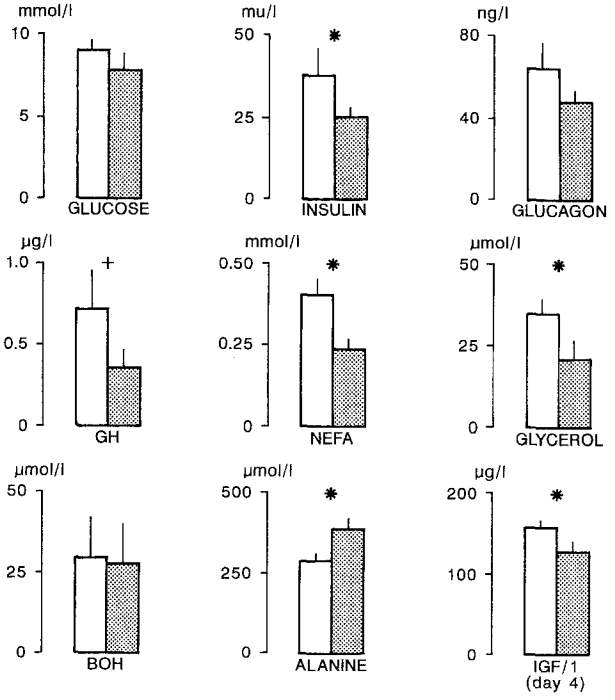

Fig 2. Mean ± SEM values of plasma glucose and glucagon, serum insulin, GH, and NEFA, and blood metabolites taken every hour from 8 AM to 3 PM on day 3 in the control period (□) and octreotide period (■). * or $^{+}P < .05$.

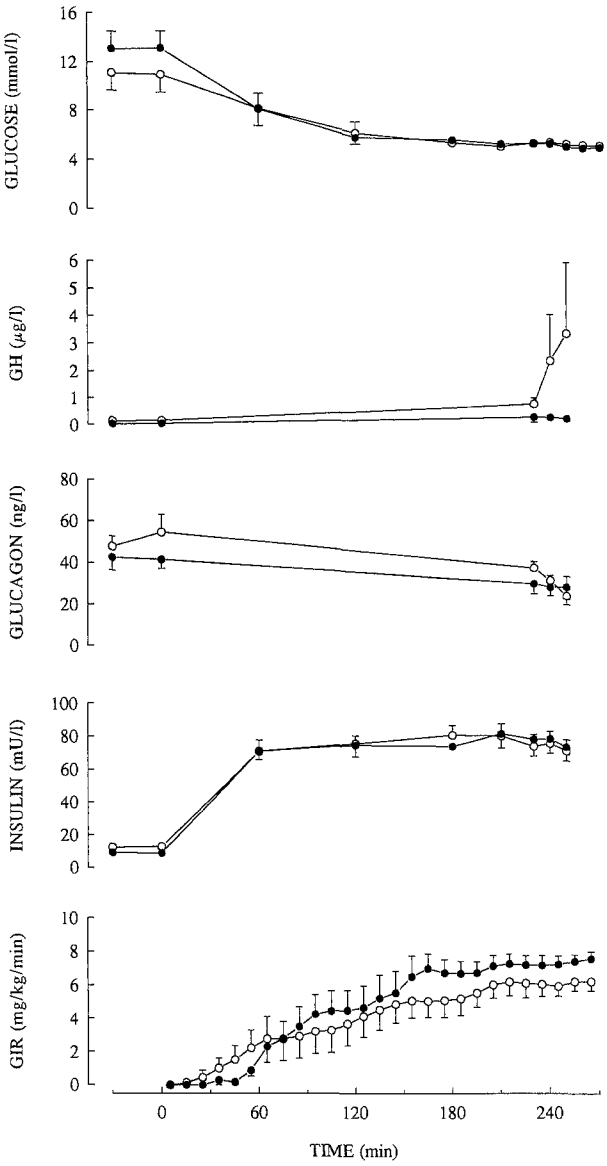

Fig 3. Mean ± SEM values of plasma glucose and glucagon, serum insulin and GH, and GIRs during the hyperinsulinemic (1 mU/kg/min), euglycemic (5 mmol/L) clamp on the fourth day in the control period (○) and octreotide period (●).

Glucose Kinetics

Octreotide infusion increased total glucose disposal (GIR: 7.33 ± 0.50 *v* 6.08 ± 0.63 mg/kg/min, $P < .05$, 220 to 270 minutes) and caused HGP to be more suppressed (−1.56 ± 0.07 *v* −0.63 ± 0.34 mg/kg/min, $P < .05$, 220 to 270 minutes) (Fig 4).

Table 1. Mean ± SEM of NEFA, Glycerol, 3-OHB, Alanine, and Lactate (μmol/L) During the Hyperinsulinemic (1 mU/kg/min), Euglycemic (5 mmol/L) Clamp Basally and in the Steady-State Period With and Without Octreotide Administration

	−Octreotide		+Octreotide	
Parameter	Basal	Steady	Basal	Steady
NEFA	1,075 ± 372	159 ± 48	915 ± 277	123 ± 24
Glycerol	61.7 ± 17.6	16.3 ± 7.8	52.4 ± 14.3	12.0 ± 4.2
3-OHB	343 ± 178	13.4 ± 9.8	299 ± 120	6.6 ± 2.3
Alanine	220 ± 15	177 ± 14	266 ± 23†	225 ± 18*
Lactate	733 ± 43	792 ± 92	636 ± 86	885 ± 89

*$P < .05$, †$P < .10$: +octreotide *v* −octreotide.

Indirect Calorimetry

There was no difference in total energy expenditure, but nonprotein energy expenditure was significantly lower during octreotide infusion (1,629 ± 54 *v* 1,764 ± 82 kcal/d, $P < .01$). The respiratory exchange ratio was slightly higher during octreotide administration (0.96 ± 0.01 *v* 0.90 ± 0.02, $P < .01$). Octreotide tended to increase oxidative glucose disposal (3.09 ± 0.24 *v* 2.7 ± 0.37 mg/kg/min, $P = .08$), whereas the difference in the rate of nonoxidative glucose disposal was insignificant (4.24 ± 0.95 *v* 3.39 ± 0.48 mg/kg/min, $P = .14$). Less lipid was oxidized when octreotide was administered (0.12 ± 0.1 *v* 0.41 ± 0.15 mg/kg/min, $P < .05$), and there was a tendency toward higher protein oxidation (1.02 ± 0.15 *v* 0.87 ± 0.12 mg/kg/min, $P = .09$) (Fig 5).

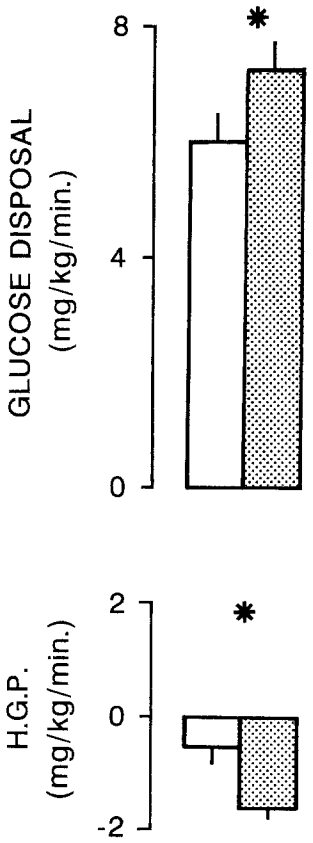

Fig 4. GIRs and HGP during the steady-state period of the hyperinsulinemic (1 mU/kg/min), euglycemic (5 mmol/L) clamp on the fourth day of the control period (□) and octreotide period (■). Values are the mean ± SEM. *$P < .05$.

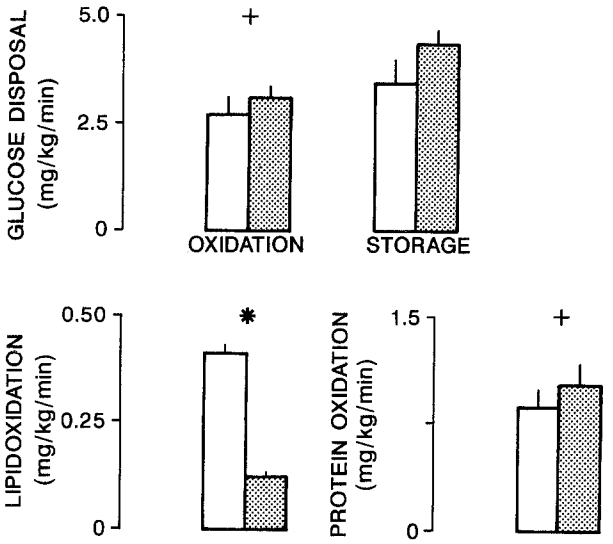

Fig 5. Rates of oxidative and nonoxidative glucose disposal and lipid and protein oxidation during the steady-state period of the hyperinsulinemic (1 mU/kg/min), euglycemic (5 mmol/L) clamp on the fourth day of the control period (□) and the octreotide period (■). Values are the mean ± SEM. *$P < .05$, †$P < .1$.

Glycogen Synthase Activity

Total activities of glycogen synthase (measured at saturating levels of G-6-P and physiologic levels of UDP-glucose) were similar (54.6 ± 6.5 *v* 51.9 ± 5.3 μmol/g protein/min, with and without octreotide, NS) (Table 2).

The fractional velocity for glycogen synthase activity was similar in the two studies (12.0% ± 3.0% *v* 15.6% ± 3.7%, $P = .30$). Likewise, sensitivity of glycogen synthase to G-6-P was unaffected by octreotide, as indicated by similar $A_{0.5}$ values.

Side Effects

Despite the gradual increase in octreotide dose, three of seven patients experienced gastrointestinal discomfort. This was most pronounced on the first study day, necessitating a gradual dose increase. None of the patients had significant gastrointestinal complaints during the last 3 study days (and only one on the first day).

Blood glucose levels were similar with and without octreotide on day 1 (8.1 ± 0.8 *v* 8.2 ± 0.7 mmol/L), day 2

Table 2. Mean ± SEM of the Sensitivity of Glycogen Synthase to G-6-P; $A_{0.5}$, Fractional Velocity for Glycogen Synthase Activity: FV and Total Glycogen Synthase Activity; GStot

Parameter	−Octreotide	+Octreotide
$A_{0.5}$ (mmol/L)	0.455 ± 0.075	0.397 ± 0.104
FV (%)	12.0 ± 3	15.6 ± 3.7
GStot (μmol/g protein/min)	51.9 ± 5.3	54.6 ± 6.5

(9.2 ± 0.7 *v* 9.4 ± 1.2 mmol/L), and day 3 (9.9 ± 1.1 *v* 9.7 ± 0.9 mmol/L). Blood glucose values less than 3.5 mmol/L (except once above 2.8 mmol/L) were registered with similar frequency in the two study periods (10 with octreotide and nine without octreotide), and subjective registration of hypoglycemia was in all instances mild.

DISCUSSION

The present study demonstrates for the first time that octreotide administration improves insulin-stimulated glucose disposal and increases the suppressive effect of insulin on the liver, indicating improvement of insulin sensitivity. GH and IGF-I levels were suppressed by octreotide, as were levels of lipid intermediates. Our study confirms that octreotide administration in IDDM subjects leads to reduction of insulin requirements without affecting metabolic control.

Most previous studies in IDDM patients have found that octreotide treatment reduces insulin requirements by 30% to 50%.[7-11] One study using a low-dose bolus regimen,[12] which has been shown to be less effective (two to three times) than continuous subcutaneous administration,[10,27] was unable to find this effect. In addition, reduced postprandial blood glucose excursions have been demonstrated.[7,11,28] These effects were attributed to GH and glucagon suppression,[2] altered substrate absorption,[29] and reduced insulin clearance.[8,30]

The capacity of octreotide to modulate hormonal secretion is obviously dose-dependent. The decision to use a low octreotide dose was based on the desire to avoid side effects such as severe hypoglycemia and gastrointestinal symptoms of such severity as to preclude a realistic evaluation of the study. The dose given had moderate effects on GH and glucagon secretion. However, even with this modest suppression, which was reflected in levels of IGF-I and lipid intermediates, insulin dosage had to be reduced by about 30% to maintain a constant blood glucose level.

The impact of octreotide on glucose metabolism and insulin sensitivity has previously been investigated in acromegalic patients.[31] Using a much higher octreotide dose, overall glucose metabolism and insulin sensitivity were improved, even though the effect, presumably due to the experimental design, which allowed short-term GH effects to occur, could only be detected in the liver.

Acute studies on nondiabetic animals indicate an effect of octreotide and somatostatin to accelerate the onset of hepatic glycogenolysis and reduce hepatic glycogen content.[32,33] These effects, which were partly reversible by glucose infusion, would be expected to reduce HGP with longer octreotide administration. Whether this mechanism could also apply to human diabetic subjects, in whom insulin is administered exogenously and only endogenous secretion of GH and glucagon is suppressed by octreotide, is uncertain.

GH has been shown to decrease insulin sensitivity both in the liver and in peripheral tissues,[17,34-36] and the suppression of GH levels is probably at least partly responsible for improved insulin sensitivity following octreotide. However, since NEFA levels were reduced following octreotide treatment, an effect to increase glucose uptake via altered substrate competition according to the glucose–fatty acid cycle[37] should also be considered. Finally, improvement of insulin resistance due to a reduction in insulin levels following octreotide may participate.[38]

Native somatostatin has been shown to increase insulin-stimulated glucose uptake in forearm tissues,[39] and a similar effect of octreotide per se cannot be ruled out. Neither oxidative nor nonoxidative glucose disposal are saturated with the insulin levels achieved in the present study.[40] Differences in total glucose disposal rates were modest, and nonoxidative glucose disposal was not significantly reduced, possibly due to the dose of octreotide, which caused hormonal changes within physiological limits. This may account for the difficulty in placing responsibility for the increase in insulin sensitivity in the periphery with more certainty at either the oxidative or nonoxidative pathway (or both). However, since glycogen synthase activities were similar, this supports our finding that nonoxidative glucose metabolism was not the major pathway affected.[17]

Further, in line with the study by Bak et al,[17] normalization of hypersomatotropinemia may also be responsible for the decrease in nonprotein energy expenditure.

Hyperalaninemia is a consistent feature of octreotide administration.[8,41,42] Possible explanations for this are reduced liver uptake due to either diminished GH and glucagon stimulation[43] or reduced splanchnic blood flow.[44] Furthermore, increased muscle release due to a reduced GH, IGF-I, and insulin protein-sparing effect could be responsible and would also account for the increase in protein oxidation rate. Infusion of another long-acting somatostatin analog did not lead to increased protein breakdown,[45] but this occurred in short-term experiments.

Our study confirms the propensity of diabetic patients to develop side effects with octreotide administration.[8,9,41] Despite the low octreotide dose, three patients were bothered by gastrointestinal discomfort, especially on the first study day, necessitating a very gradual increase in dosage. The symptoms were slight, and patients were encouraged to maintain their usual diet. Contrary to other reports,[10,46] hypoglycemic episodes were not encountered more frequently in the treatment period. This is presumably explained partly by the low octreotide dose, but the short study duration, which allowed close monitoring of blood glucose levels and continuous reduction of insulin dosage, also plays a part.

In conclusion, low-dose continuous subcutaneous octreotide infusion for 4 days decreased insulin requirements without causing deterioration in metabolic control and increased insulin sensitivity in IDDM subjects. Long-acting somatostatin analogs may turn out to be an attractive adjuvant to the treatment of selected diabetic patients.

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