Effects of octreotide on insulin-like growth factor I and metabolic indices in growth hormone-treated growth hormone-deficient patients

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Animal studies have demonstrated that in addition to inhibiting growth hormone (GH) secretion, octreotide inhibits in a direct manner hepatic or peripheral insulin-like growth factor I (IGF-I) generation. To test this hypothesis in humans we studied ten GH-deficient patients with frequent blood sampling during 38 h on two occasions. Regular GH therapy was discontinued 72 h prior to each study period. At the start of each study a subcutaneous (sc) injection of GH (3 IU/m²) was given (at 18.00 h). In a single-blinded crossover design, patients received a continuous sc infusion of either octreotide (200 μg/24 h) or placebo (saline). The pharmacokinetics of GH were similar on the two occasions. The area under the curve ± SEM of serum GH was 142.5 ± 53.6 μg·l⁻¹·h⁻¹ (octreotide) and 144.8 ± 41.8 μg·l⁻¹·h⁻¹ (placebo), (p = 0.73); Cmax (μg/l) was 12.5 ± 1.47 (octreotide) and 12.8 ± 1.42 (placebo) (p = 0.83), and Tmax (h) was 6.1 ± 0.97 (octreotide) and 5.2 ± 0.65 (placebo) (p = 0.49). Growth hormone administration was associated with an increase in serum IGF-I (μg/l), which was identical during the two studies, from 85.3 ± 19.4 to 174.25 ± 30.3 for octreotide and from 97.0 ± 26.4 to 158.8 ± 28.2 for placebo. Mean IGF-I levels (μg/l) were 138.2 ± 25.1 (octreotide) and 134.5 ± 28.6 (placebo) (p = 0.78). Similarly, the increase in IGF binding protein 3 (IGFBP-3) levels was identical. Mean IGFBP-3 levels (μg/l) were 2303 ± 323 (octreotide) and 2200 ± 361 (placebo) (p = 0.25). Mean insulin levels were significantly lower during octreotide treatment (39.9 ± 17.9 μU/l) than during placebo (59.7 ± 17.8 μU/l) (p < 0.05). Mean blood glucose levels were elevated significantly during octreotide infusion (5.98 ± 0.23 mmol/l for octreotide and 5.07 ± 0.16 mmol/l for placebo; p = 0.001). Glucagon levels decreased non-significantly (p = 0.07) and IGFBP-1 levels tended to increase during infusion of octreotide although not significantly (p = 0.41). Levels of the lipid intermediates were identical on the two occasions. Alanine and lactate levels were significantly increased during octreotide infusion. Mean levels of blood alanine (μmol/l) were 470.8 ± 24.2 (octreotide) and 360.1 ± 17.8 (placebo) (p < 0.02). Mean levels of blood lactate were 1038.1 ± 81.0 (octreotide) and 894.4 ± 73.8 (placebo) (p < 0.04). We conclude that short-term continuous sc infusion of octreotide has no direct effect on the generation of IGF-I or the pharmacokinetics of exogenous GH in GH-deficient man.

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Inhibition of growth hormone (GH) secretion in animals and humans is one of the primary effects of somatostatin and its analogs. The secretion of insulin, glucagon and certain peptides of the gastrointestinal tract is also reduced (1). The short half-life of somatostatin has limited its potential use as a therapeutic agent. Following the recent introduction of the long-acting analog octreotide, treatment of acromegaly has become possible (2, 3).

Treatment with octreotide decreases serum concentrations of GH in most patients with acromegaly, with subsequent clinical improvement (4, 5), and reduces pituitary tumor size in some patients (5, 6). The symptoms and the long-term harmful effects of GH hypersecretion on tissues are at least partly related to the increase in insulin-like growth factor I (IGF-I) levels. The octreotide-related reduction in GH levels is usually associated with a similar decrease in IGF-I levels, and a positive correlation between GH and IGF-I levels has been demonstrated in several studies (7–9). Other studies, however, have shown discrepancies between levels of GH and IGF-I in patients with acromegaly (10, 11). In some recent studies, treatment with octreotide seemed to decrease serum IGF-I relatively more than serum GH (4, 5, 12). Furthermore, control of symptoms has been reported despite minor decrease in GH levels. In a study of insulin-dependent diabetics, octreotide did not reduce circulating GH significantly; in contrast, IGF-I levels were suppressed into the hypopituitary range (13).

These observations suggest that octreotide in man may also influence the generation of IGF-I independently of its effects on GH secretion, as was the case in a study in
hypophysectomized rats (14). The rats were treated with GH and cotreated with either octreotide or saline. In the octreotide-treated group, IGF-I increased to only 40% of the level in the saline-treated group. The weight increased during GH treatment, whereas this increase was less when octreotide was added. In a more recent similar study in hypophysectomized rats (15), the hepatic expression of the IGF-I gene was inhibited during treatment with GH and octreotide. The weight did not change during treatment. In both studies the animals had free access to food.

However, it must be considered that the apparent discrepancies between GH and IGF-I status in some of the studies cited may have been due to interferences in the IGF-I assays of IGF binding proteins.

This study was carried out in GH-deficient patients to test the hypothesis that octreotide, independent of variations in endogenous GH secretion, directly influences hepatic or peripheral IGF-I generation in humans.

Materials and methods

Subjects

Ten patients with GH deficiency were studied (Table 1). Mean age was 22.8 years (range 14-43 years), mean ±SEM body mass index 25.3 ± 2.0 kg/m² and mean ± SEM body surface area 1.70 ± 0.09 m². The diagnosis was defined by a peak GH response of < 5 µg/l after at least two different GH stimulation tests (insulin-induced hypoglycemia, arginine infusion or heat exposure). In five patients receiving GH replacement therapy, treatment was discontinued 3 days prior to each study period. The study protocol was approved by the Danish Health Authorities and the Regional Ethics Committee, and conducted in accordance with the Helsinki Declaration II.

Design

The patients were admitted to the hospital twice. Each hospitalization lasted 38 h. On both admissions, at 18.00 h, the patients received a subcutaneous (sc) injection of 3 IU/m² of recombinant human GH (Norditropin®, 12 IU/ml; Novo Nordisk, Gentofte, Denmark). In a single-blinded manner the patients were randomized to receive a continuous 38-h sc infusion of 200 µg/24 h of octreotide (Sandostatin®, Sandoz, Copenhagen, Denmark), also starting at 18.00 h, on one occasion, and saline on the other. At the start of the study, baseline blood samples were drawn from a cannula inserted in an antecubital vein. At 18.00 h GH was injected sc in a lifted skinfold in the anterior femoral region. The injection depth equalled the needle length (12.5 mm).
All injections were carried out by the same physician. Growth hormone was only administered on the first night of admission. Subsequently a continuous sc infusion of octreotide or saline was initiated by means of a portable pump (Auto-syringe Inc., Hooksett, NH, USA). Very constant serum levels of octreotide have been reported using this pump for sc octreotide infusion (6).

Blood was sampled for repeated measurements of GH, IGF-I, IGF binding protein 3 (IGFBP-3), IGFBP-1, glucagon, insulin, glucose, non-esterified fatty acids (NEFA), 3-hydroxybutyrate (BOH), glycerol, alanine and lactate. During the last 14 h four samples were drawn. On the first morning at 08.00 h a carbohydrate-rich breakfast was served. For the following 2 h blood was sampled every 15 min to measure glucose and insulin levels. Lunch was served at 12.00 h, dinner at 17.30 h and a snack at 20.30 h. Normal physical activity, other than sports, was allowed. A washout period of at least 4 weeks separated the two admissions.

**Analyses**

Blood samples were assayed for serum GH, glucagon and insulin using RIA (16). Serum IGF-I was measured using a double monoclonal immunofluorimetric assay after extraction with hydrochloric acid/ethanol; the serum extracts were diluted in parallel standards. The extraction procedure used completely removed IGFBP-3 and reduced the concentration of smaller IGFBPs with a factor greater than 30 (standard range 5 ng/l–5 μg/l). The second of the two antibodies against IGF-I was labeled with Europium (Delfia, Wallac, Finland). The interassay coefficient of variation (cv) in samples was <10%; the intra-assay cv in standards as well as samples was <5% and the lower detection limit was <2.5 ng/l. The IGFBP-3 was measured by RIA using a polyclonal antibody against the acid-stable binding subunit (IGFBP-3β) as originally described by Blum et al. (17). The intra-assay cv in standards and samples was <5%, the interassay cv was <7.5% and the lower detection limit was <1 μg/l; normal range (adults) >2100 μg/l. Serum IGFBP-1 was measured by an immunoenzymometric kit using two monoclonal antibodies. The intra-assay cv was <5%, the interassay cv was <7.5% and the lower detection limit was 0.4 μg/l (Medix Biochemica AB, Kauniainen, Finland). The normal range for this assay was 0.5–28 μg/l (measured in 44 normal women) and 0.2–16 μg/l (healthy men; N = 11). Glucose was measured in non-protein-stripped plasma by a standard glucose oxidase method. Serum NEFA was measured by a radiochemical method (18). 3-hydroxybutyrate (BOH), glycerol, alanine and lactate were measured on whole blood by an automated enzyme fluorimetric method (19). Samples for measurement of glucagon and metabolites were centrifuged and stored at −30°C immediately. Samples from an individual patient were analysed in the same assay.

**Statistics**

The pharmacokinetics of recombinant human GH were estimated by the area under the curve (AUC), C_{max} and T_{max}. T_{max} is the time that it takes to reach the maximum serum concentration C_{max}. The areas under the individual serum concentration curves (AUC) were calculated according to the trapezoidal rule. The AUCs were calculated for all parameters. The mean levels (AUC divided by time) are given. Comparisons were performed by paired Student’s t-test. All parameters were evaluated by analysis of variance for repeated measurements (ANOVA); p values of <0.05 were considered significant. Results are shown as mean values ± SEM.

**Results**

The results from two of the 10 patients (nos 7 and 8) were excluded. These patients originally had negative stimulation tests. However, during the present study spontaneous endogenous GH secretion was evident in patient no. 7. In addition, basal serum levels of IGF-I and IGFBP-3 were normal. As for patient no. 8, polycystic ovaries were diagnosed after the study. This was associated with obesity (body mass index was 34.5 kg/m²) and hyperinsulinemia, so we felt that we could not exclude the fact that her suppressed serum GH was partly due to her obesity.

**Serum GH** (Fig. 1). The pharmacokinetics of exogenous human GH were identical during continuous sc infusion of octreotide and placebo, respectively. Baseline serum GH was not significantly different (p = 0.54) on the two occasions. Levels comparable to baseline levels were achieved about 24 h after administration of GH. Mean (±SEM) serum GH levels (μg/l) increased from 0.78 ± 0.16 to 10.41 ± 1.79 for octreotide and from 0.85 ± 0.13 to 10.98 ± 1.05 for placebo. The AUCs (μg·l⁻¹·h⁻¹) of serum GH were 142.5 ± 53.6 during infusion of octreotide and 144.8 ± 41.8 during placebo infusion (p = 0.73). The average peak concentration (C_{max}, μg/l) was 12.5 ± 1.47 and 12.8 ± 1.42 during infusion of octreotide and placebo, respectively (p = 0.83). The T_{max} (h) was 6.1 ± 0.97 for octreotide and 5.2 ± 0.65 for placebo; p = 0.49. Likewise, ANOVA failed to detect any difference when comparing GH profiles during octreotide and placebo.

**Serum IGF-I** (Fig. 2, upper panel). Growth hormone administration induced a significant increase in serum IGF-I concentrations (p < 0.001) from about 90 μg/l (range 11–235 μg/l) to 165 μg/l. Baseline levels (Table 1) were not significantly different (p = 0.38). The increase was identical during infusion of octreotide and placebo. Mean levels (μg/l) of IGF-I were identical on the two occasions: 138.2 ± 25.1, during octreotide infusion and 134.5 ± 28.6 during placebo infusion (p = 0.78). The patterns were not significantly different, as evaluated by ANOVA.
Serum IGFBP-3 (Fig. 2, middle panel). Baseline IGFBP-3 levels (µg/l) were 2114.8 ± 300.8 (octreotide) and 2130.5 ± 395.0 (placebo) (range 473–3686). Following administration of GH, IGFBP-3 levels decreased slightly from 0 h to 8 h (p < 0.01) and increased from 8 h to 38 h (p < 0.01). The IGFBP-3 levels were not significantly different during infusion of octreotide or placebo, as evaluated by ANOVA. Mean levels (µg/l) were 2303 ± 323 (octreotide) and 2200 ± 361 (placebo) (p = 0.25). The IGFBP-3 levels correlated with IGF-I levels during octreotide (r = 0.84, p < 0.02) but not significantly during placebo infusion (r = 0.70, p = 0.08).

Serum IGFBP-1 (Fig. 2, lower panel). The IGFBP-1 levels correlated inversely with insulin levels during infusion of placebo (r = −0.69, p < 0.02) but not significantly during octreotide infusion (r = −0.51, p = 0.09). Levels, which increased at night and decreased in the daytime, changed significantly with time on both occasions (p < 0.01 by ANOVA). Mean levels (µg/l) were not significantly different during infusion of octreotide (3.38 ± 1.04) or placebo (2.44 ± 0.8) (p = 0.41).

Serum insulin (Fig. 3, upper panel). Insulin levels were reduced during infusion of octreotide. Mean levels (mU/l) were 39.9 ± 17.9 (octreotide) and 59.7 ± 17.8 (placebo) (p < 0.05). There was a significant interaction with both time (p < 0.001) and treatment (octreotide vs placebo) (p < 0.05) when testing with ANOVA. The effect on insulin seemed strongest during the first part of the octreotide infusion, when the insulin response to meals was suppressed. Following breakfast at 08.00 h on the first morning the insulin response was significantly decreased during octreotide infusion (p = 0.02).

Blood glucose (Fig. 3, middle panel). Blood glucose levels were elevated during octreotide infusion. The effect prevailed during the first 24 h. Baseline glucose values were 5.25 ± 0.47 (octreotide) and 4.24 ± 0.23 (placebo) (p = 0.09). Mean levels (mmol/l) were 5.98 ± 0.23 (octreotide) and 5.07 ± 0.16 (placebo) (p = 0.001). The effect of octreotide was most obvious at the start of the study, when insulin levels were most markedly suppressed. Following breakfast at 08.00 h blood glucose levels increased significantly more during infusion of octreotide, as reflected by the AUCs (p = 0.005).

Serum NEFA (Fig. 3, lower panel). During the first night, NEFA levels increased significantly (p < 0.01) on both occasions, and identically during infusion of octreotide.
Fig. 2. Mean (±SEM) serum concentrations (µg/l) of insulin-like growth factor I (IGF-I) (upper panel), IGF binding protein 3 (IGFBP-3) (middle panel) and IGFBP-1 (lower panel) during infusion of octreotide (○) and placebo (●).
Fig. 3. Mean (±SEM) values of serum insulin (mU/l) (upper panel), blood glucose (mmol/l) (middle panel) and serum non-esterified fatty acids (NEFA) (mmol/l) (lower panel) during infusion of octreotide (O) and placebo (●).
Fig. 4. Mean (±SEM) blood concentrations (μmol/l) of alanine (upper panel) and lactate (lower panel) during infusion of octreotide (○) and placebo (●).

and placebo. Mean levels (mmol/l) were 0.41 ± 0.05 (octreotide) and 0.40 ± 0.02 (placebo) (p = 0.89). The increase during the second night, when GH had not been given, did not reach statistical significance. ANOVA revealed a significant time effect in both studies (p < 0.001). Levels of BOH and glycerol fluctuated similarly to NEFA levels on the two occasions (data not shown).

Serum glucagon. Octreotide infusion induced a nonsignificant decrease in glucagon levels (data not shown) as compared to placebo. Mean levels (ng/l) were 22.76 ± 3.75 (octreotide) and 30.29 ± 3.76 (placebo) (p = 0.069). Levels changed significantly over time during infusion of octreotide and placebo (p < 0.001). Levels were low during the night and increased during the day.

Blood alanine and lactate (Fig. 4). Alanine (upper panel) and lactate levels (lower panel) increased significantly during octreotide infusion. Mean levels (μmol/l) of alanine were 470.8 ± 24.2 (octreotide) and 360.1 ± 17.8 (placebo) (p < 0.02). Mean levels (μmol/l) of lactate were 1038.1 ± 81.0 (octreotide) and 894.4 ± 73.8 (placebo) (p < 0.04). Levels of alanine and lactate correlated inversely to NEFA levels during placebo (r = −0.80, p = 0.001 or alanine, and r = −0.65, p > 0.02 for lactate) but not during octreotide infusion (r = −0.48, p = 0.10 for alanine, and r = −0.43, p = 0.14 for lactate).
Discussion

Most of the circulating IGF-I derives from the liver as a result of GH stimulation (20). A considerable amount, however, represents locally produced IGF-I (21). Numerous factors, including GH and nutritional state (22), influence the generation of IGF-I (23, 24). Growth hormone-deficient patients provide an opportunity to study separately the possible GH-independent regulators of IGF-I generation.

In this study octreotide did not affect the pharmacokinetics of exogenous human GH. Any difference in the levels of IGF-I or its binding proteins during infusion of octreotide and placebo is therefore unlikely to be caused by altered absorption of exogenous human GH. The pharmacokinetic data agree with earlier reports on exogenous GH administered subcutaneously (25–27). Furthermore, a study of normal subjects, whose endogenous GH secretion was suppressed by octreotide, showed that the pharmacokinetics of exogenous human GH were unaffected by octreotide (28).

The GH stimulus on IGF-I release was identical during infusion of octreotide and placebo for 38 h. Likewise, the levels of IGFBP-3, which is quantitatively the most important binding protein for IGF-I, were similar during octreotide and placebo infusion. Treatment with human GH was discontinued 72 h prior to each study period. In view of the rather long half-life of IGFBP-3 (18–20 h), this washout period was probably too short to reach GH-deficient levels of the binding protein (21). The washout period, however, was identical in the two studies. The decrease in serum IGF-I (and IGFBP-3) and the baseline levels attained are sufficient to study whether infusion of octreotide inhibits the GH-induced serum IGF-I increase.

The effect of octreotide on IGF-I levels in this study was different from what has been reported in studies of hypophysectomized rats (14, 15). This may be due to differences between species. Another explanation may be that the reduced serum IGF-I levels in these studies could be due to a reduction of IGF-I binding protein levels induced by octreotide. Only in a small number of patients with acromegaly treated with octreotide have the IGF-I levels been reported to be relatively more reduced than GH levels (4, 5, 12). The most common finding is that IGF-I levels correlate with GH levels during octreotide treatment (7, 9). The IGF-I levels have even been reported to be unaltered or increased during octreotide treatment, despite reduced GH levels (11). In the above studies of patients with acromegaly and animals (hypox rats), octreotide was administered for a longer period than in our study, and its impact on IGF-I and IGFBP-3 levels may require more prolonged administration of the drug.

As nutrition affects IGF-I levels (29), octreotide treatment may have influenced the IGF-I levels in the animal studies (14, 15) through an effect on nutritional intake and resulting weight loss, because octreotide has been reported to cause gastrointestinal discomfort. The apparent discrepancy between the effects of octreotide on levels of GH and IGF-I in patients with acromegaly might be explained partially by the presence of an immunologically undetectable form of GH, with preserved ability to stimulate IGF-I, which is suppressed by octreotide (4, 30).

The finding of a more marked reduction of IGF-I relative to GH in patients with insulin-dependent diabetes mellitus treated with octreotide (13) appeared after 6 weeks of treatment with continuous sc infusion of octreotide. Comparison with these results is difficult because of the altered GH–IGF-I axis in diabetes, which seems to depend on the metabolic state and glycemic control.

In a recent study in patients with acromegaly (31), octreotide had a transient augmenting effect on IGFBP-1 levels. This was apparently unrelated to circulating insulin levels, a main regulator of IGFBP-1 levels (32). The IGFBP-1 might, under certain conditions, inhibit the actions of IGF-I (33), and an octreotide-induced increase in IGFBP-1 levels might be partially responsible for the rapid relief of symptoms in acromegaly following octreotide treatment. The IGFBP-1 levels appeared to be elevated during octreotide infusion, but statistical significance was not reached. The IGFBP-1 and insulin levels were inversely correlated, and from our study we were unable to prove or disprove a direct effect of octreotide on IGFBP-1.

The formation of IGF-I in the rat liver is stimulated by the action of insulin (34, 35), and very low insulin levels have been reported to suppress IGF-I (36). In our study in humans, however, the significantly reduced insulin levels during continuous infusion of octreotide did not affect IGF-I levels. Insulin levels were affected primarily at the beginning of the infusion period, when the insulin response to meals was impaired during octreotide treatment. Consequently, octreotide infusion resulted in elevated glucose levels during the initial 24-h period. Following a carbohydrate-rich breakfast taken at 08.00 h, 14 h after the infusion was initiated, the insulin response was impaired and glucose levels were elevated.

The lipolytic effect of GH was reflected by the levels of NEFA, which increased significantly the first night of the study. Growth hormone was not administered the second night. The different insulin levels seemed to have no impact on NEFA levels, which were identical during octreotide and placebo infusion.

Glucagon levels tended to be reduced during octreotide infusion, but this did not reach statistical significance. In studies of patients with acromegaly (1), normal subjects (37) and type II diabetic patients (38), glucagon levels were reduced by octreotide treatment.

Increments in circulating alanine and lactate levels during administration of octreotide have been noticed previously (37). Several factors, including decreased levels of insulin and glucagon and altered blood flow in the splanchnicus, may have contributed to this increase. Whether levels of these gluconeogenic precursors are

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elevated due to increased release from muscles and/or decreased hepatic uptake remain unsettled because isotope dilution was not used. Still, the findings may be explained to a large extent by a decreased hepatic extraction of three-carbon precursors secondary to hypoglycagomimia (39–41). The fact that the well-known inverse relationship between alanine and lipid intermediates (42) is lost during hormone suppression with octreotide adds substance to the hypothesis that this relationship is caused by fluctuations in hormone (i.e. insulin and glucagon) levels rather than direct substrate interaction. The decreased levels at night during fasting and increased levels postprandially have been reported earlier (43, 44).

In summary, continuous SC infusion of octreotide for 38 h to GH-deficient patients treated with GH was associated with:

(i) unaltered pharmacokinetics of exogenous GH;
(ii) unaltered IGF-I and IGFBP-3 concentrations;
(iii) decreased insulin levels and inversely increased IGFBP-1 levels;
(iv) elevated glucose levels but unaltered NEFA;
(v) elevated levels of alanine and lactate.

Our short-term study thus failed to detect a GH-independent effect of octreotide on IGF-I generation in humans.

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