Octreotide suppresses the incretin glucagon-like peptide (7–36) amide in patients with acromegaly or clinically nonfunctioning pituitary tumors and in healthy subjects

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Abstract

Objective: To study the effect of octreotide on glucagon-like peptide (7–36) amide (GLP-1) and insulin secretion in patients with pituitary tumors during preoperative treatment and in healthy subjects.

Design: Open design prospective clinical study.

Methods: Eighteen patients with pituitary macroadenomas (13 clinically nonfunctioning (NFA; 11/13 had GH insufficiency), 5 GH secreting (GHA)) received preoperative octreotide treatment: 3×100 µg/day s.c. for 3 months, and 3×500 µg/day s.c. for an additional 3 months. Seven healthy subjects received (for ethical reasons) only 3×100 µg/day for 10 days. A standardized meal (St-M) test, oral glucose test (oGTT) and i.v. glucose test (ivGTT) were done before octreotide therapy, on days 1, 2 and 3 (D1,2,3), after 3 months (M3) and 6 months (M6) of octreotide treatment in the patients, and before treatment, on D1,2,3 and on D8,9,10 of octreotide treatment in the healthy subjects. Serum GLP-1, insulin and GH as well as plasma glucose were determined for 180 min (oGTT, St-M) or 120 min (ivGTT).

Results: Pretreatment fasting GLP-1 concentrations as well as integrated responses (area under the curve 0–180 min) to oGTT and St-M were not significantly different between NFA, GHA and healthy subjects. During the oGTT, octreotide initially almost abolished the early (0–60 min) and diminished the late (60–180 min) GLP-1 and insulin responses in patients and healthy subjects. At M6 integrated insulin responses had significantly recovered, while the increase in GLP-1 response failed to reach significance (GLP-1: 56.5% of pretreatment at D2 versus 93.5% at M6 and 41.2 versus 63.1% in NFA and GHA respectively; insulin: 50.2 versus 71.2% and 35.5 versus 70.4%). An escape of GLP-1 and insulin in healthy subjects (D2 versus D9) was not significant. Intestinal glucose absorption was apparently not reduced, since the early glucose rise was similar before and during octreotide treatment.

During the St-M the GLP-1 and insulin responses were similarly suppressed by octreotide and recovered during ongoing treatment (GLP-1: 49.6% of pretreatment at D1 versus 79.0% at M6 in NFA and 46.9 versus 52.9% in GHA. Insulin: 27.6 versus 83.9% and 23.5 versus 54.4%). The escape was significant in NFA but not in GHA. In the healthy subjects the escape was already significant on D8 (GLP-1: 39.5% of pretreatment at D1 versus 68.3% at D8; insulin: 36.6 versus 53.8%).

During the ivGTT GLP-1 did not increase. The early insulin response (0–30 min) was abolished by octreotide, followed by a reduced peak at 60 min. The reduction of the integrated insulin response during ivGTT was similar to that during oGTT. An insulin escape reached significance only for NFA (52.6% of pretreatment at D3 versus 66.7% at M6). Glucose tolerance (K_G value) deteriorated and did not improve during ongoing treatment.

Octreotide suppressed the median GH concentration (8 h profile) of the GHA patients from 10.3 µg/l (pretreatment) to 5.8, 6.3 and 3.7 µg/l at D4, M3 and M6 with no escape. GH was 1.5 µg/l postoperatively.

Conclusions: Octreotide abolishes the early and diminishes the late GLP-1 and insulin responses to oGTT and St-M in NFA and GHA patients and in healthy subjects. In contrast to GH, both hormones partially escape from suppression during ongoing therapy. During treatment with our conventional octreotide doses suppression of insulin secretion is maximal. Under these conditions an effect of the additional loss of GLP-1 is not apparent. Basal GLP-1 concentrations and integrated responses to oGTT and St-M were similar in healthy subjects and in patients with GH excess or GH insufficiency.

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Introduction

The somatostatin analog octreotide is used for preoperative suppression of growth hormone (GH)

in acromegaly and for tumor volume reduction in GH-secreting (GHA), and sometimes clinically non-functioning (NFA) pituitary adenomas (1–4). An unwanted side-effect of octreotide is suppression of insulin secretion.

However, while GH secretion is inhibited permanently for many years, insulin secretion partially escapes despite ongoing therapy (1, 5–7). The cause of the different behavior of GH and insulin is unknown.

The insulin response to oral nutrients is augmented by the gastrointestinal incretin glucagon-like peptide (7–36) amide (GLP-1) (8, 9). Whether GLP-1 secretion is affected by octreotide treatment and whether inhibition of GLP-1 has a role in the reduced insulin secretion have not been determined. However, a small but significant suppression of GLP-1 by another (orally active) somatostatin analog (SDZ CO 611) has been described (10). GLP-1 has additional effects which could be disturbed by octreotide-induced suppression of the incretin. These include glucagon suppression and slowing of gastric motility (8, 11). A peripheral effect on glucose uptake and metabolism is controversial (12–14).

To further elucidate the effect of octreotide treatment we have determined serum GLP-1 and insulin concentrations during an oral glucose test (oGTT) in 18 patients with a pituitary adenoma (13 NFA (11 of whom were GH insufficient) and 5 GHA), who were preoperatively treated for 6 months with octreotide. Seven healthy subjects were also studied, but for ethical reasons received octreotide for only 10 days. GLP-1 is not stimulated by i.v. glucose (ivGTT) administration. An ivGTT was therefore done in an effort to separate the GLP-1-mediated from the direct octreotide effect on insulin secretion. In addition, the response to a more physiological stimulus, a standardized meal (St-M) was also studied.

Patients and methods

Eighteen patients with pituitary macroadenomas (13 NFA and 5 GHA) were preoperatively treated with octreotide in an attempt to reduce their tumor volume and suppress their GH concentration (GHA patients). Patient characteristics are given in Table 1. The diagnosis of NFA was based on a normal basal concentration of luteinizing hormone (LH), follicle-stimulating hormone (FSH), free α -subunit and prolactin (PRL). In addition, normal suppressibility of cortisol (<80 nmol/l) and GH (<1.0 μ g/l) was ascertained by a 1 mg dexamethasone test and an oGTT (100 g

respectively). Thyrotropin (TSH) and tri-iodothyronine/thyroxine (T_3/T_4) concentrations were incompatible with a thyrotropinoma in all patients. Acromegaly was diagnosed according to clinical criteria, nonsuppressibility of the plasma GH concentration to below 1.0 μ g/l during an oGTT (100 g) and an elevated, age- and sex-adjusted insulin-like growth factor-I (IGF-I) concentration. In all patients pituitary function was also determined by dynamic testing before octreotide treatment: LH-releasing hormone (LHRH) test (Relefact LHRH, Hoechst AG, Frankfurt, Germany, 100 μ g i.v.) for the LH and FSH responses; thyrotropin-releasing hormone (TRH) test (Relefact TRH, Hoechst, 200 μ g i.v.) for TSH and PRL responses; IHG (insulin-induced hypoglycemia, 0.1 IU/kg i.v.) for adrenocorticotropin (ACTH)/cortisol and GH responses. When the IHG was contraindicated, a metyrapone (ACTH/11-desoxy-cortisol) and an L-dopa test (0.5 g orally (GH)) were performed. Estrogen/testosterone and T_3/T_4 concentrations were also determined. GH, ACTH or gonadotropins (Gts) deficiency was present in 11, 2 and 9 NFA patients and Gts deficiency in 2 acromegalic patients respectively (Table 1). Patients with pituitary insufficiency received routine hormonal substitution therapy with the exception of GH.

Seven healthy subjects served as controls. All had normal basal and TRH-stimulated TSH and PRL concentrations, normal basal LH, FSH, free α -subunit, GH and IGF-I concentrations, as well as normal thyroid and gonadal hormones. The healthy subjects were considerably younger than the patients (Table 1). This was thought to be acceptable, since their data did not serve for direct comparison with those of the patients.

Octreotide treatment in the patients began with 3×100 μ g/day s.c. at 0800, 1600 and 2400 h for 3 months, followed by 3×500 μ g/day for an additional 3 months. Thereafter surgery was performed in all but one patient, who was operated on after only 3 months of octreotide treatment. For ethical reasons the healthy subjects received octreotide for only 10 days (3×100 μ g/day s.c.). This short treatment period carries no risk of gallstone formation.

The following tests were done on separate, consecutive days, beginning at 0800 h with the octreotide injection (when on treatment) and the first blood sample (-30 min sample) was taken immediately

Table 1. Patient characteristics.

	<i>n</i>	Sex (M/F)	Age (years; mean (range))	BMI ^a (mean (range))	Pituitary deficiencies ^b
NFA	13	8/5	57 (45–69)	26.7 (21.5–30.8)	GH: 11; ACTH: 2; Gts: 9
GHA	5	2/3	42 (31–52)	27.4 (24.4–31.9)	Gts: 2
Healthy subjects	7	6/1	26 (24–28)	21.3 (19.0–24.0)	–

^a BMI, body mass index (kg/m^2).

^b Indicates number of patients with complete deficiencies of the respective pituitary hormones. Thyroid function was either normal or patients were on T_4 substitution therapy.

thereafter (during the ivGTT the first blood sample (–60 min sample) was taken 30 min before the octreotide injection): (i) St-M test (46% carbohydrates, 28% protein, 26% fat, 600 kcal; (15)); (ii) oGTT (100 g); and (iii) ivGTT (0.5 g glucose/kg body weight) in this order. In the patients these tests were done before octreotide therapy, as well as on days 1, 2 and 3 (D1,2,3), at 3 months (M3) and 6 months (M6) of octreotide treatment. GHA patients had an 8 h profile (hourly blood samples) for determination of the plasma GH concentration at the same time points on the day following the other tests and again 6 weeks after surgery. The healthy subjects had tests before treatment, as well as on D1,2,3 and on days 8, 9 and 10 (D8,9,10) of octreotide treatment.

Blood samples were drawn from an antecubital vein for determination of serum GLP-1, insulin and GH as well as plasma glucose at –30, 0, 15, 30, 60, 90, 120, 150 and 180 min (oGTT and St-M), and at –60, –30, 0, 5, 10, 20, 30, 40, 50, 60, 90 and 120 min during ivGTT. The coefficient of glucose assimilation (K_G) was calculated as $(11.53[\log c_{20\text{ min}} - \log c_{40\text{ min}}])$. Blood was centrifuged immediately after withdrawal and the serum or plasma was stored at –20 °C until assayed in duplicate using commercially available RIAs: serum GH (Sorin, Saluggia, Italy, IRP 80/505), insulin (Sorin, IRP 66/304), acid-ethanol extracted plasma IGF-I (Nichols Institute, San Juan Capistrano, CA, USA, IRP 87/518). Plasma GLP-1 was determined as described earlier (16). The intra- and interassay coefficients of variation were 4.4 and 3.4% for GH, 4.7 and 8.3% for insulin, and 5.0 and 10.0% for GLP-1. Sensitivity was 0.5 µg/l for GH, 2.5 mU/l for insulin and 0.5 pmol/l for GLP-1. Plasma glucose was measured by a glucose oxidase method (Glucose Analyzer II, Beckman Instruments, Brea, CA, USA).

Statistical analysis

Median group values were calculated using the individual values, means or area under curves (AUCs). Between-group comparisons were calculated by the Mann–Whitney U test. Comparison of paired values was done using Wilcoxon's signed rank test. Adjustment for repeated comparisons was made according to Holm–Bonferroni: $P < 0.05$ was considered significant for the calculation of the first comparison and $P < 0.025$ for the subsequent second comparison. All calculations were performed using Statistica software (Statsoft Inc., Tulsa, OK, USA).

Informed written consent was obtained from all patients and healthy subjects. The study was performed according to the guidelines of the Declaration of Helsinki. The study protocol was approved by the hospital Ethical Committee.

Results

Basal pretreatment GH concentrations were high in GHA (median and range: 10.6 µg/l (8.3–25.0)) and low in NFA (0.8 (0.5–1.6)) and in healthy subjects (1.1 (0.5–3.2)). In contrast, the pretreatment fasting GLP-1 concentration of NFA, GHA and healthy subjects (8.8 (3.5–31.3), 9.0 (5.0–13.0) and 8.8 (4.3–15.5) pmol/l) as well as the GLP-1 response to oGTT and St-M (Table 2) were not significantly different. Octreotide treatment lowered the GH concentration of the GHA patients (8 h profile, medians of individual means and range) from a pretreatment value of 10.3 (9.4–37.8) µg/l to 5.8 (2.4–13.7), 6.3 (2.2–18.7) and 3.7 (2.5–22.0) µg/l at D4, M3 and M6 respectively. No escape from suppression was seen. The postoperative GH concentration was

Table 2 GLP-1 and insulin during oGTT, St-M and ivGTT in patients with NFA, GHA and in healthy subjects. Values are AUC 0–180 min for oGTT and St-M; AUC 0–120 min for ivGTT. AUCs are the median of individual AUCs, GLP-1 pmol/l × min, insulin mU/l × min. See text for significance of combined NFA and GHA data.

	<i>n</i>	Time	oGTT		St-M		ivGTT	
			GLP-1	Insulin	GLP-1	Insulin	GLP-1	Insulin
NFA	13	Pretreatment	2846	13 199	2498	6607	878	4525
		D1,2,3 ^a	1609**	6632*	1238**	1824**	564*	2381**
		M3	1793**	8355*	1148**	4058*	624*	2609**
		M6	2661*	9399*§	1974*	5544§§	819	3016**
GHA	5	Pretreatment	2929	16 386	2438	9534	981	4791
		D1,2,3 ^a	1208*	5815*	1395*	2240*	529	2927
		M3	1538*	9086*	1320*	6595	623	3174
		M6	1849*	11 542*§	1290	5188*§	734	2988
Healthy subjects	7	Pretreatment	2738	10 800	2164	5894	788	3087
		D1,2,3 ^a	1748*	4154*	855*	2159*	1072	1677
		D8,9,10 ^b	1995*	4532*	1478*§	3173*§	856	2089*

* $P < 0.05$ vs pretreatment; ** $P < 0.01$ vs pretreatment; § $P < 0.05$ vs D1,2,3; §§ $P < 0.01$ vs D1,2,3.

^a D1 for St-M, D2 for oGTT and D3 for ivGTT.

^b D8 for St-M, D9 for oGTT and D10 for ivGTT.

Figure 1 GLP-1 and insulin during oGTT in NFA, GHA and controls (healthy subjects). Medians of individual values. Δ , before treatment; $\circ$, during day 2 of octreotide treatment; $\times$, at the end of octreotide treatment (M6 in patients and D9 in controls). Curves of M3 are not shown for the sake of clarity. For numerical values (AUC) see Table 2.

1.5 (1.1–6.8) $\mu\text{g/l}$. Two of the NFA patients had intact pretreatment GH secretion, while 11 were GH insufficient. Since octreotide rendered the two GH sufficient patients completely GH insufficient, their data were included in all calculations.

GLP-1, insulin and glucose response during oGTT

Before octreotide treatment the serum GLP-1 and insulin concentrations of patients and healthy subjects attained peak values at 30–60 min. The GLP-1 increase was more prolonged in the healthy subjects (Fig. 1). On D2 of octreotide treatment the early (0–60 min) GLP-1 and insulin responses were almost abolished, followed by a sluggish rise during the 2nd and 3rd hour (late response). The integrated (AUC 0–180 min) GLP-1 and insulin responses during octreotide treatment were all significantly lower than before treatment (Table 2). However, at M3 the GLP-1 and insulin responses had improved and at M6 the insulin response was significantly higher in NFA and GHA than at the

Figure 2 (A) Glucose during oGTT in NFA, GHA and controls (healthy subjects). Medians of individual values. Δ , before treatment; $\circ$, during day 2 of octreotide treatment; $\times$, at end of octreotide treatment (M6 in patients and D9 in controls). (B) Insulin during ivGTT in NFA, GHA and controls (healthy subjects). Medians of individual values. Δ , before treatment; $\circ$, during day 3 of octreotide treatment; $\times$, end of octreotide treatment (M6 in patients and D10 in controls). Curves of M3 are not shown for the sake of clarity. For numerical values (AUC) of insulin see Table 2.

beginning of octreotide treatment (despite the increase of the octreotide dose). Due to the small number of patients in the subgroups, the escape of GLP-1 failed to reach significance. However, when the data of NFA and GHA patients were analyzed together (after conversion to percent of pretreatment values), the GLP-1 escape at M6 was also significant ($P=0.039$). In the healthy subjects the GLP-1 and insulin escape on D8 was not significant (Fig. 1, Table 2).

Plasma glucose rose higher during octreotide treatment than before octreotide in patients and healthy subjects (Fig. 2A). Despite the partial GLP-1 and insulin escape, glucose tolerance did not improve: AUC (0–180 min) as well as 120 min values during ongoing octreotide treatment were not significantly different from those on D2. Gastrointestinal absorption of glucose was not measurably reduced during octreotide treatment, since the glucose values during the first hour of

Figure 3 GLP-1 and insulin during an St-M test in NFA, GHA and controls (healthy subjects). Medians of individual values. Δ , before treatment; $\circ$, during day 1 of octreotide treatment; X, at the end of octreotide treatment (M6 in patients and D8 in controls). Curves of M3 are not shown for the sake of clarity. For numerical values (AUC) see Table 2.

the test (AUC 0–60 min) were not significantly different before and during octreotide treatment (pretreatment 431, 475 and 401 versus octreotide treatment (D2) 398, 452 and 401 mmol/l $\times$ 60 min for NFA, GHA and healthy subjects respectively).

GLP-1, insulin and glucose response to St-M

The octreotide effect on the GLP-1 and insulin responses to the St-M was similar to that during oGTT (Fig. 3). Octreotide treatment abolished the GLP-1 and insulin

responses at D1 in patients and healthy subjects (Fig. 3). A partial recovery was significant for GLP-1 and insulin in NFA at M6 and in healthy subjects already at D8 (Table 2). The glucose rise was augmented during octreotide treatment in patients and healthy subjects (data not shown).

GLP-1, insulin and glucose response to i.v. glucose

As expected, serum GLP-1 did not increase during the ivGTT before or during octreotide treatment (Table 2). GLP-1 was even slightly suppressed by octreotide treatment in NFA patients, but this was not the case in GHA and healthy subjects. The early insulin response was abolished during octreotide treatment in patients and healthy subjects (Fig. 2B), followed by a sluggish rise to a low peak at 60 min. An escape of insulin was significant at M6 in NFA, but not in GHA nor in healthy subjects at D10. Impaired glucose tolerance ($K_G < 1.2$) or overt diabetes mellitus ($K_G < 1.0$) was present before treatment in three NFA, four GHA patients and none of the healthy subjects. Deterioration of glucose disposal during octreotide treatment was significant in NFA and healthy subjects, but not in GHA (Table 3). An apparent slight improvement of the K_G value during ongoing treatment in all three groups failed to be significant.

The possible importance of a pathological glucose tolerance before octreotide treatment was also examined. The data of the glucose intolerant patients were removed and the group GLP-1 and insulin responses to St-M and oGTT before and during octreotide treatment were recalculated. The octreotide effect remained similar to that in the full groups. Thus, pretreatment pathological glucose tolerance had no apparent influence on the octreotide-induced suppression of the GLP-1 and insulin responses in these tests.

Discussion

Somatostatin and its analogs are known to suppress the insulin response to glucose and to an St-M (1, 17, 18). We now show that the response of the incretin GLP-1 to oral nutrients is also suppressed by the somatostatin analog octreotide. This must be added to the effects of somatostatin analog treatment.

Table 3 K_G values (> 1.2 , normal glucose tolerance; < 1.0 , diabetes mellitus) of patients and healthy subjects in the ivGTT. Data are medians of the respective groups.

	n	Pretreatment	D3	D10	M3	M6
NFA	13	1.39	0.75**	—	0.86**	0.81**
GHA	5	0.91	0.59	—	0.44	0.64
Healthy subjects	7	2.12	0.86*	1.13*	—	—

* $P < 0.05$ vs pretreatment; ** $P < 0.01$ vs pretreatment.

The octreotide effect on GH is unabated even after several years of treatment (19). In contrast, insulin escapes partially from suppression during ongoing therapy (1) and this is also the case for GLP-1. The escape apparently progresses slowly over several months. Although the hormone responses were already higher at M3, it was only at M6 that the improvement became significant. The healthy subjects had a more homogeneous distribution of GLP-1 and insulin concentrations and their GLP-1 and insulin escape was already significant in the St-M after only 1 week of treatment. An early escape of insulin and lack of GH escape have also been found during treatment with the somatostatin analog BIM 23014 (18).

The mechanism behind the different behavior of GH (no escape) on the one hand and insulin and GLP-1 (escape) on the other hand is not clear. GH suppression is mainly affected through the subtype 2 (SSTR2) of the somatostatin receptor and insulin suppression through the SSTR5 receptor (20). Octreotide has a weaker affinity for SSTR5 than for SSTR2. We therefore speculate that the GLP-1 escape may indicate that octreotide acts on the intestinal GLP-1-secreting cells preferentially via the SSTR5 receptor.

All insulin responses were higher in NFA and GHA than in the healthy subjects. This was probably due to insulin resistance induced by the elevated GH concentration in the GHA and by obesity in the NFA. In contrast, GLP-1 responses (oGTT and St-M) of NFA and GHA patients were only slightly and nonsignificantly higher than those of the healthy subjects. Our results in the NFA patients thus do not support a report of diminished GLP-1 response in obesity (21). However, we are aware that the complex metabolic and endocrine profile of our patients may have obscured a more direct relationship between obesity and GLP-1 secretion.

Our data are at variance with the previous observation (reported in abstract form, Drewes *et al.* (22)) of a reduced GLP-1 response to glucose both in acromegaly and in patients with GH insufficiency. In our present patients the GLP-1 response to both oGTT and St-M was slightly higher, rather than lower in GHA (with GH excess) and NFA (11 of whom were GH insufficient), than in healthy subjects. Thus, GH status apparently does not influence GLP-1 secretion and the increased insulin concentrations in acromegaly are not mediated via increased GLP-1.

Under the conditions of our experiments the inhibition of GLP-1 secretion was probably of little importance for the reduced insulin secretion. The suppression of the insulin response as well as its escape was similar during oGTT (where physiologically GLP-1 is involved) and ivGTT (where physiologically GLP-1 is not involved). This suggests that maximal insulin suppression during the oGTT was achieved by the direct octreotide effect alone, which is in accordance with the reported insulin suppression by even lower octreotide doses than ours (17, 23). However, GLP-1 has additional effects,

including glucagon suppression, stimulation of pancreatic somatostatin release (8, 11, 24) and possibly a peripheral effect on glucose uptake/insulin sensitivity (13), although the latter remains controversial (12, 14). While a mouse model with disrupted GLP-1 receptor signaling (25) suggests that only its incretin effect is essential for glucose homeostasis, disruption of other GLP-1 actions may still be important for the fine tuning of the metabolic response to oral nutrients.

Octreotide almost abolished the early part of the GLP-1 and insulin responses, similar to the pattern already described for insulin (1, 17, 26). Decreased early glucose absorption is unlikely to explain the delayed hormone response, since the early glucose rise in the oGTT and the St-M was identical before and during octreotide. While insulin may later respond to the high glucose concentrations that are now achieved, this cannot explain the GLP-1 increase, since the latter responds only to oral glucose but not to elevated blood glucose concentrations as such. The exact mechanism(s) of the glucose and hormone kinetics during octreotide treatment remain to be determined.

We conclude that octreotide suppresses not only the insulin but also the GLP-1 response to oral glucose and to an St-M in normal subjects and in NFA and GHA patients. In contrast to GH, both hormones partially escape from suppression during ongoing treatment. During treatment with conventional doses the direct octreotide effect on insulin secretion is maximal. Hence, the loss of the GLP-1 effect is probably not important. A role of diminished GLP-1 secretion is, however, possible, when low octreotide doses are used. The consequences for other GLP-1 effects remain to be investigated. GLP-1 was not decreased in our patients with acromegaly or GH deficiency.

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