Short-Term Effects of Octreotide on Glucose Tolerance in Patients with Acromegaly

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Abstract. To elucidate the short-term effects of octreotide, a somatostatin analogue, on glucose tolerance in acromegaly, the plasma glucose and insulin responses to a 75-g oral glucose tolerance test (75-g OGTT) were examined in 6 patients. The glucose disposal rate (GDR) was also measured by the hyperinsulinemic euglycemic clamp method before and after the administration of octreotide. Before octreotide therapy, 2 patients had normal responses of plasma glucose and insulin to 75-g OGTT (normal glucose tolerance: NGT) and 4 showed hyperinsulinemia or glucose intolerance (glucose intolerance: GIT). GDR-insulin dose-response curves showed a normal pattern in patients with NGT and pattern of insulin resistance in patients with GIT. After 2–3 weeks of octreotide administration, plasma growth hormone (GH) levels decreased in all of the patients. The plasma glucose response to 75-g OGTT was not changed in any patient. In contrast, the plasma insulin response to 75-g OGTT was enhanced in patients with NGT but lessened in patients with GIT. Patients with NGT showed no significant change in GDR-insulin dose-response curves. Patients with GIT showed improvement in GDR at low levels of plasma insulin, but did not show complete improvement at high levels. These results indicate that octreotide improves insulin resistance at the insulin receptor site by lowering plasma levels of GH and insulin in acromegalic patients with glucose intolerance.

Key words: Acromegaly, Glucose intolerance, Insulin resistance, Octreotide

GLUCOSE intolerance is often associated with acromegaly [1, 2]. Soft tissue swelling and/or long-standing growth hormone (GH) hypersecretion are thought to contribute to glucose intolerance in acromegaly [3]. An increase in hepatic glucose output and a decrease in glucose uptake in peripheral muscle and fat tissue are metabolic factors that may be involved in this insulin resistance [4].

Recently, octreotide, a long-acting somatostatin analogue, has proved effective in the treatment of acromegaly [5]. The effects of octreotide on plasma levels of glucose and insulin in healthy subjects [6] and in patients with acromegaly [7–11] have been reported. However, only one study has been performed on the effects of octreotide on insulin resistance in patients with acromegaly [12].

To determine the short-term effects of octreotide on insulin resistance in acromegaly, the plasma glucose and insulin responses to a 75-g oral glucose tolerance test (75-g OGTT) were examined in 6 patients. The glucose disposal rate (GDR) was also measured by the hyperinsulinemic euglycemic clamp method before and after the administration of octreotide.

Patients and Methods

Patients

Six patients with acromegaly were diagnosed based on physical examination and elevated levels
of plasma GH, insulin-like growth factor I (IGF-I) and urinary GH. In all of the patients, pituitary adenomas were shown on computed tomography and magnetic resonance imaging. The clinical profiles of the 6 patients are shown in Table 1. Before the administration of octreotide, cases 3 and 6 received bromocriptine. Case 2 had received bromocriptine after partial hypophysectomy performed 8 years previously. No therapy had been given in cases 1, 4 and 5. None of the patients received sulfonylurea or insulin therapy for diabetes mellitus.

**Methods**

We initiated the treatment with octreotide (200–300 μg) which was injected subcutaneously 2 or 3 times daily for more than 7 days after the discontinuation of bromocriptine. The plasma glucose and insulin responses to 75-g OGTT were determined in the patients, and GDR was measured by the hyperinsulinemic euglycemic clamp method before and after the octreotide administration for 2 weeks. Plasma GH levels on TRH test were determined before and after the administration of octreotide in three patients (cases 3, 4 and 5). After an overnight fast, these examinations were performed in the morning prior to octreotide administration.

Hyperinsulinemic euglycemic clamping was performed in each patient as previously described [13, 14]. Following an overnight fast, an intravenous cannula was inserted into an antecubital vein for the infusion of insulin and glucose. Another cannula was inserted into the dorsal vein of the contralateral hand, which was warmed to 50 °C with a heating pad, to provide arterialized venous blood for sampling. GDR was calculated during the last 30 min of a 120-min intravenous infusion of regular insulin (Human Actrapid Insulin, Novo-Nordisk Pharmaceuticals Co., Copenhagen, Denmark) in a dose of 40, 100, 200 or 400 mU per min per m².

Plasma glucose levels were measured by the glucose oxidase method (A&T Co., Tokyo, Japan). Plasma insulin levels were determined by radioimmunoassay with a commercial radioimmunoassay kit (Eiken Chemical Co., Tokyo, Japan). To determine the free insulin level, 1 ml of plasma and 1 ml of 25% polyethylene glycol were mixed and centrifuged, and then the insulin level in the supernatant was determined by radioimmunoassay with a Phadeseph Insulin RIA kit (Pharmacia Diagnostics Co., Sweden). Plasma levels of GH, LH, FSH, TSH and prolactin were measured by commercial radioimmunoassay kits (Eiken Chemical Co., Tokyo, Japan, Daiichi radioisotopic Lab., Tokyo, Japan and Dinabot Co., Tokyo, Japan).

All data are expressed as mean ± SD. Statistical analysis was performed by Student's paired t-test.

**Results**

*Plasma levels of GH and IGF-I before and after the administration of octreotide (Fig. 1)*

Mean basal plasma levels of GH and IGF-I decreased after the administration of octreotide for 2–3 weeks from 61.1 ± 35.1 ng/ml to 11.8 ± 33.9 ng/ml (P<0.01) and from 822.5 ± 314.8 ng/ml to

<table>
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BC, Bromocriptine; PA, Pituitary Adenectomy.
540.8 ± 264.5 ng/ml (P<0.05), respectively.

The mean peak value of plasma GH on TRH test also decreased from 74.2 ± 33.3 ng/ml to 16.6 ± 10.4 ng/ml after octreotide administration in 3 patients (cases 3, 4 and 5), however, because analyzed cases were small, these results were not statistically significant.

Plasma glucose and insulin responses to a 75-g oral glucose tolerance test (Fig. 2)

Before octreotide therapy, 2 patients (cases 1 and 2) showed normal responses of plasma glucose and insulin to 75-g OGTT (normal glucose tolerance: NGT) and 4 patients showed glucose intolerance (GIT) based on the report of Harrison and Flier [15]. These four patients consisted of 2 patients (cases 3 and 4) who showed normal glucose response with hyperinsulinemia, one patient (case 5) who showed an impaired glucose tolerance pattern with hyperinsulinemia, and in one patient (case 6), a diabetic pattern with normoinsulinemia.

After 2–3 weeks of octreotide administration, there was no significant change in the plasma glucose response to 75-g OGTT in any of the patients. The mean ΣPG (the sum of plasma glucose levels, before, 60 and 120 min after glucose loading) in the 6 patients before and after octreotide therapy were 313.2 ± 64.8 mg/dl and 284.4 ± 79.2 mg/dl, respectively. In patients with NGT, plasma insulin responses to 75-g OGTT tended to be greater after octreotide therapy than before. The mean ΣIRI (the sum of plasma insulin levels before, 60 and 120 min after glucose loading) before and after octreotide therapy were 68.4 μU/ml and 104.4 μU/ml, respectively. The plasma insulin responses in 4 patients with GIT were lower after the therapy than before (Σplasma insulin levels: 104.9 ± 75.5 μU/ml vs. 167.2 ± 65.7 μU/ml, P<0.05).

Glucose disposal rates (GDR)-insulin dose-response curves (Fig. 3)

Before the administration of octreotide, GDRs determined at both low and high levels of plasma insulin were within the normal range in 2 patients with NGT. The normal range for the GDR-insulin dose-response curve was calculated from curves of 18 healthy controls (14 men and 4 women, mean age 29.6 years) available at our institution. GDRs were reduced at both low and high levels of plasma insulin in 4 patients with GIT, indicating the presence of insulin resistance.

After octreotide therapy, GDR at both low and high levels of plasma insulin was not changed in one patient (case 1). GDR at both low and high levels of plasma insulin decreased to the lower limits of normal in patient number 2. While GDRs at
low levels of plasma insulin increased in all 4 patients with GIT (cases 3, 4, 5 and 6). GDR at high levels of plasma insulin increased in 2 patients (cases 3 and 5), was within the lower limit of normal in one patient (case 3), and remained low in one patient (case 5). GDR at high levels of plasma insulin was not changed in 2 patients (cases 4 and 6).
mU/ml), LH (6.64 ± 6.99 mU/ml vs. 13.69 ± 15.08 mU/ml) and PRL (16.50 ± 6.35 ng/ml vs. 11.94 ± 10.92 ng/ml) before and after the administration of octreotide.

Discussion

Approximately 30%-60% of patients with acromegaly have glucose intolerance, and 10%-30% of these patients develop diabetes mellitus [1, 2]. In this study, 2 patients had normal responses of plasma glucose and insulin to a 75-g glucose load and 4 patients showed glucose intolerance. Among the latter 4 patients were 2 patients with normal plasma glucose responses with hyperinsulinemia, one patient with an impaired glucose tolerance with hyperinsulinemia and one patient with a diabetic pattern with normoinsulinemia. According to the spectrum of carbohydrate disturbance in acromegaly of Harrison and Flier [15], cases 1 and 2 were stage 1, cases 3 and 4 were stage 2, case 5 was stage 3, and case 6 was stage 3 or 4.

After 2-3 weeks of treatment with 200-300 µg of octreotide, basal and peak plasma levels of GH on TRH test decreased.

After the administration of octreotide, there was no change in plasma glucose response to 75-g OGGT in any of the patients. Regarding plasma glucose responses to 75-g OGGT after octreotide therapy, Barcan et al. [9] also reported no significant changes, while Quabbe et al. [10] and Halse et al. [11] reported a delay of peak. In general, glucose metabolism is affected by plasma levels of various hormones, including insulin, glucagon, GH, cortisol and epinephrine. In patients with acromegaly, who characteristically hypersecrete GH, different imbalances of these hormones may bring about glucose intolerance of varying severity. The effects of octreotide on these hormones may, in turn, differ with the severity of glucose intolerance. These variables may explain the discrepancies among the previous reports [9-11] and this study in plasma glucose responses to 75-g OGGT after octreotide therapy.

The effects of octreotide on insulin secretion have varied between previous reports [9, 10, 12]. In this study, the plasma insulin responses to an oral glucose load in 4 patients with GIT (cases 3, 4, 5 and 6) were lowered after the octreotide therapy, in accordance with previous reports [9, 10]. However, the responses to an oral glucose load in 2 patients with NGT (cases 1 and 2) increased after the octreotide administration in accordance with the observation of Ken et al. [12]. Chiba reported that the effects of somatostatin on insulin were different with differing levels of glucose and glucagon [16]. Our observations and these previous reports [9, 10, 12, 16] indicate that the effects of octreotide, a somatostatin analogue, as well as somatostatin itself on insulin secretion may vary according to the severity of glucose intolerance.

Regarding insulin resistance, Kahn [17] emphasized the importance of distinction between insulin insensitivity and unresponsiveness. Insulin resistance at low levels of plasma insulin (physiological level) means insulin insensitivity and is mainly ascribed to the alterations prior to the interaction of insulin with its receptor (receptor site). Insulin resistance at high levels of plasma insulin (pharmacological level) means insulin unresponsiveness and is mainly ascribed to the alterations at the intracellular steps in insulin action (post-receptor site). We tried to determine the sites of alteration by the hyperinsulinemic euglycemic clamp method, although some limitations exist in the determination of precise sites of alteration by in vivo study.

Before the administration of octreotide, GDRs were normal in 2 patients (cases 1 and 2) with normal glucose tolerance at both high and low levels of plasma insulin. GDRs were low in 4 patients (cases 3, 4, 5 and 6) at both high and low levels of plasma insulin, indicating the presence of insulin insensitivity and unresponsiveness, and disorders at both receptor and post-receptor sites, in accordance with previous reports [4, 7].

After octreotide therapy, GDR was not changed in a patient (case 1) with NGT. GDR in another patient (case 2) with NGT decreased to the lower limits of normal at both low and high levels of plasma insulin. These decreases in GDR in the patient (case 2) may reflect at least partly the down-regulation at receptor sites with hyperinsulinemia, which caused greater responses of plasma insulin to oral glucose loading after therapy. GDR in 4 patients (cases 3, 4, 5 and 6) with GIT increased at low levels of plasma insulin, indicating improvement in insulin resistance at the receptor sites. Muggeo et al. [18] reported that the number of insulin receptors on monocytes in patients with acromegaly reflects the plasma level of insulin re-
regardless of plasma glucose level. Improvement in insulin resistance at receptor sites may be mainly ascribed to the ability of octreotide to lower plasma levels of insulin, though the direct effect of octreotide on insulin receptor cannot be neglected. GDRs in 2 patients (cases 3 and 5) increased at high levels of plasma insulin, but was within the lower limit of normal in case 3 and remained low in case 5. GDRs in 2 patients (cases 4 and 6) showed no significant change. These results at high levels of plasma insulin indicate that insulin resistance at post-receptor sites persists regardless of decreases in plasma levels of GH and insulin after the short-term administration of octreotide. The short-term administration of octreotide improved insulin resistance at receptor sites in patients with acromegaly. However lowered plasma levels of GH and insulin did not improve insulin resistance at post-receptor sites. These results indicate that a primary cause of insulin resistance in patients with acromegaly may be insulin resistance at post-receptor sites and that hyperinsulinemia may contribute to insulin resistance at receptor sites.

We conclude that the short-term effects of octreotide on insulin may differ with the severity of glucose intolerance and that based on the short-term effects of octreotide on insulin resistance, the primary cause of insulin resistance in acromegaly, may be insulin resistance at post-receptor sites and secondary factors, including hyperinsulinemia, may contribute to insulin resistance at receptor sites. Further studies should address the long-term effects of octreotide on glucose metabolism and insulin resistance.

References


