

NOTE

Glucose-Dependent Insulinotropic Polypeptide Induced Growth Hormone Secretion in Acromegaly

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Abstract. Glucose-dependent insulinotropic polypeptide (GIP), a peptide released from the intestines after meals, is thought to stimulate insulin secretion. GIP receptor cDNA has recently been cloned and its mRNA has been recognized in several organs including the pituitary, but the physiological roles of GIP receptors of the pituitary have yet to be determined. We have demonstrated the possibility that GIP stimulates GH secretions from the pituitary adenoma cells of acromegalics. GIP-stimulated GH responses were studied in four acromegalics. In two acromegalics whose GH showed paradoxical secretion to oral glucose tolerance test (OGTT), GIP infusion (0.6 µg/kg/h) drove GH secretion (13.7 to 68.1, 22.5 to 76.2 ng/ml, respectively). However, in the other two acromegalics whose GH showed no paradoxical response to OGTT, GIP infusion did not induce GH secretion. One of the patients who was studied extensively had a GH that responded to OGTT. This patient's serum GH levels increased after meals while adenectomy abolished both the paradoxical GH secretions by OGTT and GH responses to the GIP infusion. These data suggested that some somatotroph adenoma cells have an aberrant response to GIP which may go toward explaining paradoxical GH secretions to OGTT in acromegalics.

Key words: Acromegaly, GIP, GH

(Endocrine Journal 50: 643–650, 2003)

GLUCOSE is known to suppress growth hormone (GH) secretion [1–4]. However, in acromegaly, absence of GH suppression by oral glucose tolerance test (OGTT) is essential to the diagnosis of GH hypersecretion [5]. Furthermore, a paradoxical GH secretion to OGTT is recognized in about 10% of acromegalics [5]. However, the mechanism of this paradoxical secretion has yet to be clarified.

We observed one acromegalic (described below as case 1) who exhibited paradoxical GH secretion to OGTT, and showed GH secretion after meals but did not show GH secretion after intravenous glucose load.

These observations suggested that some gastrointestinal hormone might be involved in these paradoxical GH secretions.

Glucose-dependent insulinotropic polypeptide (GIP) is a gastrointestinal hormone, which is released from the intestinal endocrine cells after meals and is thought to play a role in stimulating insulin secretion [6]. GIP is known to be most highly secreted gastrointestinal hormone after oral glucose load [7]. Moreover, GIP receptor cDNA has recently been cloned and its mRNA was detected in the central nervous system and several peripheral tissues including the pituitary [8].

On this basis, we attempted to investigate the hypothesis that GIP might be involved in paradoxical GH secretions to OGTT in acromegalics. GIP stimulated GH responses were compared between acromegalics whose GH showed paradoxical GH responses to OGTT and acromegalics whose GH did not respond to OGTT. Recently a condition known as food-dependent

Received: May 27, 2002

Accepted: March 25, 2003

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Cushing's syndrome has been reported [9, 10]. In these patients, the food-dependent cortisol hypersecretion is reproduced by the administration of GIP, and functional GIP receptors have been demonstrated in the resected adrenal cells [9]. We used the same methods in food-dependent Cushing's syndrome to study the GIP stimulated GH responses in acromegalics.

Patients and Methods

Informed consent was obtained from each patient before performing each test. Gunma University School of Medicine Review Board approved the GIP loading test.

Patients

We tested 4 acromegalics. OGTT was performed first to determine whether the patient had paradoxical GH responses. Two of patients showed paradoxical GH secretions to OGTT, and the other 2 patients showed no GH response. The former 2 patients, described below as case 1 and case 2, were examined extensively and the latter 2 patients were tested as controls.

Case 1: A 45-year-old Japanese woman presented with typical physical features of acromegaly. Her plasma baseline GH concentration was 18.9–32.3 ng/ml, plasma insulin-like growth factor I was 920 ng/ml (normal range 73–383 ng/ml) and X-ray film revealed enlarged sella turcia with intrahypophyseal tumor on magnetic resonance imaging (MRI) and she was diagnosed as acromegaly. Her pituitary functions examined by LH releasing hormone (LHRH) test (100 µg, iv bolus), TSH releasing hormone (TSH) test (500 µg, iv bolus), and GH releasing hormone (GRH) test (100 µg, iv bolus) were normal except for GH rise after TRH load up to 76.2 ng/ml. Her base line prolactin (PRL) levels were normal (7.4–7.9 ng/ml), and GH secretion was not stimulated by LHRH. She had impaired glucose tolerance and fasting blood glucose level was 87–97 mg/dl.

After clinical loading tests including OGTT, intravenous glucose loading test, intravenous GIP loading test and plasma GH measurement after meals, she had a transsphenoidal adenomectomy. After operation, OGTT and GIP loading tests were performed once again.

Case 2: A 67-year-old Japanese woman with typical acromegalic features was tested. Her plasma baseline GH concentration was 9.9–33.5 ng/ml, plasma insulin-like growth factor I was 860 ng/ml and X-ray film revealed enlarged sella turcia with intrahypophyseal tumor on MRI and she was diagnosed as acromegaly. Her PRL level was normal (7.9 ng/ml), and plasma GH elevated by LHRH loading up to 146 ng/ml. OGTT, intravenous glucose loading test and GIP loading test were performed, but she did not get adenomectomy.

The other 2 patients whose GH did not respond to OGTT also got intravenous GIP loading test.

Clinical studies

Seventy five gm oral glucose load and 10 gm intravenous glucose load were performed after overnight fasting. Plasma glucose and GH were measured.

In case 1, plasma GH and glucose levels were measured before and 2 h after each meal on the same day and plasma glucose and GH were measured every 30 min after breakfast for 6.5 h on the other day.

GIP (Beecham, Torrance, CA) was infused for one hour at a rate of 0.6 µg/kg body weight/h with 10% glucose infusion at a rate of 150 ml/h. This rate of GIP infusion was scheduled to obtain the physiological plasma concentration in the postprandial period [9, 10]. Plasma glucose, insulin (IRI), and GH levels were measured every 15 min during the infusion.

In case 1, OGTT and GIP loading test were performed on 35 and 45 days after the adenomectomy, respectively.

Hormone assays

Plasma GH concentrations were measured by radioimmunoassay with commercial kits purchased from Eiken Chemical (Tokyo, Japan) and plasma insulin concentrations were assayed with enzyme immunoassay kits from Boehringer Mannheim Yamanouchi (Tokyo, Japan).

Results

Case 1 and Case 2

GH responses to OGTT and intravenous glucose

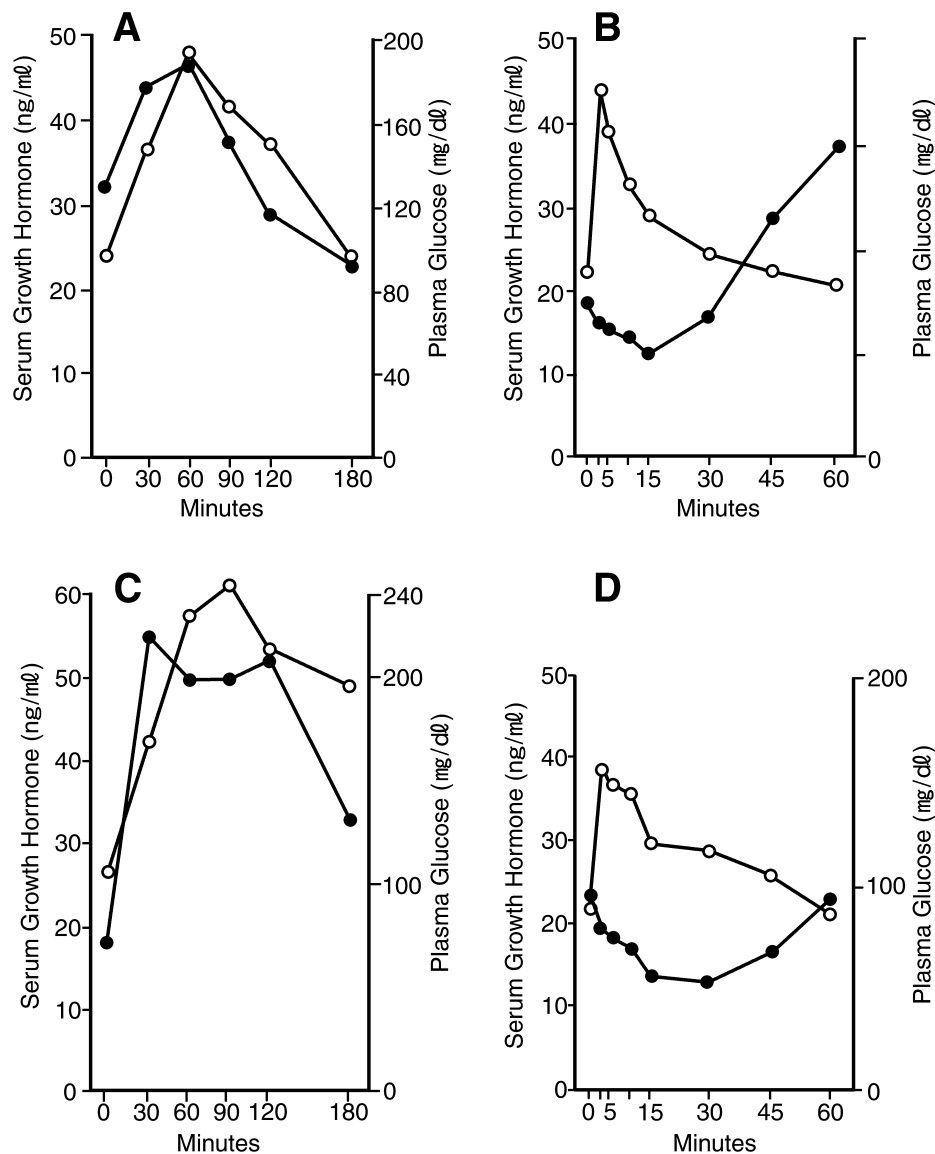


Fig. 1. GH response to the 75 gm oral glucose loading tests (Fig. A for case 1, and Fig. C for case 2) and the intravenous glucose loading tests (Fig. B for case 1 and Fig. D for case 2). GH levels are represented by closed circles and glucose levels are represented by open circles. GH levels rose in the oral glucose loading concomitant with the rise of glucose levels, but did not rise in intravenous glucose load.

loading tests in case 1 and case 2 are shown in Fig. 1. In these patients, GH responses to OGTT were paradoxical, that is, plasma GH levels increased (in case 1, from 32.3 to 47.3 ng/mL as shown in Fig. 1A; in case 2, from 17.6 to 49.9 ng/mL as shown in Fig. 1C) concomitant with the increase of plasma glucose levels. On the contrary, in the intravenous glucose load test, plasma GH levels did not change with elevation of blood glucose as shown in Fig. 1B and Fig. 1D for case 1 and case 2, respectively. On the other hand, plasma GH levels elevated after meals on case 1 as

shown in Fig. 2.

The GIP infusion with glucose to case 1 and case 2, increased plasma GH levels concomitant with the increase of plasma insulin levels under the stable blood levels (Fig. 3A for case 1, and Fig. 3B for case 2).

The GH responses to OGTT and intravenous GIP infusion, which were performed on case 1 after operation, reversed to normal as shown in Fig. 4.

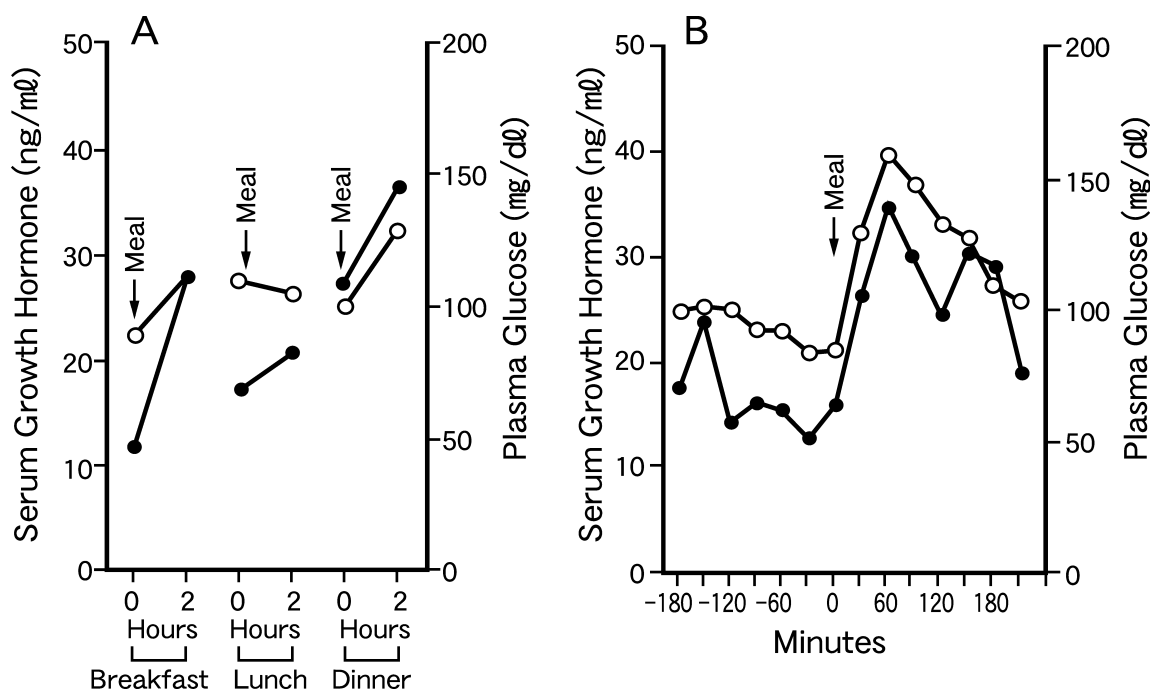


Fig. 2. GH responses to meals (Fig. A). Serum glucose (open circle) and GH (closed circle) were measured before meals and 2 h after meals on the same day. GH levels were elevated after each meal. GH responses to breakfast were taken after overnight fast (Fig. B). Plasma glucose and GH levels were measured every 30 min for 6.5 h before and after breakfast. GH levels elevated after breakfast concomitant with the rise of plasma glucose levels.

The other 2 cases

Intravenous GIP loading did not increase plasma GH levels in the 2 acromegalics who did not show the paradoxical GH secretions to OGTT as shown in Fig. 5 (the results of one case are shown).

Discussion

The present paper is the first to demonstrate the possibility that GIP is a cause of the paradoxical GH secretions to oral glucose load in acromegaly. The evidence showed that acromegalics whose GH showed paradoxical responses to OGTT exhibited GH secretions to the GIP stimulation, whereas acromegalics whose GH showed no response to OGTT did not exhibit GH secretions to the GIP stimulation.

It is well known that GH secretion is mainly stimulated by GRH and inhibited by somatostatin [12]. However, the mechanism of the suppressing effect of hyperglycemia on GH secretion in normal subjects is not clear, nor is the cause of paradoxical secretion to oral glucose in acromegaly [13–15]. It was reported

that an acromegaly induced by an ectopic GRH-producing tumor, had a paradoxical GH secretion to oral glucose, but that an exogenous GRH load did not induce GH secretion, therefore GRH was thought not to be involved in the paradoxical GH response to oral glucose load in acromegaly [16]. Hence, some other mediator but not GRH has been speculated to be involved in the paradoxical GH secretions in response to oral glucose load. Some hypothalamic hormones, such as TRH or LHRH [17], also induce the paradoxical GH secretions in acromegaly. However, these hypothalamic hormones cannot be the mediators of paradoxical GH secretions induced by oral glucose, because none of these hormones are secreted by oral glucose load.

It is thus reasonable to assume that some gastrointestinal hormones other than hypothalamic hormones are the cause of paradoxical GH response to oral glucose load. Recently, vasoactive intestinal polypeptide (VIP) and peptide histidine methionine (PHM), both gastrointestinal hormones, have been reported to drive GH secretions in acromegalics *in vitro* [18–20] and *in vivo* [18, 21] but not in normal subjects [18–21]. GIP as well as PHM is a member of the VIP

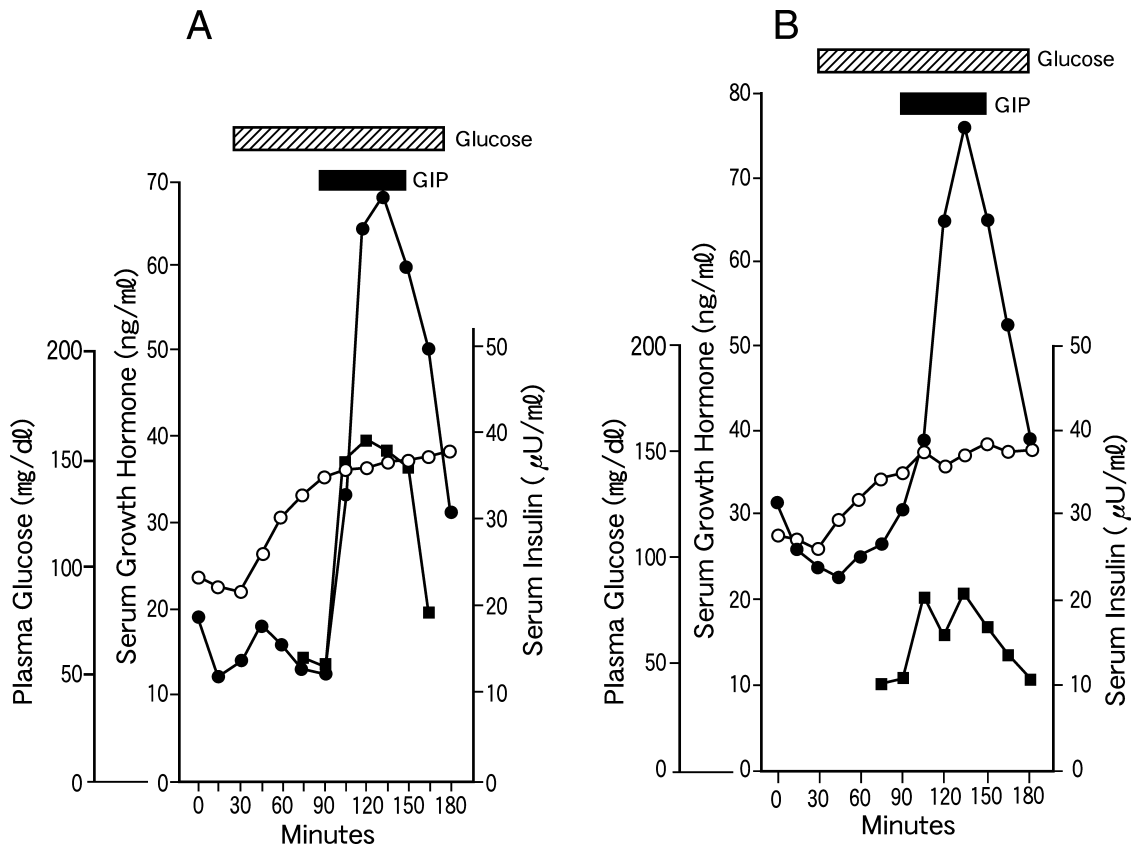


Fig. 3. GH responses to the GIP infusion. GIP was infused ($0.6 \mu\text{g/kg/h}$) for 1 hour during the infusion of 10% glucose (150 ml/h) for 150 min. Blood samples were taken every 15 min for 180 min. GH levels (closed circle) increased after GIP infusion concomitant with the rise of plasma insulin (square). Glucose levels are presented as open circles (Fig. A for case 1, and Fig. B for case 2).

family, and has structural homologies with VIP. Their structural homologies might enable GIP to have similar actions on the hypothalamic-pituitary unit [22–23]. According to these reports, it is reasonable to assume that GIP has an action that stimulates GH secretion [22].

One explanation for the mechanism of GIP action to the somatotroph adenoma cells is that the stimulative action of the physiological level of GIP in patients implies the existence of specific membrane receptors on somatotroph adenoma cells, because GIP has no stimulative effect on the somatotrophs of normal subjects. This aberrant receptor may newly appear on somatotroph adenoma cells as a result of genetical alteration [5], as is the case with most forms of human neoplasia [24, 25]. Actually GIP receptor bearing cells have already been reported in human gastric cancer cell line [26] and hamster pancreatic beta cell line [27, 28], and also demonstrated in food-dependent Cushing's syndrome [9, 10].

On the other hand, GIP receptor cDNA has recently been cloned and its mRNA has been detected by *in situ* hybridization in several organs including the adrenal cortex and the pituitary in rats by Usdin *et al.* [8]. In that report, Usdin *et al.* proposed that GIP might normally affect adrenal steroid release and that the cause of aberrant response to GIP in food-induced Cushing's syndrome might not be the ectopic GIP receptor expression but a problem in the regulating pathway of GIP to affect adrenal steroid release. The same mechanism can be proposed in this GIP-induced GH secretion in acromegalics. Another explanation of the mechanism of aberrant response to GIP on somatotroph adenoma cells may not be the ectopic GIP receptor expression but a disorder in the regulating pathway of GIP on GH secretion from the somatotroph cells. Human GIP receptor cDNA can be cloned by using the cloned rat receptor cDNA. Thereafter it is possible to test the hypothesis of whether ectopic or increased GIP receptor causes aberrant GH responses

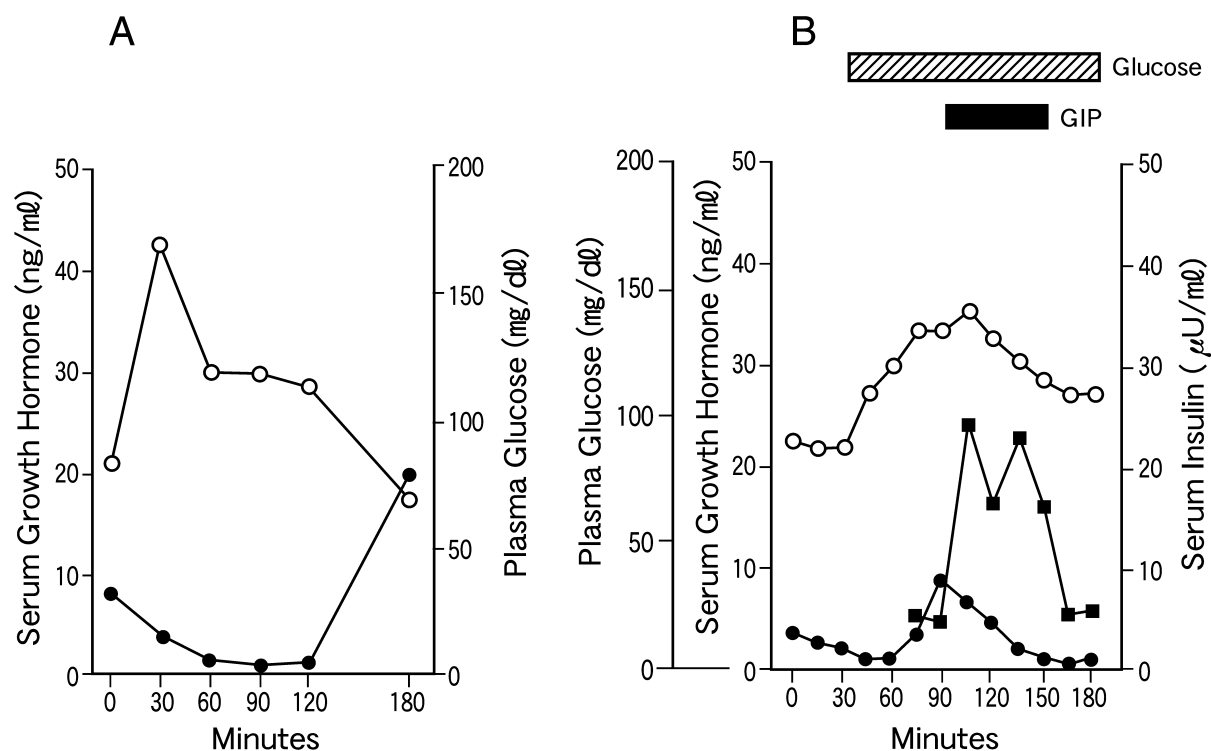


Fig. 4. GH responses to 75 gm oral glucose load taken 35 days after operation (Fig. A). GH levels (closed circles) were suppressed to less than 2 ng/ml concomitant with the rise of glucose levels (open circles). GH responses to GIP infusion on 45 days after operation (Fig. B). GIP was infused and blood samples were obtained as shown in Fig. 3. Insulin levels (squares) increased after GIP infusion, but GH levels did not change.

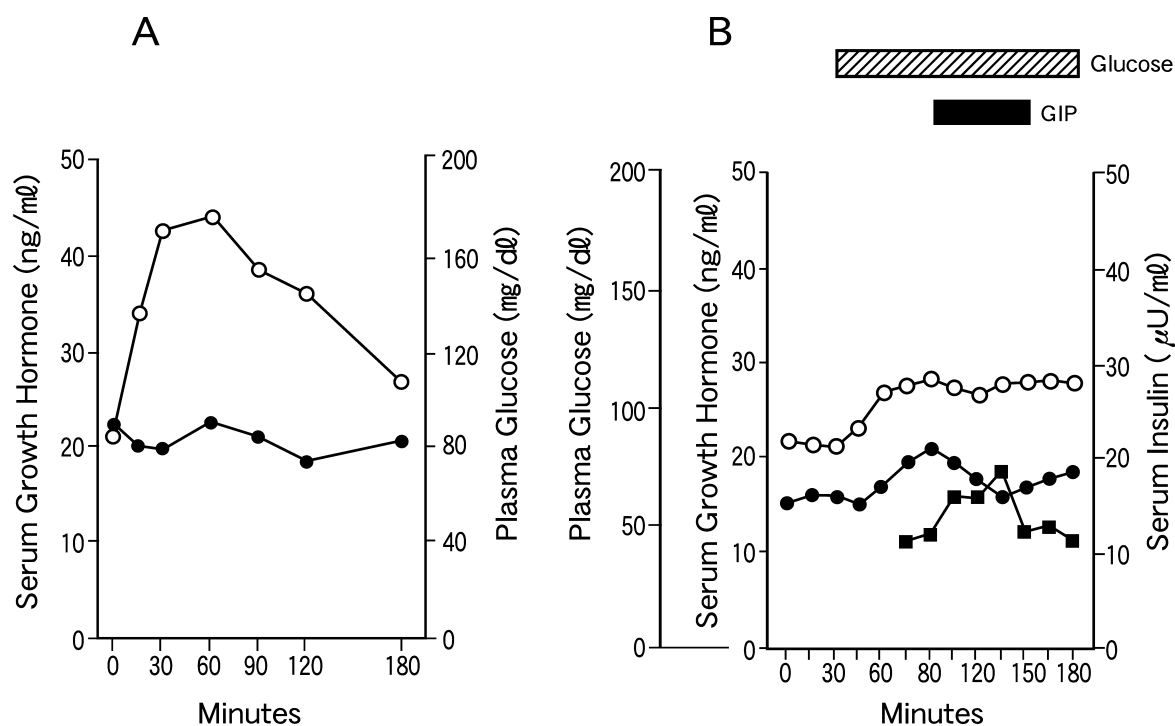


Fig. 5. GH responses to the 75 gm oral glucose loading and the intravenous GIP loading test. An acromegalic patient whose GH levels (closed circles) did not change on glucose load (Fig. 5A) and did not show GH response to GIP infusion (Fig. 5B) instead of the rise of insulin levels. Open circles and squares represent glucose levels and insulin levels, respectively.

in acromegaly, by comparing GIP receptor mRNA levels of adenoma cells between patients with paradoxical GH responses to OGTT and patients without paradoxical GH responses.

Paradoxical GH responses induced by the oral glucose load have been reported in premature infants [29], tall stature children [30] and adolescents [30, 31]. The cause of this paradoxical secretion has not been explained, but it was presumed that the paradoxical responses in these patients might be induced when hyperglycemia could not abolish the endogenous GRH action to drive GH rise in spite of the involvement of somatostatin [32]. The GIP action to secrete GH may be able to explain the paradoxical GH response in these patients. Existence of GIP receptor mRNA in the pituitary reported by Usdin *et al.* [8] supports this view and prompts the study of the role of GIP in these children. Further studies on GIP action on GH secretion will clarify the cause of the paradoxical rise of GH not only in these children but also in acromegalics.

This aberrant response to GIP in acromegaly is similarly observed in food-dependent Cushing's syndrome [9, 10, 33], where the GIP receptor expression is thought to be a primary cause of this syndrome.

However, in our cases the aberrant responsiveness to GIP cannot be the primary cause of acromegaly, because high blood GH concentrations are observed at fasting time. However, it is conceivable that this aberrant GIP responsiveness has adverse effects in acromegalics through the exaggerative action on GH secretion after meals.

Whether or not other peptides or some yet determined substances stimulate the somatotroph adenoma cells of our patients is unknown from our present observations.

In conclusion, we have presented new evidence that, at least in some acromegalics, GIP stimulates GH secretion, and that this action is the cause of paradoxical GH secretion to oral glucose load.

Acknowledgments

The authors wish to thank Dr. Jacques Mahoudeau (Département d'Endocrinologie, G.H.U. Côte de Narce Caen, France) and Dr. André Lacroix (Division of Endocrinology, Hôpital-Dieu de Montréal, Canada) for the information about preparing and handling of GIP.

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