Effect of Glucocorticoids on the Paradoxical Growth Hormone Response to Thyrotropin-Releasing Hormone in Patients With Acromegaly

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It has been hypothesized that in acromegalic patients, as well as in normal subjects, acute increases in serum cortisol levels may cause an enhancement of hypothalamic somatostatin secretion, which in turn may be responsible for the glucocorticoid-mediated growth hormone (GH) inhibition. The aim of this study was to investigate short-term effects of an intravenous (IV) infusion of hydrocortisone on the GH response to thyrotropin-releasing hormone (TRH) in acromegaly. We studied six adult patients with active acromegaly. The group was composed of four women and two men with a mean age of 55.8 ± 6.4 years (range, 27 to 68) and a mean body mass index of 26.7 ± 1 kg/m² (range, 23.3 to 30). All patients underwent the following treatments: (1) hydrocortisone alone: a bolus IV injection of hydrocortisone succinate 100 mg in 2 mL saline at time −60 minutes, followed by a 120-minute IV infusion of hydrocortisone succinate 250 mg in 250 mL saline from −60 to 60 minutes; (2) TRH + hydrocortisone: a bolus IV injection of TRH 200 μg 60 minutes after initiation of a 2-hour hydrocortisone infusion; (3) TRH alone: a bolus IV injection of TRH at time 0, 60 minutes after initiation of a 2-hour saline infusion. In all six patients, TRH induced large GH increases (absolute peak GH level, 58.1 ± 23.2 μg/L; maximum % GH change with respect to baseline, 1,397.8% ± 807.8%; range, 205% to 5,219%). In the whole group of acromegalic patients, hydrocortisone infusion did not significantly affect the mean GH response to TRH (absolute peak GH level, 45.4 ± 19.5 μg/L; maximum % GH change with respect to 0-minute level, 894.8% ± 320%; range, 106% to 1,988%). After hydrocortisone + TRH administration, all six patients showed significantly higher absolute GH values as compared with values obtained with hydrocortisone alone from time 15 to 45 minutes. Our data show that the paradoxical GH response to TRH in acromegaly is resistant to the inhibitory action of an acute and sustained elevation of serum cortisol level.

IN ACROMEGALY, circulating growth hormone (GH) levels are elevated. Moreover, GH secretory dynamics in acromegalic patients are usually abnormal. These abnormalities include incomplete inhibition or paradoxical elevation of GH after glucose ingestion, a decrease in GH after administration of L-dopa or galanin,[1,2] and a paradoxical GH response to thyrotropin-releasing hormone (TRH).[2] The increase in GH after intravenous (IV) TRH administration is usually observed in ≥50% of acromegalic patients, but not in normal subjects. A paradoxical GH response to TRH has also been observed in dispersed GH-secreting adenomatous cells that probably express specific TRH receptors.[3,4] Moreover, disappearance of the paradoxical GH response to TRH after selective removal of the GH-secreting adenoma has been reported.[5] These observations suggest that the paradoxical GH response to TRH in acromegaly is due to the presence of adenomatous tissue. However, the role of somatostatin in the regulation of TRH-stimulated GH secretion in acromegalic patients remains to be elucidated.[6,7]

Both adults and children treated long-term with supraphysiologic doses of glucocorticoids,[8-10] as well as patients with Cushing's disease,[11] show blunted GH responses to various physiologic and pharmacologic stimuli and decreased spontaneous GH secretion[10,12] as compared with normal subjects. It has been suggested that these effects of glucocorticoids on GH secretion could be due to an in vivo glucocorticoid-mediated enhancement of hypothalamic somatostatin release.[13-15]

Acromegalic patients show decreased baseline and GH-releasing hormone (GHRH)-stimulated GH levels after either short- or long-term treatment with pharmacologic doses of glucocorticoids. It has been hypothesized that in acromegalic patients glucocorticoids may decrease GH secretion via somatostatin.[16-20] No data are available on the effect of glucocorticoids on the paradoxical GH response to TRH in patients with acromegaly.

The aim of our study was to investigate the short-term effects of an IV infusion of hydrocortisone on the GH response to TRH in acromegaly.

SUBJECTS AND METHODS

Patients

We studied six adult patients with active acromegaly. The group was composed of four women and two men with a mean age of 55.8 ± 6.4 years (range, 27 to 68) and a mean body mass index of 26.7 ± 1 kg/m² (range, 23.3 to 30). One patient was untreated (no. 5), and five were under medical treatment with octreotide (no. 4) or bromocriptine (no. 1, 2, 3, and 6). Three patients (no. 2, 3, and 4) had previously undergone transsphenoidal removal of the GH-secreting pituitary adenoma, which was combined in one case (no. 2) with radiotherapy (Table 1). One of the patients (no. 2) was receiving hormone replacement therapy (cortisone acetate 12.5 mg/d, thyroxine 100 μg/d) for concomitant hypopituitarism. All patients were submitted to a 30-day wash-out period in which they received no pharmacologic therapy before entering the study. All patients had typical signs of acromegaly and elevated insulin-like growth factor-I levels for their age (485.7 ± 47 ng/mL). They also had elevated baseline GH levels, measured on at least four samples, which did not decrease to less than 2 μg/L after an oral

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Table 1. Clinical Characteristics of Acromegalic Patients

Patient No.	Sex	Age (yr)	BMI (kg/m²)	Duration of Disease (yr)	IGF-I (ng/mL)	Previous Treatment
1	F	68	28	10	361	Bc
2	F	65	24	7	387	TS, RT, Bc
3	M	49	27.7	4	430	TS, Bc
4	F	63	27.4	8	610	TS, O
5	M	27	23.3	1	491	—
6	F	63	30	10	635	Bc
Mean ± SEM		55.8 ± 6.4	26.7 ± 1	6.7 ± 1.4	485.7 ± 47	

Abbreviations: BMI, body mass index; IGF-I, insulin-like growth factor-1 (mean of three samples drawn on the mornings of the three tests); Bc, bromocriptine; TS, transsphenoidal surgery; O, octreotide; RT, radiotherapy.

glucose load. Patients underwent three experimental trials on nonconsecutive days.

Protocol

The study was performed according to a single-blind crossover randomized design.

After an overnight fast, each subject was admitted to the Clinical Research Unit. Patients rested in a recumbent position throughout the experiment. Two antecubital vein catheters (for independent infusion and blood sampling) were inserted percutaneously and kept patent by slow saline infusion. After a 30-minute stabilization period, all patients underwent the following treatments: (1) hydrocortisone alone: a bolus IV injection of hydrocortisone succinate 100 mg in 2 mL saline at time −60 minutes, followed by a 120-minute IV infusion of hydrocortisone succinate 250 mg in 250 mL saline from −60 to 60 minutes; (2) TRH + hydrocortisone: a bolus IV injection of TRH (TRH; Ares-Serona, Milano, Italy) 200 μg 60 minutes after initiation of a 2-hour hydrocortisone infusion; (3) TRH alone: a bolus IV injection of TRH at time 0, 60 minutes after initiation of a 2-hour saline infusion.

Blood samples for GH, prolactin, and cortisol assays were taken at −75, −60 (time of beginning of hydrocortisone infusion), −45, −30, −15, 0 (time of TRH injection), 15, 30, 45, 60, 90, and 120 minutes. Blood samples for thyrotropin (TSH) assay were taken at time 0 and 20 and 40 minutes after TRH + hydrocortisone and TRH alone.

Results are expressed as the mean ± SEM. GH responses to hydrocortisone are expressed as percent changes with respect to the mean of −75- and −60-minute levels. GH responses to TRH are expressed as absolute values and as percent changes with respect to the 0-minute level (time of TRH injection). Statistical analysis was performed using the nonparametric technique of Wilcoxon due to nonhomogeneous variances. $P < .05$ was considered statistically significant.

Assays

Commercial kits were used for the estimation of GH (immunoradiometric assay; Allegro hGH, Nichols Institute, San Juan Capistrano, CA; interassay and intraassay coefficients of variation, ±5.4% and ±2.3%, respectively; sensitivity limit of the assay, 0.2 μg/L); insulin-like growth factor-I (radioimmunoassay; Nichols Institute; after acid ethanol extraction); prolactin (immunoradiometric assay; Ares, Serono, Italy; interassay and intraassay coefficients of variation, ±6.4% and ±2.1%, respectively; sensitivity limit of the assay, 0.3 μg/L); TSH (immunoradiometric assay; Elsa 2, Cis, France; interassay and intraassay coefficients of variation, ±3.4% and ±3.7% respectively; sensitivity limit of the assay, 0.2 mU/L); and cortisol (RIA-coat Cortisol, Byk-Sangtec Diagnostica, Dietzenbach, Germany; sensitivity limit of the assay, 0.05 μg/dL). Blood glucose level was measured with the glucose oxidase method (Beckman II Glucose Analyzer, Palo Alto, CA). All samples from the same subject were assayed together in duplicate.

RESULTS

Kinetics of GH responses to TRH + saline and TRH + hydrocortisone in acromegalic patients are shown in Fig 1. Moreover, a comparison between responses to hydrocortisone alone and TRH + hydrocortisone is reported in Fig 2.

Baseline GH values, the mean of four baseline samples drawn at −75 and −60 minutes on the mornings of the two tests, were significantly elevated in all patients (8.6 ± 1.1 μg/L) with respect to the normal range (0.5 to 6 μg/L).

In all six patients, TRH induced large GH increases (absolute peak GH level, 58.1 ± 23.2 μg/L; maximum % GH change with respect to 0-minute level, 1,397.8% ± 807.8%; range, 205% to 5,219%). In the whole group of acromegalic patients, hydrocortisone infusion did not significantly affect the mean GH response to TRH (absolute peak GH level, 45.4 ± 19.5 μg/L; maximum % GH change with respect to 0-minute level, 894.8% ± 320%; range, 106% to 1,988%). The percent GH increase was calculated in these instances over the 0-minute level (time of TRH injection) to correct for the inhibitory effect as determined by hydrocortisone versus saline infusion from −60 to 0 minutes (Fig 1). Moreover, hydrocortisone infusion did not cause any significant change in mean absolute

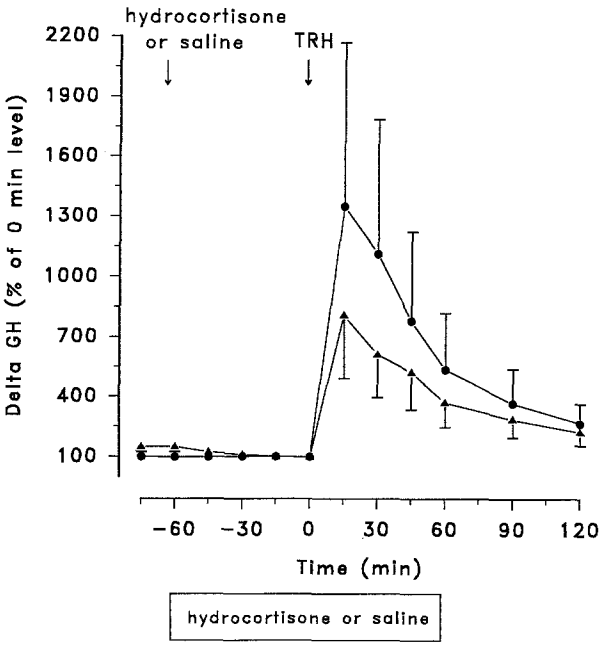

Fig 1. Delta GH values (mean ± SEM) expressed as % of 0-minute level after TRH + saline (●) and TRH + hydrocortisone (▲) in six acromegalic patients. No significant differences in GH levels were observed at any time after TRH in the two experimental conditions.

GH levels at any time after TRH injection as compared with TRH + saline administration. Significant GH peaks over baseline levels after TRH injection during hydrocortisone infusion were observed in five of six patients. Only in one patient (no. 2) was the GH increase after TRH + hydrocortisone below the 200% of the 0-minute value (106%). Data reported in Fig 1 are mean levels calculated on the whole group of acromegalic patients.

In all acromegalic patients, during hydrocortisone succinate infusion GH values decreased as compared with basal levels (nadir range, 27.6% to 83.2%; mean, 47.7% ± 8.8%; $P < .05$ with respect to the mean of −75- and −60-minute levels), with a nadir between 60 and 180 minutes after initiation of hydrocortisone infusion. After hydrocortisone + TRH administration, the percent GH change with respect to the mean of −75- and −60-minute levels was significantly higher as compared with that of hydrocortisone alone from 15 to 45 minutes (Fig 2).

Hydrocortisone caused a slight but nonsignificant decrease in the TSH response to TRH (TRH + saline, TSH peak 4.3 ± 1.1 mU/L; TRH + hydrocortisone, TSH peak 3.4 ± 0.8). Hydrocortisone infusion did not affect the prolactin response to TRH (TRH + saline, prolactin peak 23.6 ± 10.8 μg/L; TRH + hydrocortisone, prolactin peak 29.2 ± 12.7).

In all patients, hydrocortisone infusion resulted in serum cortisol levels greater than 80 μg/dL from −45 to 120 minutes. Blood glucose levels did not show significant variation after hydrocortisone with respect to baseline levels. TRH injection caused nausea in two patients.

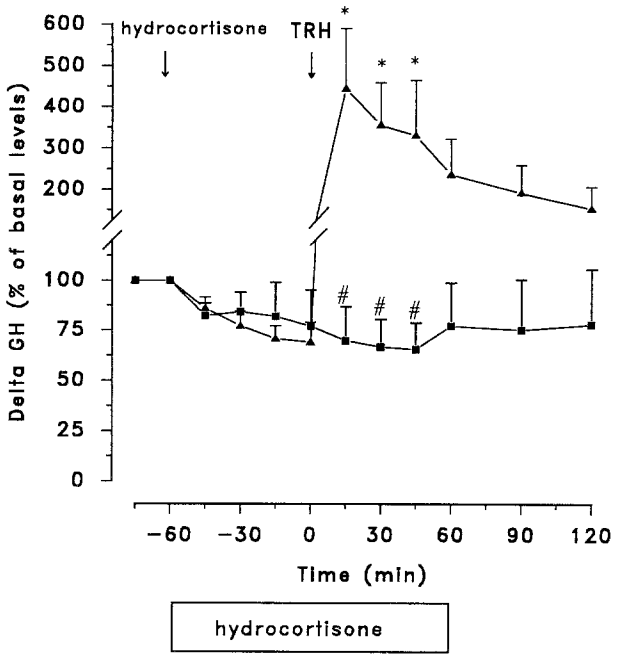

Fig 2. Delta GH values (mean ± SEM) expressed as % of −60-minute level after hydrocortisone alone (■) and TRH + hydrocortisone (▲) in six acromegalic patients. *$P < .05$ *v* hydrocortisone; #$P < .05$ *v* basal levels. Basal levels were calculated as the mean of −75- and −60-minute samples.

DISCUSSION

Our data confirm that an acute and sustained increase in serum cortisol levels decreases circulating GH levels in acromegaly. Our results show that acute hypercortisolism cannot inhibit the paradoxical GH response to TRH in patients with acromegaly.

Previous studies have demonstrated that large doses of glucocorticoids administered for several days can inhibit circulating GH levels[16] and the GH response to GHRH[17] in acromegalic subjects. We have previously demonstrated that an acute and sustained increase in serum cortisol levels obtained through a 2-hour IV infusion of hydrocortisone succinate not only decreases circulating GH levels[18] but also abolishes the GH response to GHRH in acromegaly.[19]

Glucocorticoid-mediated inhibition of GH secretion in man has been shown to be attenuated by administration of either the acetylcholinesterase inhibitor pyridostigmine[10,21] or the amino acid arginine,[22] agents thought to decrease hypothalamic somatostatin tone.[23,24] Moreover, it has been shown that arginine can also counteract the inhibitory effect of a hydrocortisone infusion on circulating GH levels in patients with acromegaly.[20] On the other hand, several investigators have shown that dexamethasone can increase GH secretion from cultured GH-secreting adenomatous human cells.[16] Therefore, it also seems likely that in acromegalic patients, as well as in normal subjects, sustained increases in serum cortisol levels, even if acute, may cause an enhancement of hypothalamic somatostatin secretion.[25]

A paradoxical GH response to TRH is observed in the 50% to 80% of acromegalic patients with a pituitary GH-secreting adenoma.[2,26] However, the mechanisms underlying this paradoxical GH response to TRH remain unclear.[27] Clinical and in vitro evidence seems to suggest that TRH may directly stimulate GH secretion at the adenoma level by interaction with specific receptors expressed by the adenomatous somatotrophs.[3,5] On the other hand, a paradoxical GH response to TRH has been described in various pathologic conditions other than GH-secreting adenomas, including several psychiatric diseases, hepatic and renal failure,[28] primary hypothyroidism,[29] insulin-dependent diabetes mellitus,[30] and somatotroph hyperplasia.[31] A paradoxical GH response to TRH has also been described in tall adolescents[32] and in normal subjects pretreated with GHRH.[33] Finally, Adams et al[4] showed that in some instances normal somatotrophs may respond to TRH in vitro. These latter studies seem to suggest that the paradoxical GH response to TRH may be a functional feature of several pathophysiologic states characterized by altered somatostatin control of GH secretion.[26]

Therefore, it appears highly relevant to investigate whether and to what extent the paradoxical GH response to TRH in acromegaly may be sensitive to somatostatin inhibition. Surprisingly, only a few and contrasting studies have tried to clarify this issue. In vitro studies have shown that somatostatin may either inhibit[34] or not affect[35] the GH-stimulatory effect of TRH. Moreover, in vivo studies

have shown that high-dose (1,000 μg/h)[7] but not low-dose (100 μg/h)[6] native somatostatin infusion blunts the GH response to TRH in acromegaly. Long-term treatment with the long-acting somatostatin analog octreotide inhibits the paradoxical GH response to TRH in the majority of patients with acromegaly.[36]

Our results show that an acute and sustained increase in serum cortisol levels, which has been previously shown to increase somatostatin tone,[18-20] did not significantly affect the GH response to TRH in a group of six acromegalic patients who were classified as TRH responders, ie, who showed a GH increase of at least twice the basal level to a value greater than 5 μg/L.[2] A large variability in the GH response to TRH has been observed in our population, probably due to the intrinsic secretory characteristics of each adenoma and in part to the heterogeneity of the group in terms of sex and age.[37] However, in only one of six patients was the paradoxical GH response to TRH blocked by acute hypercortisolemia. These data seem to suggest that the paradoxical GH response to TRH in acromegaly is resistant to the acute increase of hypothalamic somatostatin tone caused by glucocorticoids. Our data are in agreement with the results of a previous experiment showing that infusion of native somatostatin at doses commonly used in clinical practice (100 μg/h) does not interfere with the stimulatory action of TRH.[6] It can be hypothesized that somatostatin and TRH interact with different receptors on the surface of adenomatous cells but may have a common second messenger, ie, intracellular calcium.[38,39] The two peptides could be hypothesized to cause opposite changes of this second messenger at the intracellular level. Therefore, in the presence of TRH, only high-dose short- or long-term somatostatin administration[36] may reverse the stimulatory effect of TRH on GH secretion. This hypothesis may well fit with the postulated direct action of TRH at the pituitary level.[3,5]

Glucocorticoids have an inhibitory role in the regulation of TSH and prolactin secretion in humans.[40] Our data show that at least in acromegaly, the acute glucocorticoid-mediated increase in somatostatin tone does not blunt either the TSH or prolactin response to TRH. These results are consistent with the hypothesis that somatostatin and TRH may compete, also within pituitary cells that normally express the TRH receptor, for a common second messenger.

In conclusion, our data show that the paradoxical GH response to TRH in acromegaly is resistant to the inhibitory action of an acute and sustained elevation of serum cortisol levels. These data suggest that the paradoxical GH response to TRH may be relatively resistant to the inhibitory action of somatostatin.

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