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Thyrotropin Secretion During Oral Glucose Tolerance Test in Acromegalic Patients and Control Subjects

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It has been suggested that acute hyperglycemia stimulates somatostatin release from the hypothalamus, thus causing inhibition of growth hormone and thyrotropin secretion. Abnormal growth hormone secretory pattern to glucose load is characteristic of acromegaly, and it might reflect alterations in somatostatin release. We evaluated the sensitivity of serum thyrotropin response to presumed somatostatin inhibition during oral glucose tolerance test in 29 patients with active acromegaly, in 13 patients with inactive disease, and in 19 control persons suspected of impaired glucose tolerance. Both the acromegalic patients and the control subjects were euthyroid. Serum insulin, growth hormone, thyrotropin, free triiodthyronine, free thyroxine, and glucose were collected before and 30, 60, 90, and 120 min after the ingestion of 75 g glucose. While the free triiodthyronine and free thyroxine values did not change during the glucose test, the thyrotropin levels progressively and significantly declined in all groups. The basal to nadir thyrotropin ratio was higher in active acromegaly than in inactive disease and in control subjects ($p < 0.01$), suggesting that the glucose load inhibited thyrotropin stronger in active acromegalic patients. These data suggest that there is a possible strong somatostatin response to glucose load in acromegalic patients, which inhibits thyrotropin secretion. These data do not support the concept of decreased somatostatin drive in acromegaly.

Key Words: TSH secretion; acromegaly; acute hyperglycemia.

Introduction

Acromegaly is usually caused by a GH-secreting adenoma of the pituitary gland. It has been postulated that a reduction of the hypothalamic somatostatin (SS) activity could also play a role in the excess of GH secretion *(1)*. It also has a physiological role in the control of TSH secretion. It is known that SS has an inhibitory effect on TSH release in humans *(2–5)*. SS exerts its inhibitory effect on TSH secretion via several mechanisms, including the increase of thyrotrop sensitivity to thyroid hormones *(6)*, decrease of thyrotrop responsiveness to TRH *(7)*, decrease of exocytosis *(8)*, as well as regulation of pituitary deiodinases *(9)*. At present there is no direct method available to measure the hypothalamic somatostatinergic activity in humans. Yang et al. *(10)* previously demonstrated that oral glucose administration suppresses the TRH-induced TSH response. It has been suggested that acute hyperglycemia stimulates SS release from the hypothalamus, thus causing inhibition of TSH secretion *(11,12)*. Shibashaki et al. reported that the degree of suppression of TSH secretion in acromegaly was significantly less than in normal subjects during a glucose tolerance test *(13)*; Therefore, it is, suggested that SS release in response to acute hyperglycemia is impaired in most acromegalic patients. Other studies suggested a similar SS tone in acromegalic patients and in normal subjects *(14)*, the derangement of SS control with either preserved or decreased SS tone *(12)*, and a wide intersubject variability of the hypothalamic somatostatinergic activity in acromegaly *(15)*.

The present study was designed to indirectly evaluate the hypothalamic SS tone by means of acute hyperglycemia, which is thought to increase SS tone. Changes in TSH levels during an oral glucose tolerance test (OGTT) were compared in patients with active and inactive acromegaly and in control subjects.

Results

Although the blood glucose and serum insulin increments showed a trend to be higher in the active acromegaly group, but this did not reach statistical significance (Table 1). Thyroid hormone levels were within normal limits and did not

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Table 1
Free T_3, Free T_4, Glucose and Serum Insulin Levels During Oral Glucose Tolerance Test (Mean ± SEM)

		0 min	30 min	60 min	90 min	120 min
Free T_3 (pmol/L)	Active acromegaly	3.6 ± 0.2	3.6 ± 0.2	3.6 ± 0.2	3.7 ± 0.2	3.7 ± 0.2
	Inactive acromegaly	3.5 ± 0.2	3.5 ± 0.2	3.4 ± 0.2	3.3 ± 0.2	3.4 ± 0.2
	Control	4.0 ± 0.2	3.9 ± 0.2	3.8 ± 0.2	3.8 ± 0.1	3.7 ± 0.2
Free T_4 (pmol/L)	Active acromegaly	14.0 ± 0.6	13.9 ± 0.5	13.7 ± 0.5	13.7 ± 0.5	14.0 ± 0.6
	Inactive acromegaly	11.7 ± 0.7	11.6 ± 0.7	11.6 ± 0.7	11.4 ± 0.7	11.4 ± 0.7
	Control	12.8 ± 0.5	12.8 ± 0.5	12.6 ± 0.5	12.9 ± 0.6	12.7 ± 0.5
Blood glucose (mmol/L)	Active acromegaly	6.1 ± 0.3	10.0 ± 0.6***	12.0 ± 0.7***	10.5 ± 0.6***	9.0 ± 0.5***
	Inactive acromegaly	5.8 ± 0.3	9.2 ± 0.5***	9.7 ± 0.5***	8.8 ± 0.4*	7.4 ± 0.4
	Control	5.1 ± 0.2	8.0 ± 0.4***	10.0 ± 0.6***	8.6 ± 0.4***	7.9 ± 0.4
Serum insulin (μU/mL)	Active acromegaly	15.6 ± 0.7	60.4 ± 2.9***	99.5 ± 6.0***	78.2 ± 4.8***	60.3 ± 3.6***
	Inactive acromegaly	10.7 ± 0.5	69.9 ± 3.9*	78.2 ± 4.7**	57.9 ± 3.6*	49.0 ± 3.0
	Control	13.4 ± 0.6	44.2 ± 2.4***	69.3 ± 4.2**	61.5 ± 3.7**	37.6 ± 4.1*

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. 0 min.

change significantly during OGTT neither in the control subjects nor in the acromegalic patients (Table 1).

TSH levels progressively and significantly declined in all three patient groups (Fig. 1). No significant differences among groups were observed in hyperglycemia-induced TSH decrements, although the incremental area under the curve showed a trend to be smaller in the active acromegaly group ($p = 0.08$, Kruskal–Wallis test). The basal to nadir TSH ratio was significantly larger in the active acromegaly (2.14 ± 0.14) than in the inactive group (1.49 ± 0.06) and in control subjects (1.58 vs 0.08, $p < 0.01$; Fig. 2). In the inactive group two patients received radiotherapy previously. Evaluating the values without these patients (1.50 ± 0.06) similar results were obtained. In the active group 14 patients had paradoxical rise in GH during OGTT. There was no difference in the basal to nadir TSH ratios in patients with (2.0 ± 0.15) or without (2.2 ± 0.14) paradoxical GH elevation. The glucose-induced GH response did not correlate with the suppression of TSH response. The TSH suppression did not correlate to GH levels or to the sex and age of the patients.

Discussion

In our study we assessed the hypothalamic somatostatinergic activity in control subjects and in active and controlled acromegaly by measuring glucose-induced suppression of TSH secretion. We did not find significant differences among groups in hyperglycemia-induced TSH decrements, but the basal to nadir TSH ratio was larger in active acromegaly than in the inactive group and in the control subjects suggesting a higher SS response to glucose load in active acromegaly than in the other two subject groups. A trend was also observed for a smaller incremental area under the curve for TSH in the active acromegaly group compared to the inactive and the control group (Fig. 1), but this did not reach statistical significance. The higher somatostatinergic tone in the active disease is probably the consequence of a negative feedback by the higher GH levels.

Conflicting results were reported about the hypothalamic somatostatinergic activity in acromegalic patients. Merola et al. found that acromegalic patients without suppression of GH during OGTT showed a TSH responsiveness to the arginine-TRH test similar to that of controls, whereas acromegalics with partial glucose suppression had a decreased TSH responsiveness to the arginine-TRH test, and they concluded that acromegaly is a heterogeneous disease with respect to the somatostatinergic tone *(12)*. Another study showed that the degree of suppression of TSH levels in the glucose tolerance test was lower in acromegalic patients than in normal subjects, and it was concluded that the release of SS caused by acute hyperglycemia is not sufficient to decrease the secretion of TSH in most acromegalic patients compared to control subjects *(13)*. In the studies of Yang et al. the mean hypothalamic somatostatinergic activity of the acromegalic patients did not differ from that in normal men, it showed wide variation with low, normal, and high values *(10,16)*. Peacey et al. reported that radiotherapy can lead to an impairment of endogenous somatostatin tone *(17)*. The reevaluation of the analysis without those two patients who previously had radiotherapy in the inactive disease group did not modify the results. In our study one patient in the inactive acromegaly group had secondary ACTH deficiency and was on hydrocortisone substitution. Because glucocorticoids

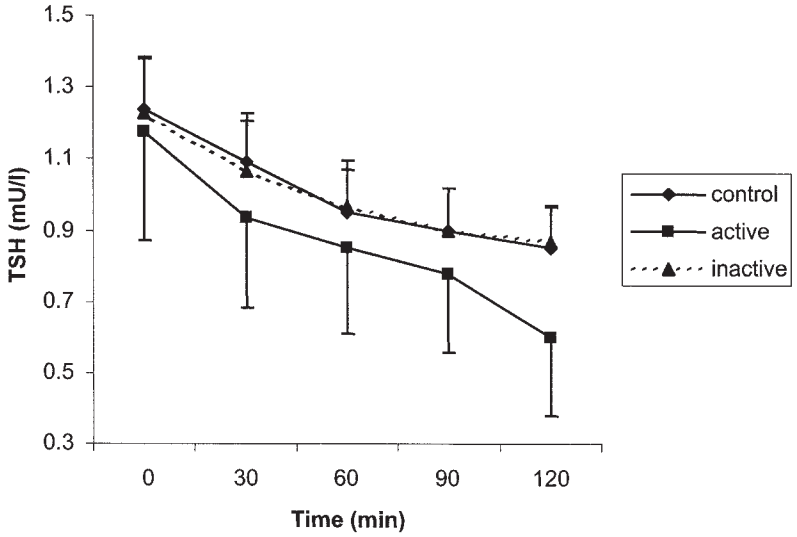

Fig. 1. TSH levels after ingestion of 75 g glucose in normal subjects and acromegalic patients. Control: 30 min vs baseline: $p < 0.01$; 60, 90, and 120 min vs baseline: $p < 0.001$; Active acromegaly: 30, 60, 90, and 120 min vs baseline: $p < 0.001$; inactive acromegaly: 30 min vs baseline, $p < 0.01$, 60, 90, and 120 min vs baseline: $p < 0.001$. Each point represents the mean ± SEM of the observations. No significant differences among groups were observed, although the incremental area under the curve showed a trend to be smaller in the active acromegaly group ($p = 0.08$).

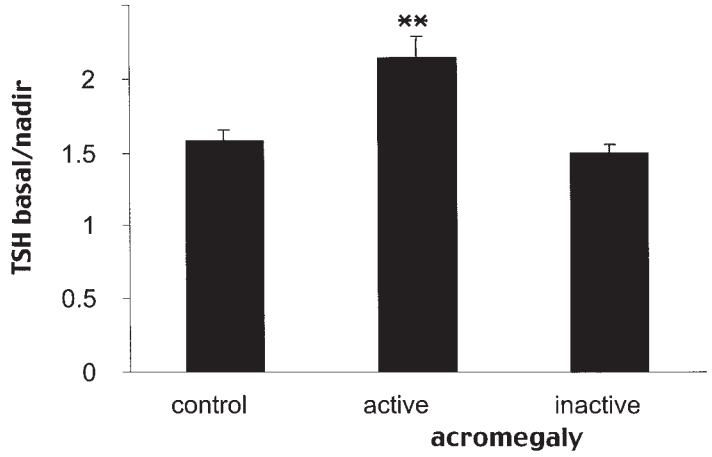

Fig. 2. Effect of acute hyperglycemia on the basal to nadir TSH ratio. **$p < 0.01$ vs inactive acromegaly and controls.

can suppress TSH secretion only in pharmacological dose, the replacement therapy did not modify the TSH serum levels *(18)*.

In summary, our present study is the first report of the effects of an OGTT on TSH secretion in patients with active and inactive acromegaly. We suggest that the reduction of hypothalamic somatostatinergic tone is not a primary cause of acromegaly, on the contrary, in active acromegaly the hypothalamic SS reserve seems to increase.

Materials and Methods

Patients

Twenty-nine patients with active acromegaly [GH concentrations remainded above 2 μg/L during OGTT *(17)*], 20 women and 9 men, mean age 53 yr, range 24–75, body mass index (BMI): 28.8, range: 23–35 kg/m^2, 13 patients with inactive disease (GH concentration decreased below 2 μg/L during OGTT), 9 women and 4 men, mean age 56 yr,

range 27–72, BMI: 29.0, range: 24–34 kg/m^2, and 19 control subjects with suspected impaired glucose tolerance prior to the OGTT (14 women and 5 men, mean age 43 yr, range 23–68, BMI: 27.9, range: 23–31 kg/m^2) were included into the study. All patients in the inactive acromegaly group underwent transsphenoidal surgery, two of the patients also received radiotherapy, while none of them received SS analog therapy. Patients in the active acromegaly group were awaiting transsphenoidal surgery and were not receiving SS analog therapy. One patient in the inactive group was on hydrocortisone substitution therapy. The mean IGF-I was 702.0 ± 51.9 in the active and 186.5 ± 51.7 μg/L in the inactive group ($p< 0.05$). Both the acromegalic patients and the control subjects were euthyroid, based on normal TSH and peripheral thyroid hormones. Because multinodular goiter is common in acromegaly and also iodine-deficient areas, like Hungary, patients with multinodular goiter were excluded from the study. OGTT with 75 g glucose was performed. Blood samples for blood glucose, insulin, GH, free T_3, free T_4, and TSH was collected every 30 min for 2 h.

Methods

Serum GH (Wallac DELFIA, IFMA, normal range: 0–5 μg/L sensitivity: 0.01 μg/L; intraassay coefficient of variation [CV]: 3.9%, interassay CV: 6.3%), IGF-I (Nichols RIA, normal range: 84–398 μg/L in males, 104–450 μg/L in females, sensitivity: 20 μg/L; intraassay CV: 2.9%, interassay CV: 9.8%), free T_4 (Abbott AxSYM, MEIA, normal range: 8.5–20.0 pmol/L, sensitivity: 5.15 pmol/L, intraassay CV: 2.78%, interassay CV: 5.16%), free T_3 (Abbott AxSYM, MEIA, normal range: 2.52–5.3 pmol/L, sensitivity: 1.69 pmol/L; intraassay CV: 3.79%, interassay CV: 3.67%), TSH (Abbott AxSYM, MEIA, normal range: 0.3–4.0 mIU/L, sensitivity: 0.03 mIU/L; intraassay CV: 3.01%, interassay CV: 3.2%), and insulin (Abbott AxSYM, MEIA, normal range: 5–25 μU/mL, sensitivity: 1 μU/mL; intraassay CV: 2.6%, interassay CV: 2.9%) were measured.

Statistical Analysis

Data were analyzed using the SPSS 10.0 statistical program. ANOVA for repeated measures, Pearson's correlation test, Student's *t*-test, and the Kruskal–Wallis test were used as appropriate. Area under the curve was calculated by the trapezoidal method. Data are expressed as mean ± SEM, unless otherwise stated, p values less than 0.05 were considered significant.

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