Effects of methimazole treatment on growth hormone (GH) response to GH-releasing hormone in patients with hyperthyroidism

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Abstract. In vitro studies have demonstrated that thyroid hormones can enhance basal and stimulated growth hormone secretion by cultured pituitary cells. However, both in man and in the rat the effects of high thyroid hormone levels on GH secretion are unclear. The aim of our study was to test the GH response to human GHRH in hyperthyroid patients and to evaluate the effects on GH secretion of short- and long-term pharmacological decrease of circulating thyroid hormones. We examined 10 hyperthyroid patients with recent diagnosis of Graves' disease. Twelve healthy volunteers served as controls. All subjects received a bolus iv injection of GHRH(1-29)NH₂, 100 μg. Hyperthyroid patients underwent a GHRH test one and three months after starting antithyroid therapy with methimazole, 10 mg/day po. GH levels at 15, 50, 45, 60 min and GH peak after stimulus were significantly lower in hyperthyroid patients than in normal subjects. The GH peak was also delayed in hyperthyroid patients. After one month of methimazole therapy, most of the hyperthyroid patients had thyroid hormone levels in the normal range, but they did not show significant changes in GH levels after GHRH, and the GH peak was again delayed. After three months of therapy with methimazole, the hyperthyroid patients did not show a further significant decrease in serum thyroid hormone levels. However, mean GH levels from 15 to 60 min were significantly increased compared with the control study. The GH peak after GHRH was also earlier than in the pre-treatment study. In conclusion, the GH response to GHRH is inhibited and delayed by hyperthyroidism and returns to the normal pattern after long-term euthyroidism has been achieved with methimazole.

Growth hormone synthesis and secretion are regulated by the hypothalamic peptides GH-releasing hormone, which has an excitatory role, and somatostatin, which has an inhibitory role (1). Several peptides and monoamines are able to affect GH secretion, usually by influencing GHRH and/or somatostatin secretion and action (2).

In vitro studies demonstrate that thyroid hormones enhance basal and stimulated GH secretion by cultured pituitary cells (3,4). Hypothyroidism causes a decreased GH response to GHRH in humans which returns to normal in the euthyroid state (5,6). However, both in man and in rat, the effects of high thyroid hormone levels on GH secretion are unclear. In hyperthyroid patients either normal (7) or reduced (8,9) GH responses to pharmacological stimuli are described; reduced spontaneous nocturnal GH secretion in hyperthyroid men has also been reported (10). In the hyperthyroid rat the GH response to GHRH has been described to be either decreased (11) or normal (12).

Recently, studies in man have also given conflicting results on the GH response to GHRH in hyperthyroid patients before and after antithyroid therapy (13,14).

The aim of our study was to test the GH response to human GHRH(1-29)NH₂ in hyperthyroid patients and to evaluate the effects of short- and long-term pharmacological decrease of circulating thyroid hormones on GH secretion.
Patients and Methods

Ten hyperthyroid patients with recent diagnosis of Graves’ disease were studied. They were 8 females and 2 males; the age range was 22-66 years; the body mass index (BMI) range was 16-22 kg/m²; the medians and ranges of pretreatment levels of serum free triiodothyronine (FT₃), serum free thyroxine (FT₄), and serum TSH are reported in Table 1. Twelve healthy volunteers (4 females and 8 males; age range 22-35 years; BMI range 19-25 kg/m²) with no family history of endocrine or metabolic disease served as controls. None of the subjects were taking any medication at the start of the study. The study protocol was approved by the Local Ethical Committee.

After an overnight fast the subjects were admitted to the Clinical Research unit. They were placed in a recumbent position and an indwelling catheter was inserted into an antecubital vein. The catheter was kept patent by slow saline infusion. A 30-min period was allowed for stabilization of the subjects after venipuncture and then the first blood sample for GH, FT₃, FT₄, TSH and blood glucose assay was drawn at time -15. Fifteen minutes later a second blood sample was drawn (time 0). Immediately thereafter all subjects received a bolus iv injection of 100 μg GHRH(1-29)NH₂ (Geref®, Serono, Italy) in 1 ml of saline. Blood samples for GH assay were then taken at 15, 30, 45, 60, 90 and 120 min. Hyperthyroid patients underwent subsequent GHRH tests using the same procedures one and three months after starting antithyroid therapy with methimazole, (Tapazole®, Eli Lilly, Italy, 10 mg/day po). The GH secretory responses were expressed either as the absolute values (μg/l) or as the maximum GH levels (peak; μg/l).

All results are expressed as median values and ranges. The results in Fig. 1 are given as mean±SEM for clarity purposes. All data were analysed by the non-parametric technique of Wilcoxon for paired and unpaired data owing to non-homogenous variances.

Assays

Commercial radioimmunoassay kits were used for the measurement of GH (Allegro HGH, Nichols Institute, CA; intra-assay coefficient of variation, CV, 4%; inter-assay CV 7%; sensitivity limit of assay 0.06 μg/l), FT₃ and FT₄ (Amerlex, Slcavo, Italy). An immunoradiometric assay was used for TSH assay (Elsa 2-TSH, Gis, France). Blood glucose was measured by the glucooxidase method (Beckman II analyzer). All samples from the same subject were assayed together in triplicate.

Results

The kinetics of the GH response to GHRH in hyperthyroid and normal subjects are shown in Fig. 1. Pretreatment study: all hyperthyroid patients showed much higher serum thyroid hormone levels than the upper limit of normal ranges. Serum TSH levels were undetectable (<0.1 mU/l) in all hyperthyroid patients and 1.2 mU/l, range <0.1-3 mU/l, in normal subjects (Table 1). Blood
Table 1.
Serum free triiodothyronine (FT₃, pmol/l), free thyroxine (FT₄, pmol/l) and thyroid-stimulating hormone (TSH, mU/l) in 12 normal subjects and in 10 hyperthyroid patients before, one month and three months after the start of methimazole therapy, 10 mg/day. Results are expressed as median and ranges.

<table>
<thead>
<tr>
<th></th>
<th>Normal values</th>
<th>Hyperthyroid patients</th>
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<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>1 month treatment</td>
</tr>
<tr>
<td>FT₃</td>
<td>6.5</td>
<td>25*</td>
</tr>
<tr>
<td>(4.6-8.6)</td>
<td>(13.3-38.4)</td>
<td>(3.7-18.4)</td>
</tr>
<tr>
<td>FT₄</td>
<td>16.6</td>
<td>80.9*</td>
</tr>
<tr>
<td>(10.3-23.1)</td>
<td>(25-248.4)</td>
<td>(9.2-36)</td>
</tr>
<tr>
<td>TSH</td>
<td>1.2</td>
<td>&lt;0.1*</td>
</tr>
<tr>
<td>(0.1-3)</td>
<td>(0.1-0.1)</td>
<td>(0.1-0.1)</td>
</tr>
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*p <0.01 vs normals

Glucose levels were not significantly different in hyperthyroid (4.7, 4.3-6.3 mmol/l) and in normal subjects (4.0, 3.5-4.8 mmol/l). Basal GH levels in hyperthyroid patients (1.3, 0.5-3.8 µg/l) were not significantly different from those of normal subjects (0.7, 0.5-2.9 µg/l). Mean absolute GH levels from 15 to 60 min (Fig. 1) and the median GH peak values after GHRH (9.2, 1.3-14 µg/l) were significantly lower (p<0.001) in hyperthyroid patients than in normal subjects (22.9, 10.1-32.2 µg/l). The GH peak was delayed in hyperthyroid patients (in 1 patient it occurred at 45 min; in 1 at 60 min; in 7 at 90 min, and in 2 at 120 min; median time of GH peak occurrence 82.5 min) compared with normal subjects (in 7 subjects the GH peak occurred at 30 min, in 3 at 45 min, in 2 at 60 min: median time of GH peak occurrence 38.7 min, p<0.001 vs the hyperthyroid patients).

After one month of methimazole therapy, values for FT₃ and FT₄ were in the normal range in 8 of the 10 hyperthyroid patients. Serum TSH levels were still undetectable in all the patients (Table 1). Blood glucose levels were unchanged (median 4.5, 4.3-6.6 mmol/l). In spite of almost normalized FT₃ and FT₄ values the GH response to GHRH was not different from the response observed in hyperthyroid patients prior to methimazole treatment (Fig. 1). Both absolute GH levels and GH peak values (7.0, 3.1-12.7 µg/l) were virtually identical. Moreover, the GH peak was again delayed (median time of occurrence: 75 min).

Three months of methimazole therapy induced only a mild insignificant further decrease in median serum thyroid hormone levels. However, at this time all hyperthyroid patients had thyroid hormone levels within the normal range. Furthermore, 3 of the 10 patients had detectable serum TSH levels (1.6, 2.9 and 3.2 mU/l, respectively) (Table 1). Blood glucose levels were unchanged compared with pretreatment levels (4.3, 3.8-6.4 mmol/l). However, mean absolute GH levels from 15 to 60 min were significantly increased compared with the hyperthyroid status and with one month methimazole therapy (Fig. 1). The median GH peak after GHRH was not significantly different from that of normal subjects (15.5, 5.7-30 µg/l, p<0.01 vs pretreatment and one month methimazole). Moreover, the GH peak occurred in 3 patients at 15 min, in 5 at 30 min, in 1 at 45, and in 1 at 60 min after GHRH injection; the median time of GH peak occurrence (28.1 min) was similar to that of normal subjects, but significantly anticipated compared with pretreatment and one-month methimazole studies.

No significant changes in BMI were found in the hyperthyroid patients after one or three months of methimazole administration.

Discussion

Our data show that in man excess of circulating thyroid hormones causes a decreased and delayed GH response to GHRH(1-29)NH₂, a synthetic fragment of human GHRH(1-44)NH₂. This analogue was shown to be as efficient as GHRH(1-44)NH₂ in stimulating GH secretion in man (15).

In vitro studies have demonstrated that when rat pituitary cells are cultured in a thyroid hormone-free medium, growth hormone synthesis and secretion are markedly decreased. Consequently, thyroid hormones have been suggested to be activators of GH gene expression (3). The addition of thyroid hormones to rat pituitary cells cultures increased the GH response to GHRH (4). However, an excess of thyroid hormones in the culture medium of human somatotropic adenoma cell cultures has been reported to decrease spontaneous GH secretion (16).

In vivo studies have shown that in hypothyroid rats GH synthesis and secretion are decreased
Hypothyroid humans also show reduced GH responses to various stimuli, such as insulin-induced hypoglycemia, arginine and GHRH. The GH response to these stimuli returns to normal in the euthyroid state (5,6,20,21).

The effect of elevated thyroid hormones levels on GH secretion has been studied in vivo by several authors with conflicting results. In the rat, pretreating animals with thyroxine has been reported to decrease the GH response to GHRH compared with the euthyroid state (11). However, other authors could not find any significant impairment of GH secretion in the same animal model (12).

In man, several studies have reported that hyperthyroid patients have reduced spontaneous sleep-induced GH surges (22), and the GH response to various stimuli, such as insulin-induced hypoglycemia (8,9) and beta-adrenergic blockers (23,24) is impaired. The GH response to GHRH in hyperthyroid patients has been reported either to be blunted (14) or normal (13).

On the basis of our data we can confirm that the GH response to GHRH in hyperthyroid patients is impaired as well as delayed compared with that in normal subjects. We can also add that one month of methimazole administration does not affect the pattern of GH secretion, whereas long-term drug-induced euthyroidism returns the GH response to GHRH to the pattern observed in healthy subjects.

In a previous study (13), the GH response to GHRH in a group of hyperthyroid patients was of a similar magnitude to the response we observed in our patients. However, the former study did not report GH values for normal subjects. This difference in experimental design may explain the different conclusions reached.

The mechanism by which the elevation in the serum concentration of thyroid hormones causes prolonged inhibition of GH secretion remains to be explained. On the basis of our results it seems unlikely that it is mediated by a decrease of hypothalamic secretion of GHRH. We can hypothesize that, as glucocorticoids (25), thyroid hormones may have a dichotomic effect on growth hormone secretion: in fact, hypothyroid patients (5,6,20,21) as well as patients with ACTH deficiency (26) have impaired growth hormone response to the stimuli. Thus, thyroid and glucocorticoid hormones may have a direct stimulatory action at the pituitary level. Conversely, in the presence of hyperthyroidism, or of hypercortisolemia (27), the GH response to GHRH is inhibited. It may be suggested that in both situations the hypothalamic somatostatin tone may be enhanced (14,28,29). Alternatively, it can be hypothesized that hyperthyroidism may suppress GH secretion directly at the pituitary level by decreasing the number and/or sensitivity of GHRH receptors or altering the synthesis and storage of GH (16). The latter hypothesis may also explain a. the delay in the GH response to GHRH in hyperthyroid patients as compared with normal subjects; b. the slow recovery of pituitary responsivity to GHRH after correction of hyperthyroidism. It should be noted, that in only 3 of our patients the GH response to GHRH normalized in parallel with the reappearance of detectable levels of serum TSH. In the other patients the lag time between achievement of euthyroidism by antithyroid drugs and reappearance of measurable serum TSH levels (30,31) appears to be longer than that necessary for the recovery of the GH response to GHRH. However, the impaired GH secretion after one month of methimazole therapy may be explained, at least in 2 of our patients, by the presence at that time of still elevated serum thyroid hormone levels. In conclusion, the GH response to GHRH is inhibited and delayed by hyperthyroidism and returns to normal after long-term euthyroidism has been achieved by methimazole treatment.

References

5. Williams T, Maxon H, Thorner MO, Froman LA. Blunted growth hormone (GH) response to GH-releasing hormone in hypothyroidism resolves in the


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