Effect of Dexamethasone on TSH Secretion Induced by TRH in Human Obesity

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ABSTRACT

Background: **The presence of an abnormally high thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) makes it difficult to distinguish some euthyroid obese subjects from subclinically hypothyroid obese patients. Here, we examine whether such distinction may be achieved after treatment with glucocorticoids, which inhibit TSH secretion at the hypothalamic-pituitary level.**

Methods: **TRH tests (200 μg as an intravenous bolus injection) were performed in 30 age- and weight-matched, obese, but otherwise healthy, men. All subjects were tested again with TRH after treatment with dexamethasone (dex) (2 mg/d in four divided doses orally for 3 days).**

Results: **In all subjects, total thyroxine and triiodothyronine concentrations were in the normal range. According to basal and TRH-stimulated serum thyrotropin (TSH) levels, subjects were divided into the following three groups: group I (n=10), euthyroid subjects; group II (n=10), euthyroid subjects with normal basal but abnormally elevated TSH responses to TRH; group III (n=10), subjects with elevated basal and TRH-induced TSH levels (subclinical hypothyroidism). Basal TSH levels were 1.8±0.4 mU/L in group I, 1.7±0.3 in group II, and 6.0±0.7 in group III. In both groups II and III, TRH-induced TSH increments were above the normal range (maximal increment>15 mU/L) and were significantly higher than in group I. After the second treatment with TRH, pretreatment with dex significantly decreased both basal TSH levels and peak TSH responses to TRH in all groups. However, a striking percentage decrease (>50%) in TRH-induced peak TSH responses was observed in euthyroid obese subjects of groups I and II, whereas hypothyroid subjects of group III showed only a slight decrement (<25%).**

Conclusions: **The sensitivity of the TSH secretory system to glucocorticoid inhibitory action is preserved in obese subjects with abnormally elevated TSH response to TRH, but not in subclinically hypothyroid obese patients. The TRH plus dex test might be useful in future studies to understand the mechanisms underlying alterations in TSH secretion in obesity. (J Investig Med 2001;49:330–334) Key Words: obesity • hypothyroidism • TSH • dexamethazone**

INTRODUCTION

Some obese subjects show an abnormally high thyroid-stimulating hormone (TSH) responsiveness to stimulation with thyrotropin-releasing hormone (TRH), despite normal circulating thyroid hormone levels and normal basal TSH concentrations.[1,2] This phenomenon is not observed in other groups of age- and weight-matched euthyroid obese subjects with similar endocrine-metabolic conditions or renal and hepatic function.[3,4] Furthermore, neither radiological pituitary alterations nor pathological conditions known to produce elevated TSH responses to TRH have been described in euthyroid obese patients with abnormal TRH-induced TSH responses, suggesting that these subjects may be affected by neuroendocrine alterations at the hypothalamic-pituitary level.[3,4]

Because of their anomalous TSH secretory pattern, euthyroid obese subjects of this subgroup are not easily distinguishable from obese subjects with subclinical hypothyroidism, in whom elevated basal and TRH-induced TSH secretion is associated with thyroid hormone levels

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within the normal range. In healthy human subjects, a treatment with glucocorticoids reduces both basal and TRH-induced TSH secretion without modifying circulating thyroid hormone levels.[5,6]

In view of various studies indicating that the effect of glucocorticoid is exerted at the hypothalamic-pituitary level, we wondered whether the anomalous TSH responsiveness to TRH observed in euthyroid obese subjects is sensitive to glucocorticoid inhibition. To answer this question, the TSH response to TRH was evaluated during glucocorticoid treatment in euthyroid obese subjects with elevated TSH responses to TRH and in obese patients with subclinical hypothyroidism.

SUBJECTS AND METHODS

Preliminary Selection

One hundred eighteen obese but otherwise healthy men were selected by collaborators in several hospital endocrine units from a large group of subjects who were visited during an 18-month period. The inclusion criteria were as follows:

- normal glucose tolerance during an oral glucose (75 g) tolerance test according to the criteria of the National Diabetes Data Group,
- exclusion of depression with the Hamilton depression rating scale according to the Research Diagnostic Criteria,[7,8]
- no clinical or laboratory evidence of gonadal disease,
- serum levels of free thyroid hormones in the normal range,
- no pharmacological treatment.

All men gave their informed consent to participate in the study. For 3 days before the study, all subjects were given a 250-g carbohydrate diet.

TRH Test

Subjects were tested at 8 AM. An indwelling polyethylene cannula was inserted into an antecubital vein in recumbent subjects fasting from the previous evening. The cannula was kept patent by a very slow infusion of normal saline (NaCl 0.9%). TRH (200 μg) was injected as an intravenous bolus after the withdrawal of three basal blood samples (time: -20, -10, and 0 minutes). Further samples were taken 10, 20, 30, 45, 60, and 90 minutes after TRH injection.

All 118 men underwent the TRH test to obtain three groups of 10 subjects with the following characteristics: group I, subjects with normal basal and TRH-stimulated TSH levels; group II, subjects with normal basal TSH levels and abnormally elevated TSH responses to TRH; group III, subjects with basal and TRH-stimulated TSH levels higher than normal. According to basal TSH levels, subjects of groups I and II are defined as euthyroid, whereas subjects of group III are classified as subclinically hypothyroid. In our laboratory, the normal range of basal serum TSH concentrations is 0.5 to 3.5 mU/L; a peak TSH response to TRH is considered normal when it does not exceed 15 mU/L.[9]

Of the 118 obese men tested with TRH, 10 were included in group II, 10 in group III (with the random exclusion of two additional subclinically hypothyroid subjects, performed to balance the number of cases in the three groups), whereas the remaining 96 were suitable to be included in group I. Ten of these subjects were randomly chosen and constituted group I. In nonobese individuals, percentages of subjects with subclinical hypothyroidism of 7 to 10% have been reported[10,11]; however, to our knowledge, euthyroid nonobese healthy subjects with an elevated TSH response to TRH have never been described. We did not find any routine clinical characteristics that could distinguish the obese men of the three groups. Computerized tomography of the sella turcica excluded abnormality in all men of the three groups.

Subjects of all groups were age- and weight-matched as follows: group I, mean weight$=117.7\pm7.0$ kg (mean$\pm$SE), mean body mass index$=40.1\pm1.7$, mean age$=32.0\pm1.6$ years; group II, mean weight$=118.7\pm7.4$ kg, mean body mass index$=41.1\pm2.0$, mean age$=31.5\pm1.6$ years; and group III, mean weight$=113.8\pm9.3$ kg, mean body mass index$=39.0\pm1.5$, mean age$=33.7\pm1.7$ years. To confirm the definition of euthyroidism in groups I and II and of subclinical hypothyroidism in group III on the basis of the secretory pattern of TSH (see above), we examined clinical, hormonal, and metabolic parameters changing in progressive thyroid failure. In fact, we wondered whether group II contained primarily hypothyroid patients at an earlier stage than in group III, but still hypothyroid. Staub et al[12] have found that, even in patients with mild subclinical hypothyroidism (grade I in their study), there are significant changes in clinical, hormonal, and metabolic parameters, such as the clinical index of Billewicz et al.[13] (in euthyroid subjects, the Billewicz score is -25 or less), serum-free triiodothyronine (T3) and thyroxine (T4) concentrations, and apoprotein AI (apo AI) levels. These indices were measured in all groups.

Dexamethasone (dex) Plus TRH Test

In all subjects, TRH tests were repeated with the same procedure described above at least 2 weeks after the previous test. Dex was administered by mouth at a dose of 2 mg/d in four divided doses for 3 days before the experimental day. In the previous TRH test, a placebo had been given by mouth instead of dex.

Assays

After each test, blood was centrifuged and serum was separated for measurement of TSH concentrations by commercial radioimmunoassay kits. All samples from a single subject were analyzed in duplicate in the same assay. The lower limit of detection for TSH was 0.02 mU/L. Intra-assay and interassay coefficients of variation were 4.5% and 6.8%, respectively. Free T3, free T4, and apo AI levels and the presence of antithyroglobulin and antithyroid microsomal antibodies were evaluated in serum samples taken at time 0 of the TRH test. Free T4 and free T3 levels were measured with lisophase kits (Sclavo, Siena, Italy). In our laboratory, the ranges of normality are 3.8 to 8.4 pmol/L for free T3 and 11.6 to 21.4 pmol/L for free T4. Intra- and interassay variability and sensitivity were 2.9%, 4.7%, and 0.8 pmol/L for free T3 and 3.0%, 5.7%, and 1 pmol/L for free T4, respectively.

The presence of antithyroid antibodies was detected using a hemoagglutination technique (Wellcome Reagents Thymuse-T and -M, Pomezia, Italy). Serum apo AI levels were measured using reagents supplied by Boehringer (Mannheim, Germany) and a nephelometer (normal range, 115–129 ng/dL).

Results were statistically analyzed with two-way analysis of variance (ANOVA; to compare the TSH responses with TRH) and Student's *t* test for paired and unpaired data (to compare basal or peak TSH levels). Results are reported as the mean±SE and percentage variation of peak TSH response to TRH.

RESULTS

Obese patients of groups I and II were euthyroid as was determined by normal free T3 and free T4 concentrations, normal values on the clinical index of Billewicz and Apo AI levels (Table), and negative antithyroglobulin and antithyroid microsomal antibodies. Basal TSH levels were similar in groups I and II (Student's t test for unpaired data). Normal TSH responses to TRH were found in group I. In contrast, the TRH-induced TSH increase was above the normal range in group II. In this latter group, the TSH response to TRH was significantly higher than in group I ($F=16.27$, $P<0.01$), whereas it was not significantly different from that observed in group III (ANOVA) (Figure 1).

Clinical, hormonal and, metabolic parameters (mean±SE) in obese groups.

	Group I (n=10)	Group II (n=10)	Group III (n=11)
Billewicz, points	−30.5±1.4	−30.0±1.2	−18.4±2.1
Free T4, pmol/L	11.8±0.7	11.5±0.5	10.4±0.4*
Free T3, pmol/L	5.2±0.2	4.9±0.3	3.9±0.4*
Apo A1, ng/dL	124.0±2.4	126.9±4.0	136.2±3.5*

**P<0.05, group III vs groups I and II. There are not significant differences between groups I and II.*

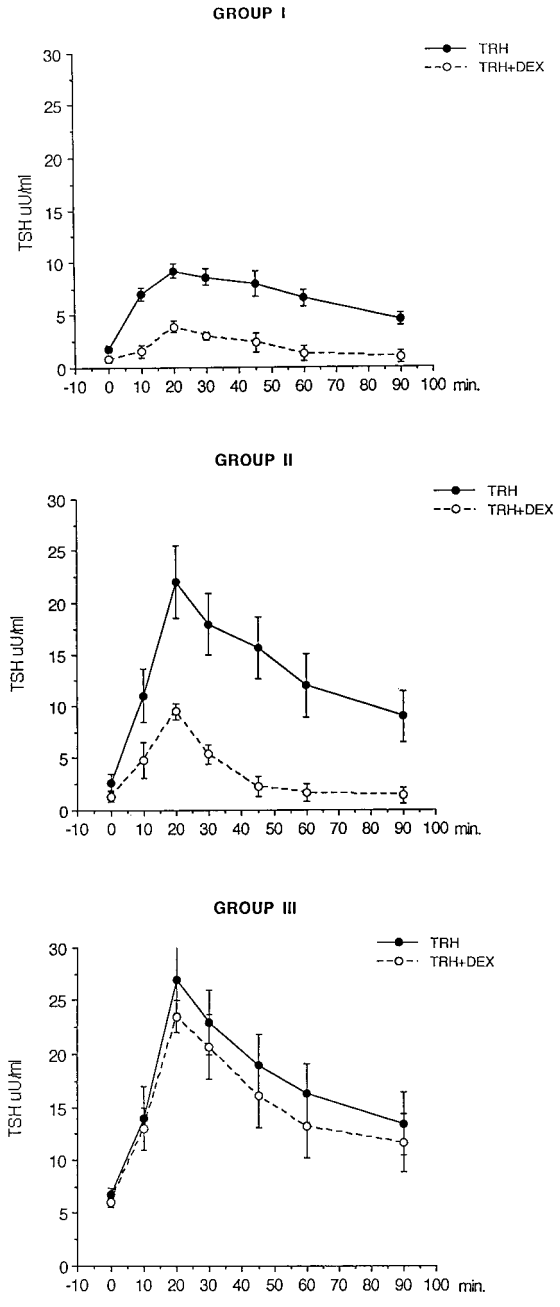

Figure 1. *Effects of TRH (solid lines) or TRH plus dex (dashed lines) on serum TSH levels in group I (n=10), group II (n=10), and group III (n=11). Each point represents the mean±SE of the observations.*

Clinical, hormonal, and metabolic parameters in group III are shown in the Table. In group III, free T4 and free T3 levels were normal; however, these patients showed significant alterations in all examined indices of subclinical hypothyroidism. In fact, the score on the clinical index of Billewicz and the circulating levels of free T3 and free T4 and apo AI were significantly lower in group III than in groups I and II (Table) (Student's *t* test for unpaired data). Antithyroglobulin and antithyroid microsomal antibodies were found in three of the subjects in group III. Basal and TRH-stimulated TSH secretion was similar in subjects with positive and negative antithyroid antibodies. All patients of group III showed high basal ($P<0.01$ vs group I; Student's *t* test for unpaired data) and TRH-stimulated TSH levels ($F=15.49$, $P<0.01$ vs group I, ANOVA) (Figure 1).

In all groups, pretreatment with dex significantly decreased both basal TSH levels ($P<0.001$ in groups I, II, and III; Student's *t* test for paired data) and peak TSH responses to TRH ($P<0.001$ in groups I and II, and $P<0.05$ in group III; Student's *t* test for paired data) (Figure 1). However, a striking percentage decrease (>50%) in TRH-induced peak TSH responses was observed in groups I and II, whereas hypothyroid subjects showed only a slight decrement (<25%) (Figure 2).

DISCUSSION

In normal subjects, pharmacological doses of glucocorticoids inhibit basal and TRH-stimulated TSH secretion, even though glucocorticoids produce an impaired T4 to T3 conversion at peripheral level. Therefore, the inhibitory control of TSH secretion has been attributed to glucocorticoid-induced impairment of thyrotrope function at a central site.[14] Studies in vitro showed inhibition by dex of TSH release from the rat anterior pituitary gland,[15] and thus, the reduced TSH response to TRH in dex-treated normal subjects might be attributed to reduced thyrotrope secretory activity.[6] However, it cannot be excluded that in vivo reduced TSH secretion might be produced by glucocorticoids through inhibition of endogenous TRH.[6] In fact, an inhibitory effect of glucocorticoids at the suprapituitary level has been hypothesized on the basis of the observation that, in humans, glucocorticoids acutely inhibit the nocturnal peak of TSH, without interfering with the TRH-induced TSH rise[16]; furthermore, subacute dex administration in humans produces a complete suppression of pulsatile TSH secretion for several hours.[16] A reduced tone of endogenous TRH would produce not only lower basal TSH secretion, but also a lower sensitivity of the thyrotropes to exogenous TRH.

In hypothyroid patients, dex has been found to be unable to decrease TRH-induced TSH secretion.[14] In our subclinically hypothyroid subjects, we have observed a slight, though significant, decrease of TSH secretion after dex treatment. This finding may suggest a lower degree of hypothyroidism in our patients than in previously studied subjects.[14] In light of the above-mentioned hypotheses about dex mechanism of action on TSH secretion, the low or absent effect of dex in hypothyroidism might be explained by a stronger endogenous TRH stimulatory tone[17] or by enhanced activity and resistance of the thyrotrope to dex inhibitory effect.

The data presented here show that, in contrast with hypothyroid obese patients, euthyroid obese subjects with high TSH responsiveness to stimulation with TRH are normally sensitive to the inhibitory action of dex. In fact, like obese subjects normally responsive to TRH, those who responded abnormally showed a 50% decrease of the TRH-induced peak TSH rise in the presence of dex. However, the TSH response to TRH was still higher in the latter than in the former group, suggesting that the neuroendocrine alteration responsible for the abnormal TSH secretory pattern is not sensitive to dex inhibitory action.

In the present study, we have identified a subset of obese men (approximately 9% of the screened population) with a pattern of TSH secretion different from euthyroid and subclinically hypothyroid obese men. The dex plus TRH test might be an useful tool to target new studies in this field.

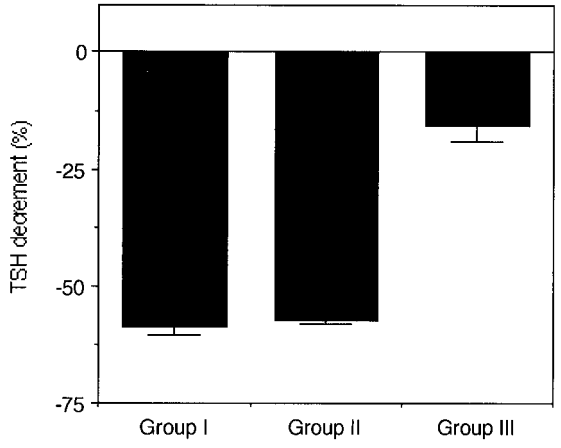

Figure 2. *TSH decrease (%) after TRH plus dex in group I (n=10), group II (n=10), and group III (n=10).*

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