The TSH receptor in the pituitary and its clinical relevance
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Graves' Immunoglobulins are Responsible for Long-Time Thyrotropin Suppression in Euthyroid, Treated Graves' Disease Patients.


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Submitted for publication
4.1 ABSTRACT

Objective To test whether TSH-binding inhibitory immunoglobulins (TBII) may cause direct suppression of TSH secretion via a pituitary TSH receptor (TSHR).

Design To relate TSH levels with TBII titres in Graves’ disease patients rendered euthyroid by blocking doses of methimazole and thyroxine.

Setting The Netherlands.

Subjects 45 consecutive patients with Graves’ hyperthyroidism.

Main outcome measures TSH levels in TBII positive versus TBII negative patients with Graves’ disease.

Results Serum TSH in TBII-positive patients (median/range 0.09/<0.01-4.30 mU/L) was lower than in TBII-negative patients (0.84/<0.01-4.20 mU/L; P = 0.015). In addition, in contrast to fT₄ or T₃, only TBII was related to serum TSH (r = -0.423; P = 0.004).

Conclusions We postulate that TBII suppress serum TSH by binding to the TSH receptor in pituitary folliculo-stellate cells that generate a signal for down regulation of TSH secretion.
4.2 INTRODUCTION

Graves' hyperthyroidism is caused by stimulating autoantibodies directed against the thyroid stimulating hormone receptor (TSHR). Treatment with antithyroid drugs renders most patients euthyroid within 4-6 weeks as manifested by normal serum free T₄ (fT₄) and total T₃ (TT₃) concentrations. Nevertheless, TSH often remains suppressed, even for many months (1). This is classically attributed to a delayed recovery of the pituitary-thyroid axis from prolonged thyroid hormone excess (2).

Recently, we reported that the TSHR is also expressed in the human anterior pituitary on the folliculo-stellate (FS) cells (3). These cells have been recognised as paracrine regulators of hormone secretion within the anterior pituitary (4). We hypothesise that this pituitary TSHR may be involved in an ultra-short loop negative feedback on pituitary TSH secretion: binding of TSH to the FS cells may result via paracrine signalling to down-regulation of TSH secretion. Likewise, TSHR stimulating antibodies (TSAb) in Graves' disease may also bind to this pituitary TSHR, because the pituitary is outside the blood-brain barrier. In our view, TSAb to a certain extent may decrease TSH secretion, regardless of circulating thyroid hormone levels.

This theory was recently supported in an animal study, in which we mimicked the human situation by injecting TSAb-containing immunoglobulins (IgG) in rats treated with methimazole and L-T₄. We found that TSAb-containing IgG suppressed TSH levels as compared to control IgG, in the absence of changes in serum thyroid hormone levels (5). The aim of the present study was to test the hypothesis that suppressed TSH levels in treated euthyroid Graves' patients correlate with the presence of TSAb in a prospective clinical study.

4.3 METHODS AND PATIENTS

We performed a prospective clinical study in 45 consecutive patients Graves' hyperthyroidism. This diagnosis was based on elevated levels of fT₄ (> 23.0 pmol/L) and/or TT₃ (> 2.75 nmol/L) in the presence of a decreased TSH (< 0.4 mU/L), a positive TBIi (TSH binding inhibitory immunoglobulins, TRAK assay > 12 U/L) and a diffuse uptake on a technetium scintigram. Excluded were patients with serious concomitant diseases, pregnancy, or on drugs known to influence the pituitary-thyroidal axis.
Patients were treated with 30 mg methimazole, and 4 with 400 mg propylthiouracil daily, to which was added L-T₄ (109 ± 36 μg) aiming at normalising fT₄ (10.0 – 25.0 pmol/L) and TT₃ (1.20 – 2.75 nmol/L) but avoiding elevated TSH values (> 4.0 mU/L).

When the patients were clinically and biochemically euthyroid for 3 months, their TBII levels were again determined and related to the levels of thyroid hormones and TSH.

Hormone assays

TSH plasma levels were measured with a highly sensitive chemiluminescent enzyme immunoassay (Immulite Third Generation TSH kit, Diagnostic Products, Los Angeles, CA). TBII titres were measured by TRAK assay (Brahms Diagnostica, Berlin, Germany). TT₄ and TT₃ plasma levels were determined by in-house radioimmunoassay (6). In order to exclude effects of oral contraceptives on total thyroid hormone levels, fT₄ was determined with a solid phase time-resolved fluoroimmuno assay (Delfia, Wallac Oy, Turku, Finland) and the fT₃ index (FT₃I) was calculated as the product of TT₃ and T₃ resin uptake.

Statistical analysis

Mann-Whitney U test was used to compare patients with negative TBII to patients with positive TBII with respect to fT₄, FT₃I and TSH. We then calculated the correlation of TBII titres with thyroid hormone and TSH levels using non-parametric two-tailed Spearmann’s rho correlation coefficients.

4.4 RESULTS

Baseline characteristics are given in Table 4.1. Mean age ± SD of the total group was 38 ± 12 yrs; female/male ratio was 37/8; median [range] duration of the thyroid disease was 6 [1-120] months.

After treatment with antithyroid drugs and L-T₄ euthyroidism was restored in all patients. Twenty-two patients still had a positive TBII titre. fT₄ and FT₃I did not differ between patients with positive TBII and those with negative values. However, the TBII-
Table 4.1. Thyroid function tests of 45 consecutive patients with Graves’ hyperthyroidism before treatment and after restoration of the euthyroid state (values as median with range).

<table>
<thead>
<tr>
<th>Test</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.01 (&lt;0.01-0.19)</td>
<td>0.37 (&lt;0.01-4.30)</td>
<td>0.4-4.0</td>
</tr>
<tr>
<td>TBII</td>
<td>29 (6-400)</td>
<td>9 (3-278)</td>
<td>≤ 12</td>
</tr>
<tr>
<td>TT4</td>
<td>250 (85-380)</td>
<td>123 (45-230)</td>
<td>70-150</td>
</tr>
<tr>
<td>T3</td>
<td>5.70 (2.65-11.40)</td>
<td>2.05 (1.25-3.65)</td>
<td>1.20-2.75</td>
</tr>
<tr>
<td>FT4</td>
<td>56.1 (11.4-75.0)</td>
<td>11.6 (5.1-26.2)</td>
<td>10.0-25.0</td>
</tr>
<tr>
<td>FTI</td>
<td>6.59 (3.31-15.05)</td>
<td>1.96 (1.21-2.85)</td>
<td>1.20-2.75</td>
</tr>
</tbody>
</table>

The positive group had significantly lower serum TSH than the TBII-negative group (median [range] 0.09 [0.01-4.3] mU/L vs. 0.84 [0.01-4.20] mU/L, resp.; P = 0.015 with Mann Whitney U; Figure 4.1a-c). Age, sex ratio, duration of the thyroid disease and the L-T4 dose used by the patients were similar in both groups.

There was a strong, negative correlation between TBII and TSH (Spearman correlation coefficient r = -0.423; P = 0.004; Figure 4.1d), whereas there was no correlation between TBII and fT4, FT3, duration of the thyroid disease, or the L-T4 dose used by the patients.

4.5 DISCUSSION

In conclusion, long-term TSH suppression in patients with Graves’ hyperthyroidism rendered euthyroid with antithyroid drugs is correlated quantitatively with the presence of TBII and not with circulating levels of thyroid hormones. This supports our hypothesis that TSH secretion by the pituitary is also under control of a TSHR expressed on FS cells. For, TBII may act as a ligand for this pituitary TSHR, resulting in down regulation of TSH secretion.

Our finding that TBII are a determinant of TSH levels in Graves’ disease may also offer an explanation for the fact that a relapse in Graves’ disease after a course of antithyroid drugs is correlated not only with goitre size and TBII levels, but also with suppressed TSH values in patients without detectable TBII. Continued suppression of TSH levels at the end of a course of antithyroid drugs may be seen as functional evidence for circulating TBII, that is undetectable by current assays.
Figure 4.1. A-C. Plasma TSH, \( \text{fT}_4 \) and \( \text{FT}_3 \) levels in euthyroid, treated Graves’ disease patients with either negative or positive TBII titres. 

- **A:** Horizontal continuous lines indicate medians. Horizontal dashed lines indicate the normal reference range. Median plasma TSH levels are significantly suppressed in TBII-positive euthyroid patients, whereas no differences are observed in mean \( \text{fT}_4 \) or \( \text{FT}_3 \) levels.

- **B:** 

- **C:**

- **D:** Correlation between serum TSH and TBII.

Our findings imply, that a suppressed TSH in patients treated for Graves’ hyperthyroidism, who are otherwise euthyroid, may be caused by elevated TBII titres. Therefore, decreased TSH levels should not always be interpreted as insufficient blockade of thyroid hormone synthesis.

### 4.6 ACKNOWLEDGEMENTS

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4.7 REFERENCES
