Enhanced Prolactin Secretion in Patients with Primary Hypothyroidism during Thyroid Replacement

SHUICHI SATO, KUNIHiko HANEW, ATSUSHI SASAKI, YASUYUKI SHIMizu, OSAMU MurAKAmI, HIROSHI FUKAZAWA, TOSHIRO SAKURADA, SHINTARO SAIto and KAORU YOSHINAGA

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980


Thyroid hormones are known to exert some influence on prolactin (PRL) secretion indirectly via the hypothalamic dopaminergic system and directly at the level of the pituitary gland. In order to study the effect of thyroid hormones on the activity of hypothalamic dopamine neurons, lactotrophs and thyrotrophs, we administered increasing doses of thyroid hormones to patients with primary hypothyroidism, and examined the changes of basal PRL, TSH and PRL responses to a dopamine receptor blocker (sulpiride). Among 24 patients with primary hypothyroidism, hyperprolactinemia was observed in 10 cases (18.0-236 ng/ml, mean ± S.E. 58.6 ± 20.0 ng/ml), while elevated TSH levels were observed in all of them (6.6-972 μU/ml, mean ± S.E. 231.4 ± 53.9 μU/ml). There was a significant negative relationship between plasma T3 or T4 levels and basal plasma TSH levels (p < 0.05), whereas a poor correlation was observed between the thyroid hormones and basal plasma PRL levels (r = -0.25, p > 0.05).

Following the administration of gradually increasing doses of thyroid hormones, plasma PRL showed paradoxical and transient increases, while plasma TSH decreased steadily. Plasma PRL response to sulpiride also became exaggerated during the treatment. The elevated basal PRL level and the enhanced response to sulpiride turned to be within the normal range when the patients became euthyroid by treatment. These results may indicate that thyroid hormones stimulate not only hypothalamic dopaminergic activity, but also the lactotroph activity in a long term hypothyroid state. Regarding the paradoxical elevation of basal PRL, one can postulate that the activation of lactotroph by a small dose of thyroid hormone may be able to overcome the hypothalamic dopaminergic inhibition.

primary hypothyroidism; thyroid hormone; prolactin; sulpiride; dopaminergic regulation

Received for publication, April 11, 1984.
This research was partly supported by a grant from the Intractable Disease Division, Public Health Bureau, Ministry of Health and Welfare, Japan.
It is well known that thyrotropin (TSH) and prolactin (PRL) secretions are under an influence of thyroid function, i.e., these hormone secretions increase in a hypothyroid and decrease in a hyperthyroid state (Snyder et al. 1973; Yamaji 1974; Feek et al. 1980).

TSH and PRL secretions are also known to be regulated by endogenous hypothalamic dopamine (Besses et al. 1975; Scanlon et al. 1977; Delitala et al. 1980). Contreras et al. (1981) have postulated depressed hypothalamic dopaminergic tone in patients with hypothyroidism based on their findings that the patients showed the inadequate PRL response to dopamine receptor blocker. However, the exact relationships between thyroid function and hypothalamic dopaminergic activity are not fully studied (Sawers et al. 1982). In order to evaluate these relationships, we examined the changes of basal PRL, TSH and their responsiveness to sulpiride (a dopamine receptor blocker) in patients with primary hypothyroidism, untreated or treated with thyroid replacement therapy.

**MATERIALS AND METHODS**

Twenty-four patients with primary hypothyroidism (8 males, 16 females) diagnosed by clinical and laboratory data were examined in the present study. None of the patients was taking any previous medication except one patient who had been thyroidectomized 2 years before. The changes of basal TSH and prolactin levels in 8 of these patients (4 males and 4 females) were studied during thyroid replacement therapy (Table 1). Several blood samples were taken within 2 or 3 hr through a plastic cannula placed in the antecubital vein. In 7 of these patients, T₃ replacement therapy was started with an initial dose of 5 μg/day for 1 month and then increasing doses of 5 μg/day every month up to a maintenance dose. The remaining one patient was treated by T₄, beginning with a small dose (12.5 μg/day) and then increasing the dose until the thyroid function became normal. After an overnight fast, sulpiride test (100 mg i.m.) was performed in 2 of these patients (Cases 1 and 2) at 9 a.m. before and during the thyroid replacement. Plasma samples were kept frozen until the assay.

**TABLE 1. Plasma T₃, T₄, TSH and PRL levels and thyroid antibody titers in 8 patients with primary hypothyroidism**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>T₃ (ng/100 ml)</th>
<th>T₄ (μg/100 ml)</th>
<th>TSH (μU/ml)</th>
<th>PRL (ng/ml)</th>
<th>MCHA</th>
<th>TGHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>M.</td>
<td>66</td>
<td>13</td>
<td>0.2</td>
<td>89</td>
<td>6</td>
<td>1</td>
<td>1,600</td>
</tr>
<tr>
<td>2)</td>
<td>M.</td>
<td>46</td>
<td>35</td>
<td>0.1</td>
<td>43</td>
<td>19</td>
<td>1</td>
<td>25,600</td>
</tr>
<tr>
<td>3)</td>
<td>M.</td>
<td>61</td>
<td>n.d.</td>
<td>0.1</td>
<td>129</td>
<td>7.5</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>4)</td>
<td>K.</td>
<td>61</td>
<td>18</td>
<td>0.8</td>
<td>9.3</td>
<td>5.5</td>
<td>1</td>
<td>409,600</td>
</tr>
<tr>
<td>5)</td>
<td>C.</td>
<td>27</td>
<td>13</td>
<td>n.d.</td>
<td>761</td>
<td>20</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>6)</td>
<td>M.</td>
<td>29</td>
<td>23</td>
<td>0.7</td>
<td>712</td>
<td>83</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>7)</td>
<td>F.</td>
<td>32</td>
<td>14</td>
<td>0.7</td>
<td>66</td>
<td>6.6</td>
<td>1</td>
<td>1,600</td>
</tr>
<tr>
<td>8)</td>
<td>I.</td>
<td>52</td>
<td>n.d.</td>
<td>0.1</td>
<td>51</td>
<td>8.3</td>
<td>1</td>
<td>25,600</td>
</tr>
</tbody>
</table>

n.d., not detectable; MCHA, microsomal hemagglutination antibody; TGHA, thyroglobulin hemagglutination antibody.
Plasma PRL and thyroid functions were measured by RIA with commercially available kits (Hanew et al. 1983; Sasaki et al. 1983). The normal ranges of these parameters were as follows: Plasma PRL (by PRL-RIA kit, CIS Co., France), 2 to 18 ng/ml; plasma T₄ (by T₄-RIA-II kit, Dainabot Co., Tokyo), 4.5 to 15 μg/100 ml; plasma T₃ (by T₃-RIA-II kit, Dinabot Co., Tokyo), 60 to 180 ng/100 ml and plasma TSH (by H-TSH kit, Daichi RI Lab., Tokyo), 0.3 to 4.0 μU/ml. Antithyroid antibodies were determined with thyroglobulin and microsomal hemagglutination tests (Thyroid test and Microsome test, Fujizoki Co., Tokyo). Antimicrosomal and antithyroglobulin hemagglutination antibodies (MCHA and TGHA) were taken to be positive when titers were higher than 1:100.

Results

The relationships among basal plasma thyroid hormones, plasma TSH and PRL levels in 24 patients with primary hypothyroidism

Among 24 patients with primary hypothyroidism, elevated TSH levels were observed in all (6.6-972 μU/ml, mean ± s.e. 231.4 ± 53.9 μU/ml; normal range 0.3-4.1 μU/ml), while hyperprolactinemia was observed in 10 cases (18.0-236 ng/ml, mean ± s.e.m. 58.6 ± 20.0 ng/ml; normal range 2-18 ng/ml). There was a significant negative correlation between basal plasma TSH and T₄ values ($r = -0.43$, $p < 0.05$), whereas poor correlation was observed between plasma PRL and plasma T₄ ($r = -0.25$, $p > 0.05$) or plasma T₃ levels ($r = -0.24$, $p > 0.05$).

The changes of basal plasma TSH, prolactin and T₃ in 8 patients with primary hypothyroidism during the thyroid replacement therapy

Following T₃ or T₄ replacement therapy, plasma TSH decreased gradually concomitantly with the elevation of the plasma T₃ level (shown as a shaded area in Fig. 1). Plasma PRL showed, however, a paradoxical increase during the

![Fig. 1. The changes of basal plasma TSH, prolactin and T₃ in 8 patients with primary hypothyroidism during the thyroid replacement therapy. Data are shown as percent of the pretreatment value. The shaded area represents the plasma T₃ levels (mean ± s.e.).]
treatment (Fig. 1). The peak value of PRL was observed at 2 months after the treatment, then the PRL level declined slowly. The peak PRL level (32.3±11.7 ng/ml) was higher than the pretreatment value (17.6±8.6 ng/ml).

Plasma PRL and TSH responses to sulpiride in Cases 1 and 2 before and during the T₃ replacement therapy

Plasma PRL responses to sulpiride were shown in the representative cases (1 and 2) before and during the T₃ replacement therapy. In Cases 1 and 2, the PRL levels elevated once during the treatment and declined later to the pretreatment values (Fig. 2).

The PRL responses to sulpiride of these 2 patients were apparently low before treatment compared to the normal subjects (peak range in normal male 71.3±13.5 ng/ml). However, the response became exaggerated initially and normalized later along with the treatment. In these cases, basal plasma TSH levels were high before the treatment and declined gradually during the treatment. Before the treatment, plasma TSH did not show any response to the administration of
sulpiride, while clear responses were seen during the treatment.

**DISCUSSION**

In the present study patients with primary hypothyroidism showed a paradoxical increase in plasma PRL and an enhanced PRL response to sulpiride during the initial period of replacement therapy, while the plasma TSH decreased steadily.

It is well known that thyroid hormone affects PRL and TSH secretions. In our series, all of 24 patients showed elevated TSH and 10 patients showed elevated PRL levels as it has been commonly reported. In primary hypothyroidism, the elevated TSH level decreased gradually with the improvement of the thyroid state by the replacement therapy. However, it has been reported that the responsiveness of plasma TSH to TRH often became exaggerated during the replacement. To this phenomenon, it has been assumed that low doses of thyroid hormone
increase TSH synthesis and decrease TSH release, resulting in increases in pituitary TSH content (D’angelo et al. 1976; Sawin et al. 1978; Aizawa et al. 1978; Yamamoto et al. 1983).

Regarding the elevation of the basal PRL level in the hypothyroid state, the following possibilities can be considered; 1) negative feedback effect of thyroid hormones on the lactotrophs, as it is reported that elevated thyroid hormones have a direct suppressive effect on the pituitary lactotrophs (Sawers et al. 1982), 2) decreased hypothalamic dopaminergic regulation on these cells or 3) increased TRH secretion (Feek et al. 1980). From these explanations, the paradoxical elevation of the basal PRL level observed in this study is difficult to understand. However, there might be one possibility that in a hypothyroid state PRL synthesis in the lactotrophs is apt to be activated by increasing thyroid hormone levels, and this activation overcomes the inhibitory effects of hypothalamic dopamine and thyroid hormones on PRL release. The magnitude of PRL response to sulpiride (a dopamine receptor blocker) indirectly reflects the degree of hypothalamic dopaminergic inhibition, since sulpiride can enhance the PRL release as a result of blocking the endogenous dopaminergic inhibition (Scanlon et al. 1981; Hanew et al. 1983). Accordingly, the increased PRL response to sulpiride during the thyroid replacement suggests that hypothalamic dopaminergic inhibition on the lactotrophs is slightly enhanced in the patients with primary hypothyroidism. The PRL level then returned toward normal as the euthyroid state was restored.

It needs further study to make clear whether activated PRL synthesis is overcome by the inhibitory effects of hypothalamic dopamine and thyroid hormone, or PRL synthesis is inhibited by thyroid hormone in the euthyroid state.

It can be concluded that small doses of thyroid hormone have a stimulatory effect on the lactotroph activity in patients with hypothyroidism.

References


