Basal and TRH stimulated serum levels of TSH in patients with hyperprolactinaemia and in subjects on oestrogen treatment

Eva M. Erfurth, Pavo Hedner and Anders Nilsson

Department of Medicine, University Hospital, S-22185 Lund, Sweden
and Department of Medicine, Central Hospital, S-25187 Helsingborg, Sweden

Abstract. In 21 hyperprolactinaemic patients without other signs of pituitary dysfunction the mean basal serum level of TSH was 4.4 ± 0.47 μU/ml that was significantly (P < 0.001) higher than controls (2.5 ± 0.16 μU/ml) and oestrogen treated individuals (2.4 ± 0.29 μU/ml). The TSH increase was more pronounced (P < 0.05) in hyperprolactinaemic patients without sellar enlargement and with moderately elevated plasma prolactin levels (155 ± 42 μg/ml) than in patients with sellar enlargement and higher plasma prolactin levels (857 ± 306 μg/ml). The serum levels of thyroxine and triiodothyronine in the hyperprolactinaemic patients did not differ significantly from controls. Patients with thyroid antibodies were excluded. The increased basal serum level of TSH in hyperprolactinaemia is compatible with the concept of a reduced dopaminergic tonus as the mechanism for both changes. In patients with advanced hyperprolactinaemia and sellar enlargement the high prolactin level may induce some inhibition of TSH release and explain their lower basal serum level of TSH that was probably not due to pituitary compression as they responded normally to TRH.

The TSH response to TRH was significantly (P < 0.05) correlated to the basal serum TSH in all groups. The regression lines were very similar for hyperprolactinaemic patients and controls suggesting that in hyperprolactinaemia the thyrotroph has not changed its mode of response to TRH. In contrast, oestrogen treated subjects in addition to dependence on basal serum TSH levels showed a genuinely augmented response to TRH (164.6 ± 20.3%, P < 0.01) compared to controls.

The serum level of TSH (S-TSH) and its response to TRH may be affected by factors that are not related to thyroid or pituitary dysfunction. Thus the TSH response to TRH is known to be influenced by dopaminergic mechanisms. It has been reported to be blunted by the administration of l-dopa (Spaulding et al. 1972; Besses et al. 1975) while basal S-TSH levels are increased in euthyroid and hypothyroid subjects by metoclopramide (Aoki et al. 1976; Healy & Burger 1977; Scanlon et al. 1977) or domperidone (Delitala et al. 1980; Pourmand et al. 1980; Scanlon et al. 1981), drugs that block dopaminergic receptors.

In patients with prolactin producing pituitary tumours a reduced central dopaminergic inhibition of prolactin release has been demonstrated and discussed as a possible aetiologic mechanism (Fine & Frohman 1978; Van Loon 1978). Thus an influence on basal S-TSH and/or its response to TRH might be expected in patients with prolactin producing tumours. Thorner (1977) also reported an augmented TSH response to TRH in 14 of 34 patients with prolactinomas. However, as the response of TSH or TRH is positively correlated to the basal S-TSH level (Beckers et al. 1972; Weeke 1974; Sowers et al. 1976; Wide & Dahlberg 1980) it is difficult to interpret the nature of a changed TSH response to TRH without relating it to the basal level of S-TSH.

We have analyzed the TSH responses to TRH as related to basal S-TSH in 21 patients with hyperprolactinaemia before pharmacological or surgical treatment. They were compared with the responses of 89 individuals without known pituitary or thyroid dysfunction and without medication. They were also compared with the TSH responses to TRH in 19 individuals taking oestrogen containing
preparations, a treatment that may cause hyperprolactinaemia (Ramey et al. 1975; Reyniak et al. 1980) and an exaggerated TSH response to TRH as well (Faglia et al. 1973; Smyth et al. 1977).

Subjects and Methods

Patients with hyperprolactinaemia

The diagnosis hyperprolactinaemia was made when plasma prolactin (P-prolactin) was found elevated on several sampling occasions later than 10 a.m. and prolactin increasing factors like drugs, stress, pregnancy, and liver disease had been carefully excluded.

All patients were investigated before any treatment had been instituted, and they were not taking any drugs. The pituitary function of hyperprolactinaemic patients was routinely investigated in our departments by – hGH and cortisol responses to insulin induced hypoglycaemia. – Urinary 17-OHCS or plasma ACTH or plasma 11-deoxycortisol response to metyrapone, 750 mg 6 times daily for 1 day. – Plasma FSH and plasma LH responses to LRH. – S-TSH and P-prolactin responses to TRH. – Plasma oestosterone (men) and plasma oestradiol (women). – Serum triiodothyronine (S-T3) and serum thyroxine (S-T4).

The TRH tests were selected for analysis in the present investigation only if the results of the other investigations mentioned above fell within the normal ranges.

Of the 23 patients fulfilling these criteria 2 were excluded due to the finding of thyroid antibodies in their sera. Of the remaining 21 two were men and 19 were women. Their mean age was 30 years, range 17–46 years. Their P-prolactin levels ranged from 44 to 3000 μg/l (normal range for this laboratory: < 25 μg/l in men, < 35 μg/l in women). Ten patients had an enlarged sella on X-ray films of the skull. Four of these patients had visual field defects, and in them a pituitary tumour was found at transfrontal operation with the histological appearance of a chromophobe pituitary adenoma. The 6 patients with sellar enlargement that were not operated upon, and the patients without sellar changes, were selected for treatment with bromergocryptine.

Subjects on oestrogen treatment

One man and 18 women were included in this group. Their mean age was 31 years, range 15–54 years. Sixteen

| Table 1. |
| Mean values ± sem for serum or plasma hormone levels in control, hyperprolactinaemic, and oestrogen treated subjects, respectively. |

<table>
<thead>
<tr>
<th>Control subjects</th>
<th>Hyperprolactinaemic subjects</th>
<th>Subjects on oestrogen treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With sellar enlargement</td>
<td>Without sellar enlargement</td>
</tr>
<tr>
<td>Number</td>
<td>89</td>
<td>10</td>
</tr>
<tr>
<td>Mean basal S-TSH, μU/ml</td>
<td>2.5 ± 0.16</td>
<td>3.4 ± 0.52</td>
</tr>
<tr>
<td>TSH response to TRH in % of control response</td>
<td>100</td>
<td>94.1 ± 7.3</td>
</tr>
<tr>
<td>S-T3 nmol/l</td>
<td>2.20 ± 0.07</td>
<td>2.17 ± 0.18</td>
</tr>
<tr>
<td>S-T4 nmol/l</td>
<td>106.7 ± 3.0</td>
<td>98.9 ± 8.9</td>
</tr>
<tr>
<td>Mean basal P-prolactin</td>
<td>–</td>
<td>857 ± 306*</td>
</tr>
<tr>
<td>Prolactin response to TRH in % of basal P-Prolac</td>
<td>–</td>
<td>126.3 ± 12.2</td>
</tr>
</tbody>
</table>

* = P < 0.01, ** = P < 0.001 versus controls, * = P < 0.05, hyperprolactinaemic groups compared.
women were on oral contraceptives containing 30–50 μg ethinylestradiol plus gestagen. Two women were on conjugated oestrogens (USP XIX) due to climacterial symptoms, and the man took oestradiol in the treatment of prostatic carcinoma. The subjects in this group were on no other medication, and none of them had any known pituitary disease and did not prove to have thyroid dysfunction.

**Control subjects**
The 89 control subjects, 27 men and 62 women, were not on any medication. Their mean age was 38 years, range 17–70 years. Their thyroid hormone values were within the normal reference limits of the laboratory (S-T₃: 1.0–3.2 nmol/l, S-T₄: 57–154 nmol/l). Upon follow up 6–25 months later none exhibited any signs of thyroid or pituitary disease and none was on any drug therapy.

**Methods**
The TRH test was performed by blood sampling for S-TSH determination before and 20 and 30 min after the iv injection of 200 μg TRH (Thyrefact Hoechst). In the hyperprolactinaemic patients the blood sampling was extended to 180 min with 30 min intervals but in none of them the maximum S-TSH was found later than 30 min after the injection of TRH. The TSH response to TRH was calculated as the difference between the basal S-TSH and the highest S-TSH reached after TRH.

All measurements of hormone levels in serum or plasma were made by radioligand assay. S-TSH was measured by radioimmunoassay with a double antibody technique (Pekary et al. 1975). The intra-assay variation was 7.8%, the inter-assay variation 14.7%. The radioligand assays for S-T₃, S-T₄ and P-prolactin showed intra- and inter-assay variations of less than 7.5%.

**Results**
The hormone levels in the different groups are summarized in Table 1. The mean basal S-TSH of the hyperprolactinaemic patients was higher than control, more pronounced in the patients without sellar enlargement who had lower mean P-prolactin. The values from only women were also calculated separately to eliminate a possible influence of different sex distribution in the groups. The mean basal S-TSH in control women was 2.7 ± 0.20 μU/ml, that of hyperprolactinaemic women 4.4 ± 0.40 μU/ml (P < 0.001). In the oestrogen treated group the mean basal S-TSH did not differ significantly from controls. Five patients who had normalized P-prolactin and regular menstruations under treatment with bromergocryptine all showed a lower basal S-TSH compared to pre-treatment level.

In the control subjects the TSH response to TRH was significantly correlated to the basal S-TSH level (r = 0.71, P < 0.001). The regression line (y = 3.90 x + 2.52) appears in Fig. 1 together with the corresponding regression lines for the hyperprolactinaemic patients (y = 3.37 x + 4.04; r = 0.62, P < 0.01) and the oestrogen treated individuals (y = 5.21 x + 6.08; r = 0.48, P < 0.05). The regression line of the hyperprolactinaemic patients agreed well with that of the controls while that of the oestrogen treated group showed a steeper slope and a higher ordinate intercept.

As a significant correlation between the basal S-TSH and the response to TRH was demonstrated the TSH response of the hyperprolactinaemic group could not be directly compared to that of the control group that had a significantly lower basal
S-TSH level. Therefore, in each patient the TSH response to TRH was expressed as per cent of the expected response in the control group with the same basal S-TSH level. The expected response in the control group was calculated from the equation for its regression line. The TSH response to TRH in the two hyperprolactinaemic groups then did not differ significantly from each other, nor from controls, but in the oestrogen treated group a significantly augmented response was obtained (Table 1) that remained significant (P < 0.01) also when values of male subjects were excluded. The P-prolactin response to TRH in hyperprolactinaemic patients with sellar enlargement was similar to the response in those without sellar enlargement (Table 1). The values for S-T3 and S-T4 were similar in controls and in hyperprolactinaemic patients (Table 1). As might be expected the values of oestrogen treated subjects were higher, but they had normal values for effective thyroxine ratio (mean: 118.5 ± 6.0 nmol/l) and for effective triodothyronine ratio as well (mean: 2.32 ± 0.10 nmol/l).

Discussion

In the control subjects individual thyroid hormone levels all fell within the normal limits of the laboratory, and the mean values for S-T3 and S-T4 in the group were close to the centers of the normal ranges for these parameters. These facts together with the absence of thyroid or other disease upon later follow up, and absence of present or later medication, indicates that this group should be representative for healthy individuals. However, this control group contained more women than men. A greater TSH response to TRH has been found in women compared to men (Ormston et al. 1971), while the reports on the influence of age are contradictory (Snyder & Utiger 1972; Wenzel et al. 1974). However, as might be expected, there was a high proportion of young women also among the patients with hyperprolactinaemia and in the group taking oestrogen preparations as well, and the differences were comparatively small between the different groups regarding age. Therefore, differences in age and sex distribution between controls and the other groups should bias the comparisons made between them only to a minor degree, and the differences were still present when the values of women were calculated separately.

In severe primary hypothyroidism hyperprolactinaemia may occasionally occur concomitant with grossly elevated S-TSH levels (Van Wyk & Grumbach 1960; Snyder et al. 1973) but the hyperprolactinaemia in our patients cannot be explained by hypothyroidism as they all had basal S-TSH, S-T3 and S-T4 within the normal limits of the laboratory.

However, even if the hyperprolactinaemic patients had individual S-TSH values within normal limits their mean S-TSH was higher than control. Völker & v z Mühlen (1979) also found a high proportion of hyperprolactinaemic patients with increased basal and TRH-stimulated S-TSH levels corresponding to manifest (9%) or subclinical (27%) hypothyroidism while Scanlon et al. (1981) did not find any change of basal S-TSH in their hyperprolactinaemic patients. A common cause of slightly or moderately increased basal S-TSH is a decreased thyroid functional capacity. However, we excluded patients who might have a damage to the thyroid by thyroid antibodies. The fact that the increased S-TSH in our patients was not associated with any significant change in peripheral thyroid hormone levels is in agreement with the observations of Völker & v z Mühlen (1979) and may raise the possibility that the TSH in these patients may not have full biological activity.

An elevated S-TSH in patients with elevated P-prolactin would agree well with a reduced central dopaminergic activity as the mechanism for both changes. A reduced dopaminergic activity has been demonstrated in patients with hyperprolactinaemia (Fine & Frohman 1978; Van Loon 1978), and in healthy subjects an acute reduction of dopaminergic impulses by domperidone increased S-TSH and P-prolactin in parallel (Scanlon et al. 1981). However, in patients with hyperprolactinaemia given domperidone the increase in S-TSH was exaggerated compared to controls while the increase in P-prolactin was blunted (Scanlon et al. 1981). This was interpreted as a feed back effect by prolactin leading to an augmented dopaminergic inhibition of TSH release. In our hyperprolactinaemic patients and in those of Völker & v z Mühlen (1979) as well the elevated S-TSH levels were found predominantly in patients without sellar enlargement and with moderately increased P-prolactin while those with X-ray signs of pituitary tumour and much higher P-prolactin had lower S-TSH that did not differ from control.

A lowered S-TSH under bromergocryptine treatment gives no clue to the mechanism of the
elevated S-TSH in hyperprolactinaemia as dopaminergic stimulation lowers also the high S-TSH in primary hypothyroidism (Rapoport et al. 1973).

We found the TSH response to TRH to be significantly correlated to the basal S-TSH in all groups. A similar dependence of the TSH response on the basal TSH levels has been found in several investigations of healthy and hypothyroid subjects (Beckers et al. 1972; Weeke 1974; Sowers et al. 1976; Wide & Dahlberg 1980; Bastenie et al. 1980). With the approximation of a rectilinear relationship the regression lines for controls and hyperprolactinaemic patients proved to be very similar indicating that in hyperprolactinaemia the thyrotroph has not changed its mode of response to TRH and depends on the basal S-TSH in the same way as seen in controls. The comparatively high TSH responses to TRH seen in hyperprolactinaemia thus were not higher than should be expected with respect to their basal S-TSH levels. On the contrary, oestrogen treated subjects in addition to dependence on basal S-TSH had a genuinely augmented TSH response to TRH. Oestrogen substances bind to pituitary receptors and increase the number of TRH binding sites in animal experiments (DeLéan et al. 1977) which is in agreement with the augmented response of TSH to TRH seen in the present investigation.

References


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