Twenty-Four Hour Secretory Pattern of Thyroid-Stimulating Hormone in Hyperprolactinemic Women with Pituitary Microadenoma

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Abstract

In order to determine whether endogenous dopaminergic tone has any role in the diurnal variation in TSH secretion, the 24-h secretory pattern of TSH and the TSH response to a dopamine antagonist, metoclopramide (MCP), were evaluated in normal women (n=4) and in hyperprolactinemic-amenorrheic women with pituitary microadenoma (n=6). TSH concentrations expressed as percent deviation from the 24-h mean significantly differed with respect to time of day in normal women and hyperprolactinemic women. They were significantly higher during the night (2000–0700h) than during the daytime (0800–1900h). Whereas MCP administration induced no significant changes in serum TSH levels in normal women, it significantly increased serum TSH levels in hyperprolactinemic women. Thus, the diurnal variation in TSH secretion was demonstrated in hyperprolactinemic women with pituitary microadenoma in the face of an increased dopaminergic inhibition of TSH secretion. The present study did not provide evidence that the diurnal pattern of TSH secretion is related to the endogenous dopaminergic tone.

There is considerable evidence suggesting that there is dopaminergic modulation of thyroid-stimulating hormone (TSH) secretion in man (Miyai et al., 1974; Refetoff et al., 1974; Besses et al., 1975; Burrow et al., 1975; Sowers et al., 1976; Delitala 1977; Healey and Burger 1977; Leblanc et al., 1978; Kaptein et al., 1980; Quigley and Yen 1980; Seki et al., 1982). Greater TSH release was found after the administration of a dopamine antagonist, metoclopramide (MCP), in hyperprolactinemic patients than in normal women (Quigley and Yen 1980; Seki et al., 1982). Thus, an increased dopaminergic inhibition of TSH release was considered operative in hyperprolactinemic patients. The twenty-four hour (h) secretory pattern of TSH is characterized by a nocturnal increase (Patel et al., 1972; Chan et al., 1978). However, the mechanism to account for it is unknown. Exogeneous administration of a dopamine agonist, bromocriptine, reportedly abolished the nocturnal increase in TSH secretion in man (Sowers et al., 1982). Therefore, the diurnal variation in TSH secretion may be, in part, regulated by a dopaminergic mechanism. In an attempt to determine whether endogenous dopaminergic tone has any role in regulating the diurnal variation in TSH secretion...
secretion, 24–h secretory pattern of TSH was presently evaluated in hyperprolactinemic-amenorrheic women with pituitary microadenoma in whom dopaminergic inhibition of TSH release was considered to be increased.

Materials and Methods

The subjects of this study were 4 normal women during the early follicular phase and 6 hyperprolactinemic-amenorrheic women. All subjects were found to be euthyroid by clinical examination, and none of them had struma. The 4 normal women showed ovulatory cycles by the basal body temperature chart. In 6 of the 6 patients with hyperprolactinemia, a diagnosis of pituitary microadenoma was made by CT-scan (GE CT/T, section thickness of 1.5 mm), and it was confirmed by surgery in 4 of them. All subjects were free from any medication for at least 6 weeks and slept in the same room for at least 3 days prior to examination. Hourly blood samples were obtained from each subject through an indwelling catheter placed in a wrist vein. During this study, normal feeding was continued at 0800 h, 1200 h and 1700 h, though activity was restricted to the patient's room. Lights were turned off between 2100 and 0600 h. On a separate occasion, each subject received 10 mg of MCP as an iv bolus at 1000 h. Baseline samples were collected at -15 and 0 min and sampling thereafter was at 15, 30, 60, 120 and 180 min. Mean basal concentrations were obtained by averaging two baseline samples collected prior to MCP administration. Serum TSH, thyroxine (T4), triiodothyronine (T3) and free T4 concentrations were measured by radioimmunoassay using the CIS radioimmunoassay kits. Serum prolactin (PRL) concentrations were measured by radioimmunoassay with the radioimmunoassay kit obtained from the Daiichi Radioisotope Laboratory, Japan. The sensitivity of the TSH assay was 1 μU/ml, and the intra- and interassay coefficients of variation were 8.5% and 9.2%, respectively. All samples from any individual were measured for TSH in the same assay. Statistical analysis was performed using analysis of variance and Wilcoxon’s rank test as appropriate.

Results

Mean basal concentrations of free T4 in hyperprolactinemic patients were significantly lower than those in normal women, though the mean basal concentrations of T4 and T3 in hyperprolactinemic patients were similar to those in normal women (Table 1). The 24-h mean concentrations of TSH were significantly higher in hyperprolactinemic patients than in normal women (Table 1). Analysis of variance revealed that TSH concentrations expressed as a percentage deviation from the 24-h mean significantly (p<0.05) differed with respect to the time of day both in normal women and in hyperprolactinemic patients (Fig. 1). They were significantly (p<0.001) higher during the night (2000–0700 h) than during the daytime (0800–1900 h) (normal women, \(-9.6\pm2.0\%\), mean ±SE, vs 11.2±2.6%);

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Normal Women (n=4)</th>
<th>Hyperprolactinemia (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26.5 ± 3.7</td>
<td>29.0 ± 2.0</td>
</tr>
<tr>
<td>PRL</td>
<td>11.4 ± 3.3</td>
<td>160 ± 70*</td>
</tr>
<tr>
<td>T4</td>
<td>6.6 ± 0.3</td>
<td>7.1 ± 0.5</td>
</tr>
<tr>
<td>T3</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>free T4</td>
<td>2.1 ± 0.2</td>
<td>1.5 ± 0.1*</td>
</tr>
<tr>
<td>TSH</td>
<td>3.4 ± 0.3</td>
<td>6.1 ± 0.5**</td>
</tr>
</tbody>
</table>

* p<0.05 vs Normal Women.  ** p<0.01 vs Normal Women.
Fig. 1. The mean (±SE) percent deviation from the 24-h mean concentrations of TSH in normal women and hyperprolactinemic women with pituitary microadenoma are plotted vs. time of day. Each point represents mean percent deviation from the 24-h mean. * p<0.05 vs. 0800 h.

Fig. 2. Serum TSH concentrations (mean±SE) in normal women (left panel) and hyperprolactinemic patients with pituitary microadenoma (right panel) before and after MCP administration. Mean basal concentrations were obtained by averaging two baseline samples collected just prior to MCP administration. * p<0.05 and * p<0.01 vs. basal hormone concentrations.
Discussion

As previously reported by others (Patel et al. 1972; Chan et al., 1978), a distinct diurnal pattern of serum TSH with higher levels during the night was observed in normal women. Although the 24-h mean concentrations of TSH were significantly higher in hyperprolactinemic patients than in normal women, a nocturnal increase in serum TSH levels was observed in hyperprolactinemic patients. To our knowledge, there are no reported studies which evaluate 24-h secretory pattern of TSH in hyperprolactinemic patients with pituitary microadenoma. However, the nocturnal increase in serum TSH observed in our hyperprolactinemic patients is in keeping with the results of Rodriguez-Arnao et al. (1983) who observed elevated TSH levels at 2300 compared with 1100 h in hyperprolactinemic patients. MCP administration increased serum TSH levels in hyperprolactinemic patients, but not in normal women. Our failure to detect significant changes in serum TSH after MCP administration in normal women may be accounted for by the inadequate sensitivity of the TSH assay or the small number of subjects studied. Thus, a diurnal pattern of TSH secretion was observed in the face of an increased dopaminergic inhibition of TSH release in hyperprolactinemic patients. Further, the TSH response to a dopamine antagonist, domperidon, was reported to be greater at 2300 h than at 1100 h in hyperprolactinemic patients and normal women (Rodriguez-Arnao et al., 1983; Scanlon et al., 1980). Therefore, increased TSH levels at night cannot be accounted for by the increased endogenous dopaminergic tone. We have previously reported a nocturnal increase in serum PRL levels in 4 of the 6 hyperprolactinemic patients (Seki et al., 1984). The present study did not provide evidence that the diurnal pattern of TSH secretion is related to the endogenous dopaminergic tone. The low free T4 concentration in hyperprolactinemic patients was not unexpected since the free T4 index was reported to be at or below the lower limit of normal in 8 of 55 hyperprolactinemic patients (Holdaway et al., 1984). The decreased free T4 level and increased 24-h mean TSH concentration in hyperprolactinemic patients may reflect a state of compensation to maintain euthyroidism in the face of an increased dopaminergic inhibition of TSH release. Alternatively, the low free T4 concentration may be the result of direct action of PRL on the thyroid. However, experimental data which support this contention are lacking.

References

Holdaway, I. M., M. C. Evans, A. Sheehan and H. K. Ibbertson (1984). Low thyroxine levels in some hyperprolactinemic patients due to


