Pulsatile thyrotropin and prolactin secretion in a patient with a mixed thyrotropin- and prolactin-secreting pituitary adenoma

Ria Adriaanse, Georg Brabant1, Erik Endert, Frederique J Bemelman and Wilmar M Wiersinga

Department of Endocrinology, Academic Medical Center, University of Amsterdam. The Netherlands: Medizinische Hochschule1, Hannover, Germany


The circadian and pulsatile thyrotropin (TSH) and prolactin (PRL) release was investigated in a patient with slight hyperthyroidism due to a mixed TSH- and PRL-secreting pituitary adenoma. Blood was withdrawn every 10 min for 24 h (before and after medical treatment); pulse characteristics were analyzed by Desade and Cluster programs (values as mean ± SD). The inappropriately high mean 24-h TSH concentration of 3.55 ± 0.31 mU/l was associated with a higher mean 24-h TSH pulse amplitude but unaltered mean 24-h TSH pulse frequency relative to healthy controls. The nocturnal TSH surge (absolute surge 0.5 mU/l, relative surge 16%) was low, related to a loss of the usual nocturnal increase of TSH pulse amplitude and TSH pulse frequency. Chronic treatment with octreotide resulted in a modest clinical and biochemical improvement of the hyperthyroid state; addition of bromocriptine at a later stage had no further beneficial effect. At the end of the follow-up period the mean 24-h TSH paradoxically had increased to 5.33 ± 0.81 mU/l. The nocturnal TSH surge also increased (absolute surge 1.9 mU/l, relative surge 42%), but circadian changes in TSH pulsatility remained absent. In the untreated period the increased mean 24-h PRL concentration of 2.34 ± 24 μg/l was associated with an increased mean 24-h PRL amplitude, whereas the 24-h PRL pulse frequency (N = 4) was lower relative to controls. No circadian PRL rhythm was present. After octreotide and bromocriptine treatment the mean 24-h PRL concentration and mean 24-h PRL pulse amplitude were unchanged, but a clear nocturnal increase of PRL now was observed. Analysis of the temporal coupling between TSH and PRL release by bivariate autoregressive modeling revealed significant cross-correlations in all three periods investigated (coefficients in the range 0.34–0.76, median 0.52; p < 0.01) between TSH and PRL concentrations with a lag time of 10–20 min. We conclude that pulsatile TSH and PRL release in this mixed TSH- and PRL-secreting pituitary adenoma was autonomous in nature. The observed dampening of the nocturnal increase of TSH and PRL is putatively related to a lack of TRH receptors in these tumors. The observed co-secretion of TSH and PRL suggests synthesis of both hormones by the same cell.

R Adriaanse, Department of Endocrinology F5-171, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Hyperthyroidism due to a TSH-secretion pituitary adenoma is a rare condition, characterized by detectable TSH levels despite elevated plasma thyroid hormone concentrations. Thyrotropin secretion by these adenomas appears to be autonomous to a large extent because it is not appropriately regulated any longer by TRH or T3; in the majority of patients the release is not stimulated by exogenous TRH (1–14) or inhibited by exogenous T3 (1, 2, 15–17). It is thus of interest to study pulsatile TSH release in such patients, especially to evaluate whether it differs from the pulse characteristics and the usual nocturnal TSH surge in healthy subjects. Medical treatment of TSH-secreting pituitary adenomas in general is not very effective: dopamine agonists are mostly ineffectual in the suppression of TSH (3, 7, 18–21), whereas the reported effectiveness of octreotide ranges from very good to poor (21–26). The TSH-secreting adenomas frequently secrete other adenohypophysial hormones, like PRL (1, 2, 4, 11, 18, 20). The hyperprolactinemia is sometimes, but not always, corrected by bromocriptine treatment (1, 2, 4, 11, 18, 20). We report circadian and pulsatile TSH and PRL release in a patient with a mixed TSH- and PRL-secreting pituitary adenoma before and after treatment with octreotide and bromocriptine.

Patient and methods

Case report

A 29-year-old man was admitted with blurred vision, which he had had for 9 months. Physical examination revealed a nervous young man with a slightly wet skin and a pulse rate of 90 beats/min. His thyroid was slightly enlarged. Visual acuity was abnormal (left eye, 7/10; right eye, 9/10) and visual field evaluation demonstrated bitemporal defects. The basal TSH level (at 0.900
h) was in the normal range but inappropriately elevated relative to the increased T₃ level (Table 1), indicating central hyperthyroidism. Also, the levels of α-subunits and prolactin were elevated. Computed tomography (CT) revealed a pituitary adenoma with suprasellar extension. After 6 weeks of treatment with octreotide there was a slight clinical and biochemical improvement (Table 1): the basal metabolic rate decreased and the body weight increased. Visual acuity was restored completely, and visual field defects disappeared. After 3 months of follow-up there was a steady state of the clinical and biochemical findings. However, on CT scan the tumor mass was unchanged and transphenoidal surgery was performed.

Methods

The circadian and pulsatile TSH and PRL secretion was studied by blood sampling for TSH and PRL analysis via an indwelling intravenous catheter over a 24-h period every 10 min, starting at 09.00 h. At the end of the sampling period blood was taken and tested for thyroid hormones and a TRH test was done. The response of TSH, PRL and α-subunits was measured at 20 and 60 min after 200 μg of TRH iv (Relefact, Hoechst). The study had been approved by the local committee on medical ethics, and informed consent was obtained. Meals were given at 08.30, 12.30 and 17.30 h. Sleep was allowed between 23.00 and 07.00 h. The patient was studied on three occasions: before treatment, after 6 weeks of treatment with octreotide (100 μg sc three times a day) and after another 6 weeks of octreotide (300 μg/day) in combination with 10 mg of bromocriptine orally (twice a day).

The blood samples were centrifuged immediately and stored at −20°C until analysis. All PRL and TSH samples were analysed in the same assay run in duplicate by PRL RIA (27) and TSH immunoradiometric assay (IRMA) (Immunotech, France), respectively. The detection limit of the TSH assay is 0.1 mU/l (three times the so of the zero standard) and the intra-assay variations are 5–10% and 3–5%, at TSH concentrations of 0.3–1.0 and 1.0–80 mU/l, respectively. Serum T₄ and T₃ were measured by in-house RIAs (28) and serum α-subunits by a sensitive IRMA (Immunotech, France).

The pulsatile TSH secretion was evaluated by two different methods: Cluster analysis (29) and Desade analysis (30), as described previously (31). The absolute nocturnal TSH surge was the difference between the mean TSH-night (all samples taken between 24.00 and 04.00 h) and the mean TSH-day (all samples taken between 15.00 and 19.00 h) (31). The relative nocturnal TSH surge was defined as the percentage increase of the mean TSH-night over the mean TSH-day. The pulsatile PRL secretion was evaluated by Desade analysis, assuming a single decay rate of 45 min for PRL (32). The blood samples taken over the periods 08.00–20.00 and 20.00–08.00 h were used to calculate the TSH and PRL pulse frequency and amplitude during the day and night, respectively (31, 33). Data on the pulsatile and circadian TSH release in the patient were compared to those of 16 healthy controls reported previously (31) and of the PRL release to those of 12 normal young men reported by Veldhuis and Johnson (34).

To search for significant cross-correlations between the TSH and PRL time series, data were subjected to cross-correlation analysis, as described previously (34).

The basal metabolic rate was measured by indirect calorimetry, using the method of the ventilated hood with a mass flow meter, a zirconium–oxygen sensor and an infrared absorption carbon dioxide analyzer (Model 2900, Computerized Energy Measurement System, Sensor Medics, Anaheim, CA, USA) (35). Prior to each study, the flow meter and the oxygen and carbon dioxide

<p>| Table 1. Clinical and hormonal data of a patient with a mixed TSH- and PRL-secreting pituitary adenoma before and after treatment |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Basal (week 0)</th>
<th>Octreotidea (week 6)</th>
<th>Octreotide + bromocriptineb (week 12)</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₄ (nmol/l)</td>
<td>180</td>
<td>108</td>
<td>108</td>
<td>90–110</td>
</tr>
<tr>
<td>FT₄-index</td>
<td>22</td>
<td>2</td>
<td>2</td>
<td>70–130</td>
</tr>
<tr>
<td>FT₃ (pmol/l)</td>
<td>175</td>
<td>148</td>
<td>148</td>
<td>10–20</td>
</tr>
<tr>
<td>T₃ (nmol/l)</td>
<td>3.55</td>
<td>3.08</td>
<td>3.08</td>
<td>1.35–2.45</td>
</tr>
<tr>
<td>09.00 h TSH (mU/l)</td>
<td>3.5</td>
<td>3.6</td>
<td>3.6</td>
<td>0.4–4.0</td>
</tr>
<tr>
<td>Peak TSH–TRH (mU/l)</td>
<td>4.3</td>
<td>4.5</td>
<td>4.5</td>
<td>2.8–22</td>
</tr>
<tr>
<td>α-subunit (U/l)</td>
<td>22</td>
<td>16</td>
<td>16</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>α-subunit–TRH (U/l)</td>
<td>24</td>
<td>17</td>
<td>17</td>
<td>44±7%</td>
</tr>
<tr>
<td>α-subunit/TSH molar ratio</td>
<td>90</td>
<td>63</td>
<td>63</td>
<td>0.3–5.7</td>
</tr>
<tr>
<td>09.00 h PRL (μg/l)</td>
<td>205</td>
<td>203</td>
<td>203</td>
<td>2.5–15</td>
</tr>
<tr>
<td>PRL–TRH (μg/l)</td>
<td>370</td>
<td>300</td>
<td>300</td>
<td>9.5–34</td>
</tr>
</tbody>
</table>

a 3 x 100 μg of octreotide sc daily.
b 3 x 100 μg of octreotide sc + 2 x 10 mg of bromocriptine orally daily.
Fig. 1. The course of plasma TSH (left panels) and PRL (right panels) over 24 h in a patient with a mixed TSH- and PRL-secreting pituitary adenoma: (A) before treatment; (B) after 6 weeks of treatment with octreotide; (C) after 12 weeks of treatment with octreotide and bromocriptine.
analyzer were calibrated with predefined volumes and calibration gases, respectively. Before measurement, the patient was instructed thoroughly. The transparent hood was then placed over his head and ventilated with an air flow of 40 l/min. Expired gas concentrations were averaged at 1-min intervals. The oxygen consumption and carbon dioxide production were measured continuously for 30 min. To allow for adaptation to the hood, the results of the first 10 min were discarded.

Differences in the patient before and after treatment were analysed by Student’s paired t-test and differences between the patient and controls by Student’s unpaired t-test or Wilcoxon’s rank sum test. All data are expressed as means ± SD. The level of significance was taken as p < 0.05.

Results

Thyrotropin release

The mean 24-h TSH concentration in the patient before treatment was higher than in the healthy controls. This was related to a higher mean 24-h TSH pulse amplitude by Desade analysis but not by Cluster analysis. The mean 24-h TSH pulse frequency was not altered relative to controls, with approximately 10 pulses/24 h. The pattern of plasma TSH concentrations over 24 h is depicted in Fig. 1A (left panel). The absolute nocturnal TSH surge was in the lower normal range, but the relative nocturnal rise in TSH was lower than in healthy controls (Fig. 2). In order to evaluate the nocturnal TSH surge in relation to changes in the TSH pulsatility, we compared pulsatile TSH secretion during the day (08.00–20.00 h) and night (20.00–08.00 h) (Table 2).

The usual nocturnal increase in TSH pulse amplitude observed in the control subjects (31) was absent in the patient, whereas the usual nocturnal increase in TSH pulse frequency (31) was preserved, as was apparent in Cluster analysis (Desade analysis was less informative in this respect because during the day no pulses were observed).

After 6 weeks of treatment with octreotide the absolute and relative nocturnal TSH surge increased (Fig. 2). Circadian TSH pulse characteristics remained abnormal (Table 2). The loss of the usual nocturnal increase of TSH pulse amplitude was now evident also in Desade analysis, whereas the nocturnal TSH pulse frequency decreased in Cluster analysis but not in Descade analysis. After another 6 weeks of treatment with octreotide in combination with bromocriptine, the mean 24-h TSH concentration had increased slightly (Fig. 1C, left panel), related to a further increased mean 24-h TSH pulse amplitude (Table 2). The absolute and relative nocturnal TSH surge also had become higher (Fig. 2): the absolute TSH rise was now in the upper normal range but the relative rise was still below normal. There was, however, no nocturnal increase of TSH pulse amplitude or TSH frequency, either in Desade or Cluster analysis (Table 2).

Prolactin release

The elevated mean 24-h PRL concentration in the patient before treatment was associated with a higher mean 24-h PRL pulse amplitude but a lower mean 24-h pulse frequency relative to healthy controls (Table 3). No differences were observed in mean PRL concentration or in PRL pulse amplitude between day (08.00–20.00 h) and night (20.00–08.00 h) (Table 3 and Fig. 1A, right panel), in contrast to the usual nocturnal increase of PRL related to an increase in PRL pulse amplitude (34). After treatment with octreotide for 6 weeks the mean 24-h PRL concentration had increased, as had the PRL pulse amplitude and pulse frequency. A clear nocturnal increase of PRL was now observed (Table 3 and Fig. 1B, right panel). After another 6 weeks of treatment with octreotide in combination with bromocriptine the mean 24-h PRL concentration and PRL pulse amplitude had returned to pretreatment values: nocturnal PRL values were higher than daytime PRL values (Table 3 and Fig. 1C, right panel).

Relationship between TSH and PRL release

Autoregressive modeling revealed a significant cross-correlation between serum TSH and PRL concentrations in the three investigated periods. The cross-correlation coefficients at zero lag ranged from 0.34 to 0.76 (median 0.52; all with p < 0.01). These results indicate that TSH and PRL concentrations increase and decrease simultaneously. The TSH and PRL series exhibited significant partial cross-correlations at a lag time of at least 13 min.
between TSH and PRL. This indicates that an increase of TSH is followed by an increase of PRL at least 13 min later, and vice versa.

Discussion

Pulsatile TSH release in the described patient with a mixed TSH- and PRL-secreting pituitary adenoma differed from the pattern in healthy controls. The slightly elevated TSH levels—inappropiate in view of the increased plasma T₃ and T₄ concentrations—were related to an increased mean 24-h TSH pulse amplitude relative to the controls under preservation of a normal TSH pulse frequency. The second abnormality was a dampening of the nocturnal TSH surge in the untreated state, related to a loss of the usual nocturnal increase of TSH pulse amplitude.

The absence of circadian variation in TSH release in patients with TSH-secreting adenomas has been reported previously (11, 17, 36, 37). However, a normal
circadian TSH rhythm has been observed as being the exception rather than the rule (38). In one of the four reported cases the acrophase was even shifted completely to the daytime (11). We now report that the diminished nocturnal TSH surge is related to loss of the usual nocturnal increase of TSH pulse amplitude (and possibly also to the loss of the usual nocturnal increase of TSH pulse frequency). A probable explanation for this interesting finding is the lack of receptors for TRH in TSH-secreting pituitary adenomas, as reported earlier (39), in line with the non-responsiveness to TRH in our patient.

An alternative explanation might be the suprasellar extension of the pituitary adenoma, because we reported recently a diminished nocturnal TSH surge (also associated with a loss of the usual nocturnal increase of TSH amplitude) in euthyroid patients with pituitary tumors and suprasellar extension (40). This explanation, however, seems less likely because suprasellar extension per se is not associated with a loss of the usual nocturnal increase of TSH pulse frequency (40), and also because during follow-up of our patient the lack of a nocturnal increase of TSH pulse amplitude and pulse frequency became more evident despite an increase of the nocturnal TSH surge itself. Thus, it appears that the secretion of TSH by TSH-producing adenomas occurs rather autonomously: despite maintenance of its pulsatile character, its regulation is erratic.

Although the TSH pulse characteristics were quite similar when analysed by the Desade or Cluster program, in line with our previous experience (31), an obvious difference between both programs was observed in the untreated state of our patient: Desade analysis (in contrast to Cluster analysis) detected no TSH pulses during the day (Table 2). The discrepancy has been noted before in another patient with a TSH-secreting pituitary adenoma who had 6 TSH pulses/24 h by Cluster analysis but 0 TSH pulses/24 h by Desade analysis (37). This might be related to changes in the half-life of TSH secreted by TSH-producing adenomas because Desase analysis employs a fixed half-life of TSH whereas Cluster analysis is not dependent on the half-life of TSH (29, 37). Unfortunately, no data are available on the metabolic clearance rate of TSH in patients with TSH-secreting adenomas.

Treatment with octreotide resulted in a slight improvement of the clinical state, as evidenced by weight gain and a decrease in the basal metabolic rate. It was accompanied by a modest decrease of plasma T4 and T3 concentrations. Interestingly, vision was restored and visual field defects disappeared upon octreotide medication, although there was no shrinkage of the pituitary tumor on the CT scan. This suggests a beneficial effect of octreotide directly on the retina and the optic nerve, as reported recently (41–43). The modest clinical improvement with octreotide treatment was associated with a slight decrease of α-subunits but an increase of TSH in the plasma. The response suggests the presence of somatostatin receptors in the pituitary adenoma, which indeed indirectly were demonstrated by a clear uptake of [111]In octreotide in the tumor at scintigraphy. Whereas a favorable response to octreotide is generally accompanied by a decrease of plasma TSH (44, 45), the contradictory feature in our patient was a rise of TSH in the presence of declining T4 and T3 values. A putative explanation is a change in the biological activity of TSH.

The biological activity of TSH is increased in patients with TSH-secreting pituitary adenomas, accounting for hyperthyroidism in the presence of normal TSH levels (19, 46). It can be speculated that octreotide induces secretion of less bioactive TSH (e.g. via changes in glycosylation), which may be more potent in the IRMA used (19, 23, 42).

Chronic octreotide treatment in other conditions, however, does not affect plasma TSH or TSH pulse characteristics (47). In acute experiments, somatostatin or dopamine infusions decrease the nocturnal TSH surge and TSH pulse amplitude (44, 45). The contrary was observed in our patient: during chronic treatment with octreotide and bromocriptine the nocturnal TSH surge and TSH pulse amplitude increased. An alternative explanation for the observed changes during treatment in our patient is thus that pulsatile TSH characteristics were not influenced by the medication but were dictated by inherent properties of the tumor itself. In favor of this view is the pronounced absence of the usual nocturnal increase of both TSH pulse amplitude and TSH pulse frequency at the end of the follow-up period. It underlines once more the autonomous TSH production in TSH-secreting pituitary adenomas, which are heterogeneous in nature, as evident from the many differences between patients with this condition (11, 36, 37, 46).

Our findings suggest further that the mechanism responsible for the pulsatile TSH release arises in the tumor itself.

In healthy controls PRL (like TSH) is released in a pulsatile fashion (34), superimposed on a circadian rhythm with the major increase occurring shortly after the onset of sleep (32, 34). The nocturnal increase of PRL is related to a nocturnal increase in the PRL pulse amplitude, whereas the number of PRL pulses is distributed evenly throughout the 24-h time-span (34). In our patient, elevated PRL levels were related to an increased mean 24-h PRL pulse amplitude relative to controls, whereas the 24-h PRL pulse frequency was slightly lower. Furthermore, the circadian PRL release in the untreated period was absent, related to a loss of the usual nocturnal increase of the PRL pulse amplitude. The mechanism responsible for the loss of circadian changes in the PRL pulsatility remains unknown. It can be speculated that this (like in the case of TSH) is related to the lack of TRH receptors for TRH in these tumors. Bromocriptine therapy did not decrease the number of pulses (48), in contrast to studies in women with hyperprolactinemia due to microprolactinoma (48). It thus appears that the secretion of PRL, like that of TSH, occurs autonomously in these adenomas.
Stepwise autoregressive fitting disclosed that increases or decreases in serum TSH concentrations at any given instant could be predicted to a significant degree by corresponding increases or decreases in serum PRL concentrations, occurring either simultaneously or approximately 13 min earlier. Thus, it is likely that there is a significant co-secretion of TSH and PRL by this mixed TSH- and PRL-secreting adenoma. The precise mechanism for this temporal coupling might be the synthesis and release of both TSH and PRL by the same tumor cells. Previous immunohistochemical studies (4) indeed have demonstrated co-localization of PRL and TSH-α in the same tumor cells.

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References

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