The role of glucocorticoids
in the regulation of thyrotropin

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Abstract. The potentially inhibitory action of endogenous or exogenous synthetic glucocorticoids on TSH secretion was investigated. Pulsatile and circadian TSH and cortisol rhythms were measured in healthy subjects (12 rhythms), but no correlation between the hormones could be detected. Acute stimulation of endogenous cortisol secretion by CRH tests (1 µg/kg of ovine CRH) at 20.00 h in 9 healthy volunteers did not significantly alter the nightly increase in TSH. Chronic elevation of endogenous cortisol serum levels in patients with Cushing’s disease revealed a heterogeneous pattern. In 2 patients serum TSH and thyroid hormone levels showed a normal 24-h rhythm, whereas the other 2 patients had low TSH serum levels. Acute treatment of 9 healthy volunteers with 0.5, 1 or 2 mg dexamethasone po at 23.00 h resulted in a significant dose-dependent suppression of mean basal TSH levels 9 h later. Treatment with 30 mg of prednisone for 1 week in 7 patients with Crohn’s disease did not influence basal TSH. The TSH response to TRH was only temporarily suppressed on day 3, but not on day 7 of treatment. The results suggest that under physiological conditions glucocorticoids have no regulatory influence on pulsatile and circadian TSH secretion.

The suppressive influence of pharmacological doses of glucocorticosteroids on the endogenous TSH secretion is well documented (1–6). We could recently demonstrate that high pharmacological doses of dexamethasone immediately suppress basal serum TSH levels and completely inhibit the pulsatile secretion of the hormone. As the pituitary responsiveness to an exogenous stimulus with TRH is still preserved, these findings suggest a primarily hypothalamic mechanism of glucocorticoid action (6). However, it is still not clear whether physiological changes in endogenous cortisol secretion or low pharmacological doses of glucocorticoids used on a long-term basis in clinical medicine have any influence on the pulsatile or circadian TSH pattern. The following study was designed further to elucidate these questions.

Materials and Methods

Five different experimental approaches were used:

1. A possible correlation between TSH and cortisol pulses was investigated by measuring the 24-h basal rhythms of TSH and cortisol simultaneously. In 4 subjects, a total of 12 24-h rhythms of TSH and cortisol were performed by sampling blood every 10 min for TSH and every 30 min for cortisol via an indwelling venous catheter starting at 18.00 h. Pulsatile secretion of the hormones was determined by computer-assisted programmes (Pulsar by Merriam & Wachter, 7) and Cluster (8), and cross-correlation (9) was used to look for a possible influence of cortisol pulses on TSH secretion.

2. By stimulating endogenous cortisol secretion by a challenge with CRH, the impact of acute changes in endogenous cortisol secretion on TSH was evaluated. CRH tests (1 µg/kg of ovine CRH) were performed at 20.00 h in 9 healthy male volunteers (age 25 to 31 years) and blood for TSH evaluation was sampled every 15 min until 23.00 h. The results were compared with basal TSH values of these volunteers taken during the same time span at a different occasion.

3. The influence of chronically elevated endogenous cortisol serum levels on TSH was investigated in patients...
with Cushing's disease. In 4 patients with Cushing's disease owing to a pituitary ACTH-producing tumour basal cortisol serum levels were measured and TSH was sampled every 10 min for 24 h using the same experimental setup as described above.

4. The effect of acute pharmacological glucocorticoid application on endogenous TSH secretion was established by testing the dose dependency of the inhibitory influence of dexamethasone on TSH serum concentrations. Nine healthy male volunteers (age 23 to 31 years) participated in this study, taking on successive occasions either no drug as control or 0.5, 1 or 2 mg dexamethasone po at 23.00 h. The suppressive effect of these doses on the TSH secretion was examined by measuring TSH in 3 blood samples taken the morning after between 08.00 and 09.00 h.

5. The influence of pharmacological doses of steroid treatment, as commonly used in clinical medicine, was studied in patients with Crohn's disease before and under treatment with prednisone. Seven patients with acute exacerbation of Crohn's disease, who had not been treated with glucocorticoids before, were investigated as to their thyroid status before treatment by measuring T3, T4, and TSH serum concentrations before and TSH 30 min after stimulation with TRH (200 μg, Antepan®, Henning, Berlin, FRG). No sign of an immunological cause of thyroid disease could be detected in any of these patients by radioimmunological measurement of microsomal antibodies, thyroglobulin antibodies and by measuring antibodies interacting with the thyrotropin receptor (Henning Berlin, FRG). All patients underwent a standard therapy with complete parenteral nutrition. Three and 7 days after initiation of a therapy with 30 mg prednisone iv/day, measurements of T4, T3 and the TRH tests were repeated. All tests were carried out between 08.00 and 10.00 h.

All investigations were approved by the responsible Ethic Committee and informed consent had been obtained from all patients and volunteers.

TSH was measured by a commercially available highly sensitive immunoradiometric assay (IRMA) (Irmaclone, Henning, Berlin, FRG). For a control evaluation in one of the patients with Cushing's disease, a different IRMA system (Riaclone, Behring, Frankfurt, FRG) was used. The maximal coefficient of intra- and inter-assay variation (CV) in both systems was 7%. T3 and T4 were measured by commercially available RIAs (Corning, Gießen, FRG) as was cortisol (Sylvia-Merck, Darmstadt, FRG). The maximal inter- and intra-assay CV of these assays was 5.5%.

Statistical evaluation was performed by paired t-test.

Results

Repeated investigation of TSH 24-h rhythms in 4 subjects revealed the expected pulsatile pattern of TSH secretion and a circadian rise in basal TSH during the evening. In contrast, the activity of pulsatile cortisol secretion increased in the early morning hours leading to a rise in basal cortisol serum levels. The data of one of the volunteers are shown in Fig. 1 as an example. Using cross-correlation by a computer-assisted programme with a special filter to eliminate the circadian rhythm of secretion, no correlation of endogenous cortisol and TSH pulses could be detected in the 12 24-h rhythms tested.

Stimulation with CRH led to the expected rapid and highly significant increase in cortisol serum concentrations. This elevation of endogenous cortisol serum levels, however, did not alter the nightly increase of TSH compared with the control.

![Graph](image-url)
situation (Fig. 2). The small difference in TSH serum levels seen in Fig. 2 never reached the level of significance.

Pulsatile and circadian TSH secretion in 2 of the 4 patients with Cushing’s disease was indistinguishable from the situation in healthy controls despite clearly elevated serum cortisol levels. In patient No. 3 TSH serum levels were low with normal thyroid hormone concentrations, and patient No. 4 showed extremely suppressed TSH levels together with low T₃ and T₄ concentrations. Measurement of TSH by a different IRMA system confirmed these observations (Fig. 3, Table 1).

Acute treatment of healthy volunteers by low pharmacological doses of dexamethasone resulted in a significant suppression of mean basal TSH levels 9 h later compared with the control situation (Fig. 4). This inhibitory effect of dexamethasone was dose-dependent and followed a linear regression (r = −0.70, p < 0.05). Under treatment with 30 mg prednisone/day for 1 week neither TSH serum concentrations nor thyroid hormone levels were significantly altered. A slight but significant suppression of the TSH response to TRH was visible only on day 3 of treatment, but not after 7 days of therapy (Table 2).
Table 1.
Serum cortisol (± so), T₃ and T₄ levels in 4 patients with Cushing’s disease.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean 24-h cortisol (nmol/l)</th>
<th>T₃ (nmol/l)</th>
<th>T₄ (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>582 ± 116</td>
<td>1.8</td>
<td>90.1</td>
</tr>
<tr>
<td>2</td>
<td>450 ± 138</td>
<td>1.4</td>
<td>64.4</td>
</tr>
<tr>
<td>3</td>
<td>486 ± 99</td>
<td>1.8</td>
<td>96.5</td>
</tr>
<tr>
<td>4</td>
<td>538 ± 66</td>
<td>1.2</td>
<td>84.9</td>
</tr>
</tbody>
</table>

Discussion

In addition to the generally accepted effects of synthetic glucocorticoids in high pharmacological doses, a potential inhibitory influence of endogenous glucocorticoids on TSH secretion has been discussed, even though opinions differ (10—13). This inhibitory influence was mainly supported by the observation that there is a reciprocal relationship between the well known circadian pattern of both hormones with an early morning rise in cortisol and a decline in TSH serum concentrations at the same time (11). With improved assay systems and frequent blood sampling it was proved that the circadian rhythm of cortisol secretion is a result of cortisol pulses, probably governed by a hypothalamic mechanism. A variation in frequency and/or in amplitude of cortisol pulses thus leads to the circadian pattern of secretion (14). Our group and others recently demonstrated a similar pulsatile pattern of secretion for TSH by using computer-assisted methods (15,16) which may lead to the circadian variation of the hormone, probably by a hypothalamic mechanism (17). The finding that high doses of dexamethasone completely inhibited pulsatile secretion of TSH, but did not alter the pituitary response to TRH suggests an interaction of glucocorticoids with this hypothalamic mechanism involved in the generation of TSH pulses (6). Therefore, an interference of endogenous cortisol with TSH secretion expressed in a cross-correlation of cortisol and TSH pulses might be expected. In the present study no such cross-correlation between cortisol and TSH pulses could be detected and this finding provides evidence against a physiologically important interaction of endogenous cortisol secretion on TSH pulses. Our finding is supported by the results of the stimulation of endogenous cortisol by CRH where no significant alteration compared with the control situation was present in the nightly increase in TSH despite high circulating cortisol serum concentrations. This is in contrast to Salvador et al. (13) who investigated patients after surgery for a microprolactinoma. They discussed a small modulatory effect of endogenous cortisol secretion on TSH serum levels following an alteration of cortisol serum levels by metyrapone treatment.

Table 2.
TSH increment 30 min after TRH, T₃ and T₄ serum levels (± so) before therapy and under treatment with 30 mg prednisone/day. Statistical evaluation by paired t-test (before therapy vs treatment).

<table>
<thead>
<tr>
<th>TSH (mU/l)</th>
<th>p</th>
<th>T₃ (nmol/l)</th>
<th>T₄ (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.8 ± 3.2</td>
<td>2.0  ± 0.5</td>
<td>123.6 ± 25.7</td>
<td></td>
</tr>
<tr>
<td>Treatment with 30 mg prednisone/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>5.8 ± 4.5</td>
<td>0.0025</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Day 7</td>
<td>7.3 ± 3.5</td>
<td>n. s.</td>
<td>2.0 ± 0.3</td>
</tr>
</tbody>
</table>

Fig. 4.
Mean TSH serum levels (± so) in 9 healthy male volunteers under basal conditions and between 08.00 and 09.00 h in the morning after 0.5, 1 or 2 mg dexamethasone (Dex) po at 23.00 h.

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Some explanation for the discrepancy between these negative findings and the accepted inhibitory effects of high pharmacological doses of glucocorticoids on TSH may be provided by the heterogeneous results reported in patients with Cushing’s disease (2,12,18–23). The individual variation in our study reflects this considerable variation in the effects on basal or stimulated TSH secretion in Cushing’s syndrome. Thus, dosage, duration of action, and possibly the form of application may play an important role in modulating the suppressive effects of glucocorticoids on TSH secretion. This hypothesis fits well with our findings of dose-dependent effects of dexamethasone on basal TSH secretion in humans.

The important question, however, whether pharmacological doses of glucocorticoids may have inhibitory effects on the hypothalamic-pituitary-thyroid axis could be answered negatively. Studying a comparable cohort of patients, Gamsedd et al. (24) reported reduced, but not significantly altered TSH levels after 5 days of treatment with higher doses of the steroids. The discrepancies to the studies of Otsuki et al. (2), where the TSH response to TRH was completely suppressed following treatment with comparable doses of steroids, and of Jensen et al. (25), who used lower doses of prednisone, may be at least partially explained by the different and less sensitive methodology for the measurement of TSH in these studies. With sensitive methods our study confirmed early data (11) on pharmacological application of glucocorticoids that an ‘escape’ phenomenon may be present, as only after 3 days of treatment a small effect was present, but not on day 7. As a hypothalamic form of hypothyroidism is difficult to distinguish from alterations of thyroid hormones in ‘non-thyroidal illness’, a condition where patients may be treated with comparable doses of glucocorticoids, this lack of a suppressive effect on TSH seems to be particularly important for the correct evaluation of the clinical situation.

In summary, under physiological conditions cortisol seems not to be involved in the regulation of TSH secretion. Pathophysiological changes of the hormone, however, may lead to a decrease in TSH secretion by a hypothalamic mechanism, but low-dose chronic treatment with synthetic glucocorticoids is not associated with a clinically relevant change in the function of the hypothalamic-pituitary-thyroid axis.

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References


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