Effect of a Single Dose of Glucocorticoid on the Diurnal Variations of TSH, Thyroxine, 3,5,3'-triiodothyronine, 3,3',5'-triiodothyronine and Cortisol in Normal Men

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Synopsis

Plasma thyrotropin (TSH) and cortisol concentrations were suppressed immediately after an intravenous bolus dose of 8 mg betamethasone in 6 male subjects. The circadian variations of these hormones disappeared for 40 hr (TSH) and 44 hr (cortisol). Plasma thyroxine (T₄), 3, 5, 3'-triiodothyronine (T₃), 3', 5'-triiodothyronine (reverse T₃) levels did not show diurnal variations before betamethasone administration. Plasma T₃ levels decreased to 66% of the basal levels 20 hr after betamethasone administration, whereas plasma reverse T₃ levels increased to 163% of the basal levels at 24 hr. These changes were reversed by 3 to 5 days after betamethasone. The earlier recovery of the diurnal rhythm of TSH than that of cortisol suggests that the TSH rhythm is not under the direct control of circulating cortisol.

The plasma concentration of thyrotropin shows a circadian variation in normal subjects (Patel et al., 1972; Weeke, 1973). The mechanism which controls the circadian variation of thyrotropin (TSH) secretion is still unknown. Computational analysis of the data failed to reveal any correlations between the diurnal rhythm of plasma TSH levels and the fluctuations of thyroxine (T₄) or 3, 5, 3'-triiodothyronine (T₃) in plasma (Azukizawa et al., 1976). It has been suggested that the circadian rhythm of TSH secretion is the result of the inhibitory action of plasma cortisol because there is an inverse relationship between their circadian patterns (Nicoloff et al., 1970), and because of the suppressive effect of dexamethasone on TSH secretion (Wilber and Utiger, 1969). In this study, the effects of a single dose of glucocorticoid, betamethasone, on the concentrations of plasma TSH, T₄, T₃ and 3', 5'-triiodothyronine (reverse T₃) levels in relation to those of plasma cortisol levels were investigated.

Materials and Methods

Six male volunteers, 28–35 years of age, participated in this study. Volunteers who seemed to be susceptible to the side effect of glucocorticoids were excluded. Informed consent was obtained from each subject. They were allowed their usual daily activities throughout the studies. They were all euthyroid clinically and had normal plasma levels of thyroid hormone. They slept from 2300 hr to 0700 hr and were not allowed to sleep in the daytime. Blood samples of 5 ml were drawn from arm veins with heparinized syringes. Plasma was immediately separated and kept frozen at −20°C until the hormones were assayed.

Control blood samples were drawn every 6 hr from 24 to 48 hr prior to the administration of an in-
travenous bolus of 8 mg of betamethasone (Rinderon® Shionogi Pharmaceuticals, Osaka, Japan) at 0700 hr. This injection was followed by serial blood sampling hourly for 12 hr and every 4 hr after that.

Radioimmunoassays

Plasma concentrations of TSH were measured by a highly sensitive radioimmunoassay following the method of Pekary, Hershman and Parlow (1975). The concentrations of plasma T₄, T₃, and reverse T₃ were measured by radioimmunoassay kits (Eiken Immunoochemical Laboratories, Tokyo, Japan) employing 8-anilino, 1-naphatalene sulfonic acid as the inhibitor to thyroxine-binding globulin and a double antibody method for separation of bound hormone from free. Plasma concentrations of cortisol were analyzed by a competitive protein binding analysis according to the method of Murphy (1967).

Statistical Analysis

The data were analyzed by two-way analysis of variance in order to prove the statistical significance of diurnal variation in hormone levels.Paired t-test was used for the changes in hormone levels at specified sampling time.

Results

Relationship between TSH and cortisol (Fig. 1)

In the control periods of 24 to 48 hr prior to the administration of betamethasone, there was a consistent daily variation in plasma concentrations of TSH and cortisol in each of the 6 male subjects. The highest values of plasma TSH were obtained at 2300 hr and the highest values of plasma cortisol were obtained at 0700 hr in samples obtained every 6 hr. (Table 1)

Immediately after the intravenous administration of betamethasone, both plasma TSH and cortisol levels began to fall to the lowest values in the series of the samples in this study. The mean concentrations of plasma TSH remained low at about 1 µU/ml from 6 to 36 hr after betamethasone. No significant daily rhythms were detected during this period. The first significant rise in plasma TSH was noted 40 hr after the administration of betamethasone. This rise was followed by larger increases in plasma TSH levels during the next night. However, there was neither a rebound phenomenon, nor a transient increase of TSH concentration above the control values.

The concentrations of plasma cortisol also remained at very low levels, 0.5–1.7 µg/dl in the period from 6 hr to 44 hr after the intravenous dose of betamethasone. The first significant rise of plasma cortisol from these low levels was observed 48 hr after the injection or 4 hr after the first rise of plasma TSH. This rise was followed by apparent daily rhythms in plasma cortisol levels with increasing amplitude day by day until the end of the study. The peaks of plasma TSH at the circadian variations preceded those of plasma cortisol with a time interval of 4 to 6 hr in each subjects.

Effects of betamethasone on plasma T₄, T₃, and reverse T₃

Plasma T₄, T₃ and reverse T₃ levels did not show any diurnal variation in the control periods when samples were obtained every 6 hr. (Table 1) Plasma T₄ concentration was elevated from 8.3±0.5 µg/dl in the basal condition to 9.4±0.6 µg/dl 2 hr after betamethasone administration (p<0.05), whereas there were no significant fluctuations of plasma T₃ and reverse T₃ levels at this time. There were significant decrements in plasma T₃ levels 16 to 40 hr after betamethasone administration, when plasma T₄ levels did not show any significant changes. The lowest mean valve of plasma T₃ concentration was 92.7±17.4 ng/dl (66% of the value at 0 hr) appearing 20 hr after betamethasone administration. In contrast, plasma reverse T₃ concentration increase from the basal value of 40.8±9.1 ng/dl to 52.7±2.3 ng/dl beginning at 4 hr after the steroid injection. The elevation of plasma reverse T₃ was sustained for 36 hr with peak values of 66.7±5.1 ng/dl measured 24 hr after the injection of betamethasone.
Fig. 1. Effect of 8 mg of betamethasone iv given at 0 hr to 6 male subjects. The upper panel represents mean plasma TSH concentrations. The lower panel represents mean plasma cortisol concentrations. Values are shown as mean ± SEM.
Table 1. Diurnal variations of plasma TSH and cortisol, and lack of diurnal variations of plasma T₄, T₃, reverse T₃. (mean±SEM)

<table>
<thead>
<tr>
<th>Clock hour Number</th>
<th>0100</th>
<th>0700</th>
<th>1300</th>
<th>1900</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH μU/ml</td>
<td>4.33±0.62</td>
<td>3.34±0.39</td>
<td>2.70±0.36*</td>
<td>2.79±0.31*</td>
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<tr>
<td>T₄ ng/dl</td>
<td>8.27±0.37</td>
<td>7.79±0.40</td>
<td>8.07±0.48</td>
<td>8.47±0.51</td>
</tr>
<tr>
<td>T₃ ng/dl</td>
<td>143±10</td>
<td>137±7</td>
<td>137±10</td>
<td>159±13</td>
</tr>
<tr>
<td>rT₃ ng/dl</td>
<td>40.1±4.2</td>
<td>38.6±2.2</td>
<td>39.0±3.1</td>
<td>42.1±3.4</td>
</tr>
<tr>
<td>Cortisol μg/dl</td>
<td>3.6±1.0*</td>
<td>14.9±0.8</td>
<td>10.5±1.6</td>
<td>8.8±2.8*</td>
</tr>
</tbody>
</table>

Mean±SEM. * Significantly lower than the highest mean value of the day (p<0.05).

Discussion

The present study indicates that a single intravenous dose of 8 mg of betamethasone suppresses the plasma TSH levels in the basal state. Plasma TSH and cortisol levels decreased quite rapidly and the half time of the decrease of the plasma TSH and cortisol levels were 190±28 min (mean±SE) and 80±5 min, respectively. The values for TSH are considerably longer than the calculated half time determined by the radioisotopic tracer method (Odell et al., 1967), whereas the values for cortisol are comparable to those by the previous report (Hellman et al., 1970). From these data it is suggested that the secretion of TSH and ACTH was suppressed immediately after the single dose of the glucocorticoid, although the suppression of TSH secretion was not complete. Our data show that the daily increases in plasma TSH and cortisol levels were also suppressed after the single dose of glucocorticoid. This result is compatible with the previous preliminary report by Patel et al. who showed that a constant infusion of 500 mg of cortisol over at 24 hr period completely suppressed the circadian rhythm of plasma TSH levels (Patel et al., 1974). The recovery of the hormone secretion necessitated about 40 hr for TSH and 44 hr for cortisol after the administration of betamethasone. It is noteworthy that the recovery of TSH secretion was slightly earlier than that of cortisol.

Nicoloff et al. (1970) reported that there was an inverse relationship in the circadian patterns of plasma TSH and cortisol. They suggested that the diurnal variation of TSH was driven by the alteration of the plasma cortisol levels. The results of the present study, however, do not support this hypothesis, because the TSH surge appeared in spite of the continued suppression of the plasma cortisol levels. It is conceivable that the diurnal rhythm of TSH secretion itself may be independent of cortisol secretion. It has been claimed that there is a rebound phenomenon indicated by an overshoot of thyroidal iodine release, shortly after the suppression by dexamethasone (Nicoloff et al., 1970). However, we could find neither a bigger TSH surge nor an abrupt increase of plasma concentrations of T₄ or T₃ during the days following the suppression by betamethasone. This discrepancy may result from the different indicators of TSH secretion measured in the two studies.

The lack of diurnal variation in plasma T₄ and T₃ levels agrees with the results of previous reports (Azukizawa et al., 1976; O'Connor et al., 1974). Our results by the 6 hr interval sampling for 2 days do not suggest the possibility of diurnal variation of plasma reverse T₃ concentration. It is feasible that the sampling interval was too long to demonstrate the fluctuation of reverse T₃ levels considering the rapid clearance of this thyronine from plasma (Chopra, 1976).
The changes in levels of plasma T₄, T₃, and reverse T₃ after betamethasone administration were very similar to those seen in thyrotoxic patients and in hypothyroid patients treated with T₄ who were given 8 mg dexamethasone orally in four divided doses (Chopra et al., 1975). Similar results were also shown after a single dose of 12 mg dexamethasone orally since to the euthyroid subjects under treatment with 0.2 mg T₄ daily (Burr et al., 1976). Although the hypothesis that peripheral conversion of T₄ to T₃ is selectively inhibited by the glucocorticoids is intriguing, some of the T₃ decrement in this study may have resulted from the suppression of TSH secretion which is known to induce the thyroidal secretion of T₃ in preference to T₄.

Our data indicate that the effects of a single injection of a large dose of synthetic corticosteroid persist for at least 5 days. Therefore, in clinical situations, measurement of plasma thyroid hormones, TSH and cortisol should be avoided for at least a week after such treatment.

Acknowledgements

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References