Sleep-Related Growth Hormone Release in Thyrotoxic Patients Before and During Propylthiouracil Therapy

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Abstract

Hyporesponsiveness of GH to insulin-induced hypoglycemia has previously been reported in hyperthyroid patients. In order to clarify the GH secretion in thyrotoxic patients, sleep-related increases in the serum GH concentration were investigated.

Eight thyrotoxic females ranging in age from 7 to 15 were treated with PTU. Blood samples for measurement of GH were drawn every 15 minutes during the first few hours of sleep before and during the treatment lasting about three months. The mean maximum serum GH level before the treatment was 10.0±5.5 ng/ml (mean±SD); this rose to 23.2±14.6 ng/ml (P<0.02) during the treatment. The maximum value of more than 10 ng/ml was detected in only 3 out of the 8 patients before treatment. On the other hand, serum GH levels during PTU administration rose to above 10 ng/ml in all patients except one. It was revealed that sleep-related elevations of GH occurred early in sleep and in close association with a slow-wave EEG pattern.

The results show that sleep-related GH release is low in the hyperthyroid state, but becomes significantly elevated during PTU administration. However, even in the hyperthyroid state, the sleep-related secretion of GH is closely correlated with the slow-wave sleep stage as in the euthyroid condition.

A number of studies in hyperthyroid patients have shown that growth hormone (GH) response to various provocative stimuli may be decreased (Burgess et al., 1966; Giustina et al., 1971; Yeung, 1973) or normal (Katz et al., 1969; Rosenfeld et al., 1969). Yeung et al. (1973) concluded that the excess of circulating thyroxine had a direct suppressive effect on the hypothalamic-pituitary regulation of GH secretion. Recently, Nilsson et al. (1980) showed improved response of GH to insulin-induced hypoglycemia when the patients became euthyroid.

The sleep-related GH release has been considered to be a more physiological secretion than the insulin-induced secretion, and a consistent correlation has been confirmed between the elevation of serum GH and the onset of sleep, without rapid eye movement (non-REM) (Honda et al., 1969; Takahashi et al., 1968; Parker et al., 1969; Lucke et al., 1971). However, there are few reports about the sleep-related GH release in thyrotoxic patients (Finkelstein et al., 1974). We have therefore attempted to
clarify the GH secretion capacity during sleep in the hyperthyroid state and to find out the effect of the thyroid hormone excess on the relationship of the sleep stage to GH release.

**Subjects and Methods**

**Subjects**

Eight hyperthyroid females ranging in age from 7 to 15 were examined. The diagnosis of hyperthyroidism was made on clinical and laboratory examination, based on the findings of abnormally high serum triiodothyronine (T3) and thyroxine (T4) and the blunted response of thyroid stimulating hormone (TSH) to thyrotropin releasing hormone (TRH). The clinical and laboratory data are shown in Table 1.

**Methods**

The study was performed before and during the administration of PTU. The examination during PTU therapy was done in the period between 93 and 121 days (mean: 107 days) of the therapy. Polygraph recording were made during the first few hours of sleep to confirm the sleep stage. The depth of sleep was electroencephalographically classified into six stages (W, I, II, III, IV and R) similar to the classification of Dement et al. (1957) (A, 1, 2, 3, 4 and REM period). W-stage is the state of wakefulness, I-stage is the drowsy state, II-stage represents moderately deep sleep and III+IV stage is the stage of deep sleep characterized by high voltage slow waves (SW). R-stage is paradoxical sleep, i.e., the appearance of rapid eye movement (REM). Physiological saline was constantly infused from the anticubital vein to secure the route of blood sampling, and blood was drawn every 15 minutes for GH measurement (HGH-RIA, Dainabot Radioisotope Laboratories, Tokyo). The responsiveness of TSH to TRH was assessed by injecting TRH (10 µg/kg of body weight) in the morning following polygraphic examinations. The blood was drawn before, and 15, 30, 60 and 120 minutes after TRH administration. The basal serum T3, T4 and rT3 before TRH administration were measured (T3, T4 and rT3 RIA, Dainabot Radioisotope Laboratories, Tokyo). The normal serum levels of T3, T4 and rT3 are from 98 to 202 ng/dl, from 4.5 to 13 µg/dl and from 10 to 50 ng/dl respectively. A sleep related GH value of 10 ng/ml or more is considered normal (Van Wyk et al.,

<table>
<thead>
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<th>Case No.</th>
<th>Age yr.</th>
<th>Sex</th>
<th>GH ng/ml</th>
<th>T3 ng/dl</th>
<th>T4 µg/dl</th>
<th>rT3 ng/dl</th>
<th>TSH response to TRH µU/ml</th>
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ND: not done
The serum TSH for every specimen was measured in every sample by RIA (Daiichi Isotope Laboratories, Tokyo). The blood was centrifugated and sera were stored by deep freezing until simultaneous measurement. Statistical analysis was made by paired t-test. The nature and purpose of the study were explained to each subject and parent before their consent to participate was obtained.

Results

The thyroid function (Table 1)

The basal serum T3, T4 and rT3 levels were significantly high before PTU and decreased during the treatment. The TSH responses to TRH were blunted in all cases before PTU and were still blunted in four out of the six cases examined during treatment. The serum levels of thyroid hormones during treatment were normal in six out of the eight patients. In one case (24), the serum T4 level was low at 3.2 µg/dl, and TSH response to TRH was exaggerated. In another case (27), the serum T3 level (273 ng/dl) was slightly elevated.

The serum GH levels during sleep (Table 1)

The maximum GH level before treatment was 10.0±5.5 ng/ml (m±SD) and rose to 23.2±14.6 ng/ml (P<0.02) during treatment. The maximum value of more than 10 ng/ml was detected in only three cases out of the eight before treatment. On the other hand, serum GH levels during PTU administration increased to above 10 ng/ml in all cases except one.

The correlation of elevation of serum GH and sleep stage.

In the hyperthyroid state, the patients showed frequent disturbance of sleep, i.e., hyposomnia. However, the typical slow-wave EEG was recorded soon after falling to sleep. The level of GH rose immediately after the onset of sleep and the peak was noticed in accordance with sleep stages III and IV, i.e., slow-wave EEG, even in the hyperthyroid state, as in the euthyroid state. During the R-stage and W-stage, no rise in GH was observed. Representative examples of three patients (cases, 1, 4, 8) are shown in Fig. 1.

Discussion

Hyporesponsiveness of growth hormone to hypoglycemia has previously been reported in hyperthyroid patients (Burgess et al., 1966; Giustina et al., 1971; Yeung, 1973), while sleep-related GH release in the hyperthyroid state was also reported to be decreased (Finkelstein et al., 1974).

Our study confirms a significant decrease in sleep-related GH release in thyrotoxic patients when compared to that during PTU therapy. And this study also shows that the marked rise in the serum GH level is still noticed immediately following the onset of sleep and is closely related to the sleep pattern, i.e., the SW stage of non-REM.

The importance of the thyroid hormones to GH production has been reported. Some showed that GH production diminished in hypothyroidism and administration with T4 or T3 increased pituitary and plasma GH concentrations (Peake et al., 1973; Hervas et al., 1975). DeFesi et al. (1979) assessed the kinetics of changes in somatotroph in thyroidectomized rat pituitary and stated that the thyroid hormones might be important in the regulation of DNA synthesis and cell replication.

However, the mechanism of decreased GH production in thyroid hormone excess has not been clarified.

Many of the manifestations of thyrotoxicosis can be attributed to sympathetic overactivity (Blackard et al., 1968) and the signs and symptoms of thyrotoxicosis have been improved with propranolol (a non-selective adrenoreceptor β-bloking agent) administration (Lee et al., 1973; Michie et
al., 1974; Toft et al., 1978). Many studies showed that propranolol increased the release of GH during hypoglycemia (Parker et al., 1974; Blackard et al., 1968; Imura et al., 1971; Nilsson et al., 1980). Thus, these clinical and laboratory studies have indicated that the hyporesponsiveness of GH release to insulin-induced hypoglycemia in thyrotoxic patients is mediated by the \( \beta \)-adreno-receptor. However, the increase in GH response to propranolol was much greater in the controls than in the thyrotoxic patients, Yeung et al. (1973) stated that the decreased response of GH to hypoglycemia in thyrotoxicosis is due to a direct effect of thyroxine on the hypothalamic-pituitary regulation of GH secretion.

Hyporesponsiveness of GH in the thyrotoxic state has also been explained by prolonged caloric deprivation (Ingbar and Woeber, 1981). In our subjects, however, no history of caloric deprivation was revealed.

The inhibition of sleep-related GH release by somatostatin (Lucke et al., 1971; Parker et al., 1974) and enhancement of sleep-related and insulin-induced GH secretion in normal controls by piperidine (nicotinic cholinergic receptor stimulator) (Mendelson et al., 1981) were reported.

Thus, many mechanisms for the decreased sleep-related GH release in thyrotoxic patients remain to be clarified.

References


Fig. 1 B

Fig. 1 C

Fi. 1. Serum GH levels and sleep records in Patients 1, 4, and 8 with thyrotoxicosis. Heavy bars at the level of sleep stage "R" indicate REM sleep periods and at that of "W" indicate awake. The upper half of each figure shows the GH level and sleep records in the hyperthyroid state before PTU administration, and the lower half of the figure shows the results during treatment.


