Thyroid hormone therapy modulates hypothalmo-pituitary-adrenal axis

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**Abstract.** To observe the influence of thyroid hormone therapy on hypothalmo-pituitary-adrenal (HPA) axis, a group of 14 athyreotic women due to thyroid cancer treatment were studied before and after thyroid suppression therapy with thyroxine (T4). Changes in plasma adrenocorticotropic (ACTH) and cortisol levels in response to human corticotropin-releasing hormone (hCRH; 100μg, i.v.) were estimated under hypothyroid conditions and after T4 suppression therapy with 2.5 μg/kg/day for two months (n=14). A group of seven healthy women was evaluated as a control group. A greater increase in ACTH levels by hCRH was observed in patient group both before and after suppression therapy compared than that of control group. Plasma cortisol levels after hCRH stimulation were also greater in patient group both before and after suppression therapy than that of control group. In conclusion, both hypothyroidism and subclinical hyperthyroidism with suppressive doses of thyroid hormone induced a hypersensitivity of ACTH to hCRH. Considering the role of thyroid hormone on HPA axis, the mechanisms of ACTH hypersensitivity may be different between these two conditions.

**Key words:** Adrenocorticotropin, hCRH, Cortisol, Thyroid hormone, Hypothalamo–pituitary–adrenal axis

**THYROID** hormones (thyroxine, T4; triiodothyronine, T3) have intricate effects in different organs [1, 2]. Subclinical hyperthyroidism, characterized by low thyroid stimulating hormone (TSH) and normal free thyroid hormone concentrations in serum, has been associated with an independent risk factor for Alzheimer’s disease, cognitive dysfunction and cardiovascular diseases [3-5]. We have previously demonstrated that hyperthyroid patients have an adrenocorticotropin (ACTH) hypersensitivity to human corticotropin-releasing hormone (hCRH) [6]. On the other hand, another study showed a decreased response of cortisol to ACTH administration, which may be due to diminished adrenocortical reserve [7]. These findings indicate that hyperthyroidism modulates hypothalmo-pituitary-adrenal (HPA) axis. Patients on thyroid suppression therapy due to differentiated thyroid cancer usually have subclinical hyperthyroidism, which may increase the risks of a mild irregular heart rhythms and decrease in bone density [8]. However, a small number of studies have examined the consequences of thyroid suppression therapy on HPA axis [9].

In order to investigate the changes in HPA axis following thyroid hormone therapy, a group of hypothyroid patients was studied before and after administration of L-T4 (levothyroxine) suppressive doses (2.5 μg/kg/day) for two months.

**Methods**

**Patients**

Fourteen hypothyroid women aged between 30 and 57 years (mean age 42.9±3.2 years) were studied. All patients had an ablative therapy for a thyroid cancer with total surgical thyroidectomy and I\textsuperscript{131} therapy. During the study, a total body I\textsuperscript{131} scan was negative for thyroid remnants, and plasma thyroglobulin levels were below detectable concentration. One month after the ablative therapy, patients reached to hypothyroid state, which was confirmed by measuring plasma TSH concentration, whose mean levels were 89.9±7.1 mU/L with a range of 60-118 mU/L (normal range: 0.2-3.5 mU/L). No patients had any additional diseases.
Data analysis

Basal and stimulated levels of ACTH and cortisol obtained before and after treatment were compared. Maximum peaks, absolute increments and the area under the curve (AUC) were estimated in each case. Statistical analyses were performed using non-parametric Wilcoxon’s sum paired rank test. Comparisons between groups were made using the unpaired non-parametric method of Mann-Whitney. Data are presented as the mean±SEM.

Results

One month after the ablative therapy, all patients reached the hypothyroid state that was determined by TSH levels. The suppression therapy for two months produced elevation of FT4 and reduction of TSH in the range of subclinical hyperthyroidism (Table 1).

Compared with normal subjects, patients under hypothyroid condition did not show significant differences in basal levels of ACTH or cortisol. However, the response of ACTH and cortisol to hCRH were significantly greater compared with those of control group, as assessed by maximum plasma concentrations for ACTH (14.92±1.9 vs. 7.7±0.6 pmol/L, p< 0.05) and cortisol (710±32 vs. 596±34 nmol/L, p< 0.05). This elevation was also evident in the AUC for ACTH (1248±230 vs. 618±59.4 pmol/L/150 min, p< 0.05), and cortisol (78400±5892 vs. 62100±1830 nmol/L/150min, p<0.05) (Fig.1 A, B).

When the patients with the suppression therapy (n=14) were evaluated at two months after the onset of thyroid hormone treatment, we observed an increase in ACTH basal (-30, 15, 0 min) levels compared with those of pre-treatment (5.8±0.67 vs. 2.8±0.63 pmol/L, p<0.05). The ACTH levels were also greater than

A group of seven healthy, non-obese, nonsmoking women aged between 24 and 45 years (mean age 36.2 ± 8.2 years, not statistically significant from those for hypothyroid patients) were studied as a control group. Informed consent was obtained from all subjects and the ethics committee of the Navarre Clinic University approved the study.

Study design

To reduce individual variations in ACTH and cortisol levels that are usually observed in the morning, the CRH test was performed in the afternoon (10). All patients and control subjects underwent the hCRH test at 17:00 hours as follows; After three basal blood samples (3 mL/each sample) had been obtained at 15 min intervals, a bolus intravenous administration of 100 μg hCRH (Clinalfa, Weil am Rhein, Germany) was performed and blood samples were obtained at 30, 45, 60, 90 and 120 min after the injection.

After the hCRH test, all patients underwent thyroid suppression therapy with L-T4 (2.5 µg/kg/day) and the hCRH test was performed two months afterward.

Hormone assays

ACTH and cortisol levels were measured by immuno-radiometric assay (IRMA) and radioimmunoassay (RIA), respectively, as reported previously (6). Total (T) T4, TT3, Free T4 and Free T3 levels were measured by radioimmunoassay (RIA) using commercially available kits (CIS Bio-International, Gif-sur-Ivette, France), as reported previously (6). TSH concentrations were measured by IRMA (CIS Bio-International). Intra- and interassay coefficient of variation (CV) for the TSH assay were 3.5 and 4.7%, respectively. Arginine vasopressin was measured by RIA (Buhllmann Laboratories, Shönensuch, Switzerland). The sensitivity of the AVP assay was 0.7 pmol/L and the intra- and interassay CV were 9 and 15%, respectively. All samples from a single patient were analyzed simultaneously.

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Compared with normal subjects, cortisol levels after suppression therapy were greater at 30, 45 and 90 min, but not at 60 min (Fig. 1A and 2B).

Discussion

In the present study, we showed for the first time that both acute hypothyroidism by ablative therapy and subclinical hyperthyroidism induced by thyroid suppression therapy followed by the ablation have
induced a hypersensitivity of ACTH to hCRH. Basal ACTH secretions were also increased after thyroid hormone treatment. These results indicate that both hypo- and hyperthyroidism induces an alteration of the HPA axis.

In the present study, we used a high dose of T4 (2.5µg/kg/day). Such high dose is often administered to patients after an ablative therapy with combination of surgery and radioactive iodine for treatment of thyroid cancer. These series of treatment (complete thyroid ablation with high dose of thyroid hormone) are sometimes performed to reduce the recurrence of cancer [11, 12]. However, such high dose of thyroid hormone may affect HPA axis, since we have previously reported that hyperthyroid patients show hyperactivity of HPA axis with augmented ACTH responses to exogenous hCRH, but with a practically normal response of cortisol [6]. In the present study, patients with sup-

Fig. 2  (A) ACTH and (B) cortisol responses to human hCRH (100 µg, i.v.) in hypothyroid patients (n = 14) before (●) and after (△) treatment of suppressive doses (2.5µg/kg/day) of thyroid hormone. (A) Basal ACTH levels were greater with suppressive doses of thyroid hormone. However, hCRH-stimulated increases in ACTH levels were similar before and after two thyroid hormone treatment for 2 months. (B) Basal and ACTH-stimulated cortisol levels remains similar before and after thyroid hormone treatment.
Thyroid hormone and HPA axis

increase in ACTH secretion at peak level in hypothyroid patient compared with that of control (Fig. 1A), whereas the increase in cortisol secretion in hypothyroid patients is only 20% greater than that of control at peak level (Fig. 1B), indicating that adrenocortical response to ACTH is decreased by hypothyroidism. Furthermore, although cortisol levels in hypo- and hyperthyroid patients are similar (Fig. 2B), adrenal secretion of cortisol may be greater in hyperthyroid patient, since UFC secretion is significantly increased in hyperthyroid patient (Table 1), which may reduce plasma cortisol levels. Thus, although both hyper- and hypothyroidism induced hypersecretion of ACTH to hCRH, and cortisol levels were also significantly greater compared with those of normal subject, hormonal status within HPA axis may be different between hyper- and hypothyroid conditions.

In conclusion, both hyper- and hypothyroidism may induce hypersecretion of ACTH in response to hCRH treatment. Adrenocortical hormonal status is differentially altered under these conditions. Currently, the major concern on the side effect of thyroid suppression therapy has been confined within cardiovascular system and bone mineral density. However, disruption of HPA axis by altered thyroid hormone status by thyroid suppression therapy may induce abnormal stress response, which may lead to depressive or cognitive disorders.

References

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pressive dose of thyroid hormone also showed hypersensitivity of ACTH to exogenous hCRH, indicating that subclinical hyperthyroidism induced by thyroid hormone suppression therapy also activated HPA axis. A previous study has shown that hyperthyroidism induces hyperactivity of HPA axis mainly by inducing hypersensitivity of cortisol to ACTH [13]. In the present study, we have demonstrated that ACTH is also hypersensitive to hCRH under hyperthyroid condition. On the other hand, a previous study has shown that prolonged hyperthyroidism or severe hyperthyroidism induces a decrease in cortisol reserve in adrenal gland, which may result in reduced level of plasma cortisol [13]. This may be not the case in the present study, since patients’ hyperthyroidism is rather mild. Thus, cortisol reserve in adrenal gland is not decreased to respond normally to the elevated ACTH (Fig. 2B).

In the present study, not only subclinical hyperthyroid patients, but also hypothyroid patients before the suppression therapy showed a greater response of ACTH secretion to hCRH. It may seem to be strange, but a previous animal study has also shown that hypothyroidism induced a greater response of ACTH secretion to CRH administration [14], which is consistent with present study. In this previous study, cortisol secretion to ACTH was decreased, resulting in hyposecretion of cortisol [14]. In the present study, hCRH administration induced approximately two-fold increase in ACTH secretion at peak level in hypothyroid patient compared with that of control (Fig. 1A), whereas the increase in cortisol secretion in hypothyroid patients is only 20% greater than that of control at peak level (Fig. 1B), indicating that adrenocortical response to ACTH is decreased by hypothyroidism. Furthermore, although cortisol levels in hypo- and hyperthyroid patients are similar (Fig. 2B), adrenal secretion of cortisol may be greater in hyperthyroid patient, since UFC secretion is significantly increased in hyperthyroid patient (Table 1), which may reduce plasma cortisol levels. Thus, although both hyper- and hypothyroidism induced hypersecretion of ACTH to hCRH, and cortisol levels were also significantly greater compared with those of normal subject, hormonal status within HPA axis may be different between hyper- and hypothyroid conditions.

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