European Journal of Endocrinology (2000) **142** 231–235 ISSN 0804-4643

CLINICAL STUDY

The effect of thyrotoxicosis on adrenocortical reserve

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Abstract

Objective: Variations in thyroid function are known to be associated with changes in adrenocortical activity. Previous studies in animals have suggested that long-standing hyperthyroidism may be associated with diminished adrenal functional reserve despite a continuing hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis. In humans, there has been no direct assessment of adrenal secretory reserve in clinical thyrotoxicosis. This study aimed to assess adrenocortical reserve in response to low-dose ACTH, following dexamethasone suppression, in patients with severe thyrotoxicosis.
Design and methods: Ten patients (four men and six women, 30–45 years) with severe long-standing thyrotoxicosis due to Graves' disease ($n = 6$) or toxic nodular goitre ($n = 4$) were studied at diagnosis and again when in a stable euthyroid state following drug therapy for 8–12 months. All patients underwent ACTH stimulation tests at 0800 h with $ACTH_{1-24}$ (Cortrosyn; 0.1 μg/kg body weight, i.v.) following overnight suppression of the HPA axis with dexamethasone (1 mg per os at 2300 h). Serum cortisol was assayed at −15, 0, 15, 30, 60 and 90 min after the administration of ACTH.
Results: The mean (± S.D.) peak and delta cortisol responses to ACTH (634.5 ± 164 nmol/l and 618 ± 196 nmol/l respectively), as well as the net area under the response curve (36 769 ± 12 188 nmol/l × min) in the hyperthyroid patients were significantly lower compared with the values when the same patients were euthyroid (911 ± 157 nmol/l, 905 ± 160 nmol/l and 57 652 ± 10 128 nmol/l × min respectively; $P < 0.005$). Subnormal peak cortisol responses (<500 nmol/l) were observed in two severely toxic patients. The findings were independent of the cause of thyrotoxicosis.
Conclusion: In patients with severe thyrotoxicosis, cortisol secretion in response to low-dose ACTH stimulation, following dexamethasone suppression, is lower in the hyperthyroid than in the euthyroid state. It appears that thyrotoxicosis is associated with subtle impairment of adrenocortical reserve.

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Introduction

Previous studies have extensively examined the effects of altered thyroid function on the secretion and metabolism of adrenocortical hormones. Thus, in thyrotoxic states the degradation of cortisol is accelerated but its rate of production is also increased, so that circulating levels of cortisol remain normal (1–4). These observations indicate that a degree of adrenocortical hyperactivity would be sustained in hyperthyroidism as a response to increased need. Indeed, experimental studies have provided evidence for centrally mediated hyperstimulation of the adrenals in rats with short- and long-duration hyperthyroidism (5). These studies have also shown that in long-term hyperthyroid animals, despite the continuing hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, the corticosterone response to direct stimulation with adrenocorticotrophin (ACTH), following dexamethasone suppression, was lower than normal. The latter findings suggest that in long-duration hyperthyroidism adrenal functional reserves might be compromised.

There has been no direct assessment of adrenocortical reserve in thyrotoxic states in humans. A case of thyroid storm, however, associated with subclinical hypoadrenocorticism in an elderly woman has been reported (6). Also, in thyroid storm, cortisol levels, while within the normal range, have been found to be lower than generally seen during periods of stress, suggesting relative adrenal insufficiency (7). Indeed, in thyrotoxic crisis, treatment with hydrocortisone is recommended because of the likelihood of associated adrenal insufficiency (8, 9).

Still, there is disagreement as to whether adrenal functional reserve is adequate in clinical hyperthyroidism. In this context, sensitive tests for assessing adrenal reserve become of significant importance. In recent years, stimulation with low-dose ACTH has been used as a sensitive test to detect subtle changes in adrenal function, which would be missed if the standard ACTH test is used (10–12). The low-dose ACTH test, following

dexamethasone suppression of endogenous ACTH, would therefore be a sensitive method to assess adrenocortical reserve *in vivo*.

In order to assess the impact of clinical hyperthyroidism on adrenocortical reserve we measured the cortisol responses to stimulation with low-dose ACTH, after dexamethasone suppression, in ten severely thyrotoxic patients before treatment and in the euthyroid state.

Materials and methods

Patients and study protocol

Ten patients (four men and six women, mean age 38.5, range 30–46 years) with unequivocal severe hyperthyroidism were selected consecutively for the study. None had been treated previously. The diagnosis and aetiology of hyperthyroidism were established by clinical evaluation and laboratory tests, including serum total thyroxine (TT4), total triiodothyronine (TT3) and thyrotrophin (TSH) concentrations and anti-thyroid (anti-microsomal (anti-M) and anti-thyroglobulin (anti-T)) antibodies. Six of the patients had Graves' hyperthyroidism as judged by the presence of a diffuse goitre and/or thyroid ophthalmopathy together with positive anti-thyroid antibodies. The remaining patients had toxic nodular goitre. These patients had no stigmata of Graves' disease, and were negative for thyroid antibodies, but they all had nodular goitre confirmed by ultrasound or thyroid isotope scanning (Table 1). All patients were studied in the hyperthyroid state, before starting treatment and again 8–12 months following therapy with anti-thyroid drugs, when they were in a stable euthyroid state at a maintenance dose (2.5–5.0 mg/day) of carbimazole or methimazole.

The patients were admitted to the endocrine investigation unit the day before the tests. At 2300 h each patient was given dexamethasone (1 mg per os) to inhibit endogenous ACTH and cortisol secretion. At 0800 h the next morning and while the patient was fasted, plasma samples were taken before (−15 and 0) and at 15, 30, 60 and 90 min after a bolus i.v. administration of $ACTH_{1-24}$ (Cortrosyn; Organon International, Oss, The Netherlands) at a dose of 0.1 μg/kg body weight (BW). The samples were stored at −20 °C before analysis.

Methods

Cortisol was measured with a fluorescent polarization assay using a TDX Abbott Instrument (Abbot Park, IL, USA). The intra- and interassay coefficients of variation (CVs) for the range of cortisol concentrations measured were 3–7% and 4–8% respectively. TT4 was determined by a fluorescent polarization assay in an Abbott TDX instrument. The intra- and interassay CVs were 3.6% and 4.3% respectively. TT3 was measured by a solid phase time-resolved fluoroimmunoassay (Delfia; Wallac, Turku, Finland). The intra-assay CV was 2.5% and the interassay CV 5.5%. TSH was determined by the microparticle enzyme immunoassay on an Abbott IMX instrument (intra- and interassay CVs were 3% and 4% respectively). Anti-M and anti-T antibodies were determined using a commercial kit (Thymune M, Thymune T; Wellcome Diagnostics, Temple Hill, Dartford, Kent, UK).

Statistical analysis

Results are expressed as mean ± S.D. throughout the study. The total area under the curve (AUC) of cortisol, after stimulation with ACTH, was calculated by integration of hormone levels in international (SI) units, and time of testing in minutes. The AUC net from the baseline (net AUC) was calculated as the difference between total AUC and basal AUC (baseline times length of the testing). Delta was calculated as the difference between the peak response and baseline (mean of the two basal determinations). Analyses of peak, delta, total and net AUC of plasma cortisol

Table 1 Demographic data and results of thyroid function tests at the hyperthyroid (Hyper) and euthyroid (Eu) state and anti-M and anti-T antibodies at diagnosis of the patients.

Case no.	Age (years)	Sex (M/F)	TT4 (nmol/l) (Hyper/Eu)	TT3 (nmol/l) (Hyper/Eu)	TSH (mU/l) (Hyper/Eu)	Antibodies		Diagnosis
						Anti-M	Anti-T	
1	35	F	282/104	5.5/2.1	< 0.02/1.3	1/400	1/320	GD
2	43	F	250/122	5.2/2.1	0.04/2.9	–	–	TNG
3	32	F	270/99	6.9/1.5	< 0.02/3.3	1/400	1/240	GD
4	44	M	> 322/126	8.4/1.8	< 0.02/1.3	1/960	1/320	GD
5*	32	F	> 322/93	9.8/1.8	< 0.02/2.7	1/800	1/400	GD
6	30	F	264/86	7.2/1.5	< 0.02/2.6	–	–	TNG
7*	46	F	> 322/84	10/2.0	< 0.02/1.7	1/640	1/320	GD
8	39	M	309/94	8.6/2.0	< 0.02/2.8	–	–	TNG
9	41	M	290/102	6.9/1.7	< 0.02/1.2	1/960	1/400	GD
10	43	M	304/95	7.3/1.8	< 0.02/1.3	–	–	TNG
Normal			69–154	1.5–3.0	0.5–5.0	< 1/80	< 1/40	–

* Patients no. 5 and 7 also had fever (37.8 °C) at diagnosis.
GD = Graves' disease, TNG = toxic nodular goitre.

responses were performed using one-way ANOVA followed by Fisher's paired least significant difference (PLSD). All tests for statistical significance were two tailed. An alpha of $P \leq 0.05$ was required for significance.

Results

Demographic and clinical data

The demographic data and results of the patients' thyroid function tests at the time of diagnosis and following treatment with anti-thyroid drugs are shown in Table 1. As judged from the clinical picture and the laboratory findings, all patients had severe thyrotoxicosis, but none was considered to be in frank thyroid storm. Patients no. 5 and no. 7 also had pyrexia (37.8 °C) and were judged to be in a more severe toxic state. Based on the history, the duration of the symptoms prior to diagnosis was estimated to be 4–6 months.

Cortisol responses to ACTH stimulation

The mean (± S.D.) plasma cortisol responses to low-dose ACTH before and after treatment in the same patients are given in Fig. 1. Cortisol levels increased rapidly and reached peak levels between 60 and 90 min in both thyroid states. The baseline plasma cortisol levels were low, consistent with adequate suppression of the endogenous HPA axis following the administration of dexamethasone.

The adrenal reserve, as indicated by the plasma cortisol responses to ACTH, was significantly attenuated in the thyrotoxic compared with the euthyroid state. Thus, not only was the cortisol response significantly lower at each time point of the study, but the mean peak, delta and net integrated cortisol responses were also significantly lower before treatment compared with the responses seen after treatment ($P < 0.005$ by ANOVA followed by Fisher's PLSD, Figs 1 and 2). The above responses were independent of the cause of hyperthyroidism. In the two patients (no. 5 and no. 7), who were judged to be more severely toxic, the peak cortisol responses were subnormal (< 500 nmol/l) by standard criteria (13).

Discussion

The present study has shown that adrenocortical reserve, as assessed by direct stimulation with low-dose ACTH, following dexamethasone pretreatment, is attenuated in severely hyperthyroid patients. This hyporesponsiveness appears to be a reversible phenomenon and returns to normal upon improvement of the clinical state.

A low, but adjusted for BW, dose of $ACTH_{1-24}$ (0.1 μg/kg BW) was used in our patients rather than the fixed 1 μg dose, in order to account for changes in the patients' weight, ensuring equivalent blood ACTH levels at both the hyperthyroid and euthyroid phase. Further, it has been reported that an injection of 5–7 μg $ACTH_{1-24}$ would achieve plasma ACTH levels equivalent to those induced by a major stress and that stimulation with this dose of ACTH would effectively detect subtle changes in the HPA axis (14, 15).

Apart from data indicating accelerated disposal of cortisol in hyperthyroidism and increased number of cortisol secretory episodes (16, 17), there are few and conflicting data regarding the impact of hyperthyroidism on adrenal functional reserve. The response to an acute challenge, such as that imposed by insulin-induced hypoglycaemia, has been reported to be normal

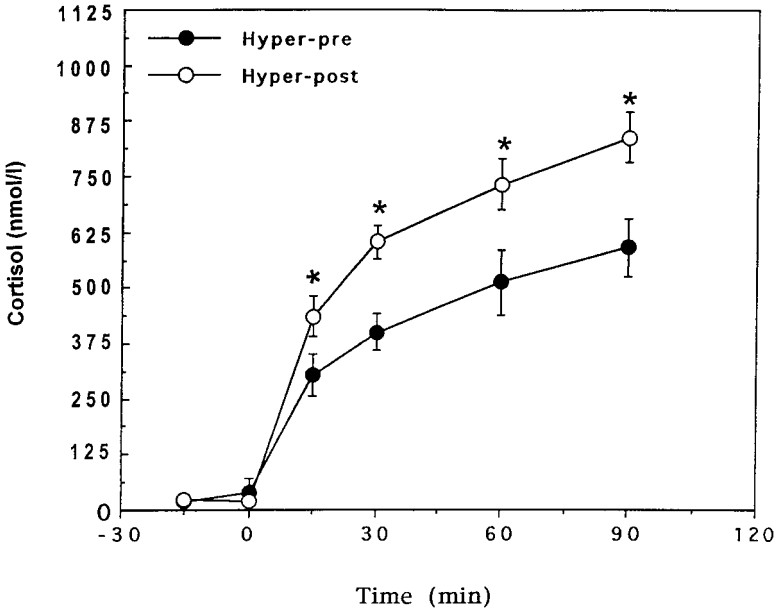
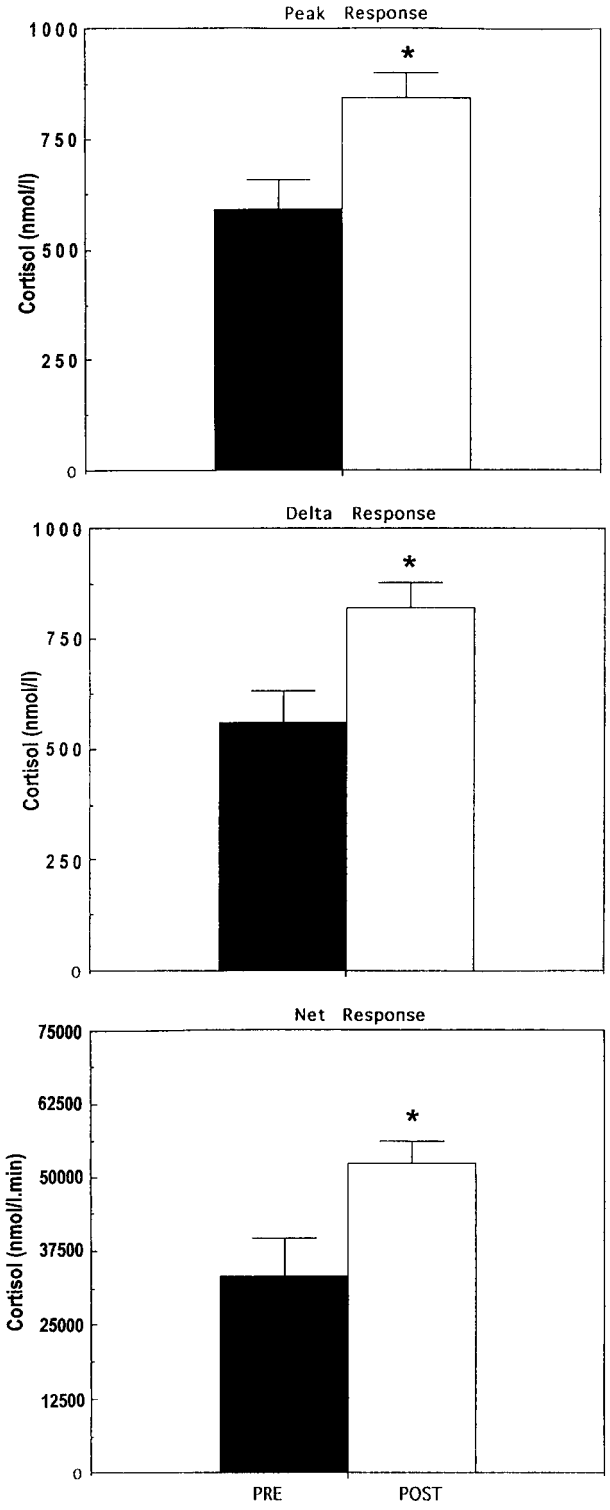


Figure 1 Responses of plasma cortisol to an i.v. bolus administration of synthetic $ACTH_{1-24}$ (0.1 μg/kg BW) in the patients at the hyperthyroid (hyper-pre) and euthyroid (hyper-post) state, following suppression of endogenous ACTH secretion by dexamethasone. Each point represents the mean of values obtained from the patients; range bars are S.D. *$P < 0.05$ vs the response elicited by ACTH in the hyperthyroid state (by one-way ANOVA followed by Fisher's PLSD).

in some, or impaired in other, more severely thyrotoxic, patients (18, 19).

At a clinical level, the present study is the first to directly assess adrenocortical reserve in patients with severe long-standing thyrotoxicosis. The results are in agreement with those obtained from experimental studies in long-term hyperthyroid rats using a similar protocol (5, 6). Previous experimental studies have also shown that adrenal steroidogenesis is impaired by pharmacological doses of T4 (20). It appears, therefore, that the duration and severity of the hyperthyroid state may be important factors determining the level of the functional capacity of the adrenals. This, in part, may explain the apparently conflicting previous clinical observations in this field. The patients in our study were judged to have had sustained and severe hyperthyroidism. In this context, in the two more severely affected patients, peak cortisol responses to ACTH stimulation were subnormal by standard criteria (13).



The mechanism for the attenuated adrenal response observed in the thyrotoxic phase of our patients is not clear considering that many factors may influence serum cortisol concentration. It has been demonstrated that thyrotoxicosis increases the secretion rate of cortisol, influences the rate of cortisol degradation and affects its metabolism qualitatively (i.e. thyroid hormones stimulate the conversion of cortisol to cortisone) (17). It may be that, in sustained thyrotoxicosis, the adrenals secrete at their maximal rate to keep up with the increased metabolic degradation of cortisol and thus their reserve in response to further stimulation with ACTH is diminished. This burden may be more severe in thyroid storm culminating in a relative adrenal insufficiency.

Two points need further consideration in the interpretation of the data. The possibility that, after injection, serum levels of $ACTH_{1-24}$ in the hyperthyroid phase were lower due to increased clearance, thereby resulting in the present findings, was not directly tested in this study. However, on the basis of existing evidence, this possibility seems unlikely. This question was addressed in a previous study, which showed that the clearance of $ACTH_{1-24}$ from plasma was not significantly affected under similar conditions of testing in experimentally induced hyperthyroidism (5). Furthermore, if the findings were simply the result of the increased clearance of ACTH and/or cortisol, it would be expected that not only the magnitude of the cortisol response in the hyperthyroid phase would be smaller but also the duration of the response would be shorter and this was not evident in our data. In addition, the prior

Figure 2 Peak, delta and net AUC plasma cortisol responses to an i.v. bolus administration of synthetic $ACTH_{1-24}$ (0.1 μg/kg BW) in the patients at the hyperthyroid (filled columns) and euthyroid (empty columns) states, following dexamethasone suppression of endogenous ACTH secretion. Each column represents the mean of values obtained from the patients; range bars are S.D. *$P < 0.05$ vs the response elicited by ACTH in the hyperthyroid state (by one-way ANOVA followed by Fisher's PLSD).

suppression of endogenous ACTH and cortisol by dexamethasone pretreatment allowed only the *de novo* secretion of cortisol in response to acute ACTH stimulation to be measured and this would mainly reflect adrenal reserves.

The corticosteroid-binding capacity of serum, which may also influence serum concentrations of cortisol, has been reported to be normal or raised in hyperthyroidism (21, 22). This, too, was not measured in our patients, but even if this were raised in the hyperthyroid phase it would have affected serum cortisol levels in the opposite way to our findings and therefore could not account for the differences in the cortisol responses observed in our patients.

In conclusion, the present study has shown attenuated adrenal cortisol responses to low-dose $ACTH_{1-24}$ stimulation, after prior suppression with dexamethasone, in severely thyrotoxic patients. These findings would indicate that sustained severe thyrotoxicosis may be associated with diminished adrenocortical reserve.

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Received 26 August 1999
Accepted 22 October 1999