CLINICAL STUDY

Decreased pituitary sensitivity to glucocorticoids in endurance-trained men

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Abstract

Objective: Muscular exercise induces hypothalamo-pituitary-adrenal (HPA) axis activation and when regularly repeated, as in endurance training, leads to HPA axis adaptation. To assess whether non-professional endurance-trained (ET) men with a substantial training load and no clinical or biological features of HPA axis overactivity can present subtle alterations of HPA axis sensitivity to glucocorticoid negative feedback, nine ET men were subjected to HPA axis testing using the dexamethasone–corticotrophin-releasing hormone (CRH) test.

Design: Nine endurance-trained men and eight healthy age-matched sedentary men were studied. Morning plasma cortisol and 24 h urinary free cortisol (UFC) were determined and a low dose dexamethasone suppression test (LDDST) was performed followed by CRH stimulation (dexamethasone–CRH test).

Results: After a day without physical exercise, at 0800 h, plasma ACTH and cortisol concentrations, and the 24 h UFC and UFC/urinary creatinine (UC) ratio were similar in ET and sedentary men. By contrast, clear differences between the groups were seen in cortisol and ACTH responses to the dexamethasone–CRH test. In eight ET subjects, after LDDST, basal ACTH and cortisol levels were similar to those of sedentary men, whereas one ET subject displayed a poor suppression of cortisol level (131 nmol/l). After injection of CRH, however, three of nine ET men's cortisol levels were not suppressed by dexamethasone but instead displayed significant CRH-induced increase (peak cortisol: 88, 125 and 362 nmol/l). No sedentary subject exhibited any increase in cortisol levels.

Conclusion: Three of nine ET men with a mean maximum rate of O₂ uptake ($V_{O_{2, \max}}$) of 61 ml/kg per min, running 50–70 km per week, were resistant to glucocorticoid suppression during the combined dexamethasone–CRH test.

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Introduction

Muscular exercise represents a physiological challenge that activates the hypothalamo-pituitary-adrenal (HPA) axis (1). Several lines of evidence suggest that exercise-induced repeated activations of the HPA axis such as in endurance-trained (ET) men, lead to an HPA axis adaptation. More specifically, when sedentary and healthy ET men are compared in resting, unchallenged conditions, no difference in HPA axis activity is seen. Indeed, we and others have previously reported normal plasma cortisol values with preserved nycthemeral cortisol rhythm in ET men compared with sedentary subjects (2, 3), as well as normal 24 h UFC after a day with no training (4). By contrast, when the HPA axis is challenged, results from ET men differ from those of

sedentary men. For example, after an exercise-induced cortisol increase, the subsequent stimulation exerted by a meal does not elicit a rise of cortisol levels in sedentary men, whereas in ET men a marked cortisol increase occurs (3). These findings suggesting a decreased sensitivity to glucocorticoid negative feedback in healthy ET men may reflect allostatic modifications of the HPA axis due to repeated exercise-induced HPA axis activation (5).

There is a lingering belief in the literature that endurance training implies hypercortisolism (1, 6). The aim of this work is to assess HPA axis activity in ET men in order to challenge the recurrent view that repeated exercise such as endurance training induces an overactivity of the HPA axis. For this purpose, nine ET men and eight sedentary controls were submitted to

determinations of morning plasma cortisol, 24 h UFC, low dose dexamethasone suppression test (LDDST) and CRH stimulation after the LDDST.

We demonstrate here that non-professional ET men with a substantial training load (50–70 km run per week) have no clinical nor biological features of HPA axis overactivity but that well-adapted ET men may present subtle alterations of HPA axis sensitivity to glucocorticoid negative feedback.

Subjects and methods

Subjects

Two groups of healthy male adults volunteered for this study: eight sedentary men (<1 h per week of physical activity for more than 3 years) and nine ET men (50–70 km run per week for at least 4 years and having completed a marathon (42.125 km) in less than 3 h 30 min). All subjects were free of any medication. None had a personal or family history of psychiatric disorders or diabetes mellitus. None smoked or were heavy drinkers. Their mean $\pm$ S.E.M. age and body mass index were: 31.9 ± 2.5 vs 26.6 ± 2.4 years and 22.0 ± 0.4 vs 22.9 ± 1.0 kg/m², for ET vs sedentary men ($P > 0.05$ for both). The Hospital Ethics Committee approved the study and informed written consent was obtained from all the subjects.

Experimental design

The subjects reported to the laboratory on two occasions: once for a screening visit and once for a test visit (dexamethasone–CRH test). The screening visit included physical examination, venous sampling for determination of basal hormones concentrations and, in the case of endurance-trained men, progressive and exhaustive treadmill exercise to determine maximal oxygen uptake ($V_{O2\text{ max}}$), ventilatory and metabolic parameters of intermediary graduated speeds, maximal cardiac frequency. The treadmill started at 8 km/h and the speed was increased in steps of 0.5 km/h at 2 min intervals, until exhaustion. Their $V_{O2\text{ max}}$ was 61.7 ± 1.1 ml/kg per min.

During the 2 weeks preceding the test visit, in the endurance-trained group, training was standardised with four to five exercise sessions per week corresponding to 50–70 km of running per week. Previous research has shown that a single session of daytime exercise increases UFC (7). For this reason, we chose to measure 24 h UFC on a rest day during the 2 weeks preceding the dexamethasone (Dex)–CRH test. Plasma cortisol was determined at 0800 h on the following morning, after an overnight fast. Urinary free cortisol (UFC) was determined on urine samples collected from 0800 h to around 0800 h (24 h UFC). Urinary creatinine (UC) was determined on the same samples.

All subjects underwent psychological testing. The French short version of the Center for Epidemiological Studies Depression Scale was employed to detect depression (8) (a score of more than 23 is consistent with depression). The mean values were 13.8 ± 2.0 vs 14.8 ± 3.0 (ET vs sedentary men, respectively; $P > 0.05$).

For Dex–CRH tests subjects began an oral course of eight doses of 0.5 mg dexamethasone orally every 6 h, at noon 2 days before the test (9). The last dose of dexamethasone was administered at 0600 h, 2 h before the scheduled start of the CRH test. In ET men, no exercise was allowed during the 2 days of dexamethasone intake. After an overnight fast, oCRH (UCB, Braine L'Alleud, Belgium) was injected i.v. (1 μ g/kg) between 0800 and 0810 h in the outpatient endocrinology ward. Plasma samples were assayed for cortisol and ACTH at -15 and -5 min before CRH stimulation and then at 5, 10, 15, 30, 45 and 60 min after CRH. Plasma dexamethasone concentration was measured in the -15 min sample.

Assays

Plasma cortisol concentration was determined by a solid phase RIA (Cortisol, Immunotech, Marseille, France). The intra-assay coefficient of variation (c.v.) was 3.5–5% and the inter-assay c.v. was 5.5–9% for plasma cortisol concentrations for 37 and 740 nmol/l respectively. Values under the limit of detection of the assay (20 nmol/l) were considered to be 19 nmol/l for the purpose of calculations. Plasma ACTH concentration was determined by immunoradiometric assay (ACTH IRMA, Immunotech, Marseille, France). This procedure has an intra-assay c.v. between 6.9 and 9%; the inter-assay c.v. ranges between 6.1 and 9.6% for ACTH concentrations between 2.2 and 16.2 pmol/l, respectively. Values under the limit of detection of the assay (2.1 pmol/l) were considered to be 2.0 pmol/l for the purpose of calculations.

The following hormones were measured in duplicate by radioimmunoassay, according to manufacturer's instructions: plasma free testosterone (Coat-A-Count Free Testosterone, USA, distributor Behring Diagnostic, France), testosterone (³H-Testosterone, Biomérieux, France) LH and FSH (Biomérieux, France), TSH (TSH IRMA, Immunotech, Marseille, France). Plasma prolactin was measured using a chemiluminometric assay on an ACS 180: SE automate analyser (Bayer Diagnostics, France). Intra-assay c.v. for all measurements ranged from 2 to 4%, inter-assay c.v. from 2.6 to 6%.

Plasma dexamethasone concentrations were determined by high-performance liquid chromatography according to a variant of a method described elsewhere (10). The detection limit in plasma was 2 ng/ml and intra- and inter-assay c.v.s were below 10% for concentrations of 5, 10, 15 or 20 ng/ml.

All samples were run in duplicate. 24 h UFC was determined by RIA on urine samples collected from 0800 h one day to 0800 h the next day using a commercial kit (CORT-CT2, Cis Bio International; normal values: 55–276 nmol/24 h). The inter- and intra-assay c.v.s were 8.9 and 4.2% respectively. Urinary creatinine (UC) was determined by the Jaffe method.

Statistical analysis

Data are presented as means $\pm$ S.E.M. Comparisons between groups were calculated using the Mann-Whitney U test. For the purpose of analysis of the Dex-CRH test, after logarithmic data transformation because cortisol and ACTH values were non-normally distributed, an ANOVA with repeated measures was performed employing a conservative (Tukey's HSD with unequal *n*) F test. Significance was accepted at the $P < 0.05$ level.

Results

Baseline hormonal data

At 0800 h, after a day without physical exercise, plasma ACTH and cortisol concentrations were similar in ET and sedentary men: ACTH, 4.60 ± 0.70 vs 3.25 ± 0.65 pmol/l; cortisol, 608.8 ± 45.4 vs 558.0 ± 51.0 nmol/l (ET vs sedentary men, $P > 0.05$ for both). No significant differences in plasma levels of TSH, prolactin, FSH or LH were found between ET and sedentary men (data not shown). Plasma testosterone and free testosterone concentrations were lower in ET (testosterone, 20.72 ± 0.58 vs 26.71 ± 0.85 pmol/l; free testosterone, 49.43 ± 1.65 vs 78.12 ± 7.24 pmol/l; ET vs sedentary men, $P < 0.05$). Plasma free testosterone but not testosterone concentrations were below normal age-related range in ET men (testosterone, 10–40 pmol/l; free testosterone, 60–140 pmol/l).

The 24 h UFC and UFC/UC ratio realised 24 h after the last training session, were also similar in ET and sedentary men: UFC, 146.3 ± 13.3 vs 115.4 ± 9.7 nmol/24 h; UFC/UC ratio, 10.7 ± 0.9 vs 10.8 ± 1.1 nmol/ μ mol (ET vs sedentary men, $P > 0.05$ for both).

Dex-CRH testing

After completion of the LDDST, all sedentary men and eight of nine ET men had ACTH levels below 2 pmol/l and cortisol levels below 50 nmol/l (plasma cortisol threshold for a positive LDDST) (11). One ET subject had lowered only his plasma cortisol and ACTH levels (131 nmol/l and 2.2 pmol/l, plasma cortisol and ACTH respectively) compared with his 0800 h preDex cortisol and ACTH values (481 nmol/l and 4.5 pmol/l).

Figure 1 Results (means $\pm$ S.E.M.) of the Dex-CRH test in sedentary subjects (SED) and endurance-trained (ET) men. Analysis by ANOVA with repeated measures was performed followed by Tukey's HSD with unequal *n* test to describe the probability of difference in hormonal concentrations between ET and sedentary men at different times. Significance level was set at $P < 0.05$. *Significant difference at designed time between ET and sedentary men.

After CRH injection, plasma ACTH and cortisol levels did not change significantly at any time in sedentary men (peak ACTH < 2.2 pmol/l; peak cortisol < 20 nmol/l) (Fig. 1). Although plasma ACTH levels were not significantly different between both groups at any time, taken as a whole, the mean plasma cortisol levels were significantly greater in ET than in sedentary men at any time ($P = 0.001$), both before and after CRH injection. However, if individual responses are analysed, three of nine ET subjects had detectable cortisol values after LDDST (26, 37 and 131 nmol/l) that rose to 68, 57 and 203 nmol/l respectively, 15 min after CRH injection and peaked at 88, 125 and 362 nmol/l 45–60 min after CRH injection (Fig. 2). In two ET subjects with post-LDDST plasma cortisol levels below 50 nmol/l, cortisol secretion was resistant to the Dex suppression following CRH administration whereas plasma ACTH remained below the detection threshold of the assay for the first and peaked

Figure 2 Individual data from the Dex-CRH test in ET men. The results are subdivided as follows: results of the three subjects (different symbol for each) who showed resistance to Dex suppression after CRH (dashed lines) (Dex responders) and results of the remaining six Dex non responders (no symbols, continuous line).

at 2.8 pmol/l at 15 min for the second. A third ET man had inadequately suppressed plasma cortisol levels during LDDST, and his ACTH and cortisol were further stimulated after CRH (Fig. 2).

The mean plasma Dex levels measured just before CRH administration were similar in ET and sedentary men: 7.4 ± 0.5 vs 6.8 ± 0.3 ng/ml (ET vs sedentary men, $P > 0.05$). The plasma Dex levels of the three ET men with detectable plasma cortisol were 7, 6 and 9 ng/ml. Plasma Dex greater than 5.6 nmol/l is considered necessary to achieve negative feedback inhibition of the HPA axis (12).

Discussion

Our ET men showed no clinical evidence of hypercortisolism. Furthermore, 0800 h plasma cortisol and 24 h UFC were normal and similar to those of age-matched sedentary subjects. When biologically tested, eight of nine ET subjects' cortisol levels were adequately

suppressed after LDDST but three of nine ET subjects' cortisol levels were resistant to Dex suppression when stimulated by oCRH.

As we have previously reported similar plasma ACTH and cortisol concentrations between 0800 and 1700 h in resting ET men compared with resting sedentary men (3), the normal 0800 h plasma cortisol and normal 24 h UFC displayed by ET men on their day 'off' exercise training were expected. The normality of the HPA axis profile was further confirmed by the adequate suppression of plasma cortisol after the LDDST in eight of nine ET men, suggesting that the resting unchallenged set-point for glucocorticoid negative feedback was the same for ET and sedentary normal subjects.

During the Dex-CRH test, however, in 33% of ET men the HPA axis was resistant to Dex suppression when stimulated by CRH and then differed from that of sedentary men. This is comparable to the findings of Petrides *et al.* (13) who reported that 36% of moderately trained males showed Dex (4 mg) unsuppressible exercise-induced activation of the HPA axis. In our group of ET men with a higher training load (50–70 vs 24–40 km/week, our study vs Petrides' study), we report a similar prevalence of glucocorticoid 'resistance' (3/9 subjects vs 4/11 subjects). Recently, De Kloet (14) has demonstrated that Dex poorly enters the brain, implying that the major target for Dex is the pituitary. This being the case the results of Dex-CRH testing illustrate a decreased pituitary sensitivity to glucocorticoids in a subset of ET men. Vasopressin (VP) could be a key component at this pituitary level, as it attenuates the inhibitory effect of glucocorticoids on CRH-stimulated ACTH secretion (15). This suggests that a higher VP/CRH ratio may occur in humans under repeated exercise-induced HPA axis activation (16). Multiple other ACTH secretagogues such as tumour necrosis factor α and IL-6 can also influence the tissue sensitivity to glucocorticoids (17). The interactions between the HPA and the hypothalamo-pituitary-testicular (HPT) axis may also contribute. As has been previously described, free testosterone concentrations in ET men are lower than those in sedentary subjects (18–20), the apparently inappropriate normal concentrations of LH with respect to low plasma free testosterone concentrations favouring a centrally mediated effect. Viau *et al.* (21) recently reported that in male rats the inhibitory effects of corticosterone on stress-related HPA function required testosterone. These results are particularly interesting in the context of our ET men who display both decreased free testosterone concentrations and decreased pituitary sensitivity to glucocorticoids. Nevertheless, the free testosterone concentrations of the three ET men who showed resistance to Dex suppression were similar to those of the other six ET men (data not shown). On the other hand, elevated exercise-induced activation of the HPA axis may also contribute to lowering testosterone concentrations.

Cumming *et al.* (22) suggested that the elevation of cortisol itself during pre- and post-exercise may contribute to the suppression of hypothalamic release of gonadotropin-releasing hormones. Moreover, endogenous CRH exerts its inhibitory effect on the hypothalamo-pituitary-gonadal axis primarily at the level of the hypothalamic gonadotropin-releasing hormone pulse generator (23). Whatever the mechanism responsible for the decreased levels of gonadal steroids in endurance-trained athletes, it is of interest to note that considerable cross-talk exists between the HPA and gonadal neuroendocrine systems (21).

Lastly, differences in glucocorticoid sensitivity are probably not restricted to the pituitary, as we have recently demonstrated that *in vitro* sensitivity of monocytes to dexamethasone is reduced in ET compared with sedentary men (24). These modifications, within limits, may prove adaptive and protective against prolonged exercise-induced cortisol secretion.

The interindividual variability of this allostatic response to repeated exercise-induced cortisol secretion may have also relevance to understanding the processing of HPA axis adaptation to endurance training. The nine ET subjects were selected because of similar conditioning levels ($V_{O2\text{ max}}$), and similar training load (distance ran per week). Moreover, plasma Dex concentrations were equivalent and no depression features were evidenced from the depression scale. Nevertheless, the use of Dex–CRH revealed, although in a limited number of subjects, the existence of a variable sensitivity to exogenous glucocorticoids within the group of ET men with two different profiles of HPA responses: non-responders (6/9) and responders (3/9). The finding that two of the ET responders, who were adequately Dex suppressed, increased their plasma cortisol after CRH injection without concomitant ACTH increase is intriguing. The lack of significant elevation in ACTH may reflect too high an assay threshold for ACTH detection, insufficient blood sampling frequency leading to underestimation of the amount of ACTH released from the pituitary, or direct stimulation of adrenocortical cells by secretagogues other than ACTH, such as CRH (25) or VP (26). It is also tempting to speculate that enhanced stimulation of the pituitary–adrenal axis due to endurance training induces adrenal hypertrophy, a feature generally associated with increased adrenal sensitivity to ACTH. Nevertheless, this hypothesis of increased adrenal sensitivity to ACTH in endurance-trained men remains unlikely for the following reasons: (i) In 1975, Tharp (27) had suggested that the athletes may have reduced adrenal sensitivity to ACTH, a hypothesis which was in keeping with the results of Inder *et al.* (28) who found elevated basal levels of ACTH without significant elevation in cortisol levels in highly trained male athletes, compared with sedentary controls. (ii) We have previously reported an increased ACTH/cortisol ratio during post-exercise recovery in ET men compared

with matched sedentary subjects, suggesting that, at least in post-exercise recovery, ET men may have a decreased adrenal sensitivity to ACTH (3). In contrast to the huge literature about the HPA response to acute exercise, no information about adrenal weight in ET men is presently available. The third ET responder (i) was not adequately suppressed by Dex suggesting a resetting of his HPA axis at a higher point and (ii) presented true ACTH and cortisol responses to CRH after Dex. The mechanisms that operate in the different subsets of ET men cannot be inferred from the present study. Interindividual variations of glucocorticoid sensitivity due to polymorphism of the glucocorticoid receptor in normal subjects have been reported (29). Nevertheless, we believe that the heterogeneity of the sensitivity to Dex within the group of ET men, represents different adaptive responses of the HPA axis to its repeated stimulations. It is not known whether the CRH response after adequate or inadequate Dex suppression in ET men represents an intermediary step along a continuum that has the potential to progress towards an extreme end point, i.e. hypercortisolism due to overtraining, or whether they represent an end-point of successful acclimation to exercise training. Follow-up of these ET men should determine the evolution of their HPA axis profiles with regards to training load.

Lastly, one has to notice that the Dex–CRH test has been proposed for the differential diagnosis of hypercortisolism (functional vs tumoural) with no demonstrated false positive in normocortisuric (24 h UFC) control subjects (9, 30). During the Dex–CRH test, zero overlap of cortisol values between Cushing's disease (CD) and pseudo-Cushing subjects prompted the authors to propose a cortisol value of 38 nmol/l 15 min after CRH injection as a cut-off value for the diagnosis of CD (30). We report here the case of nine ET subjects, with a mean $V_{O2\text{ max}}$ of 61 ml/kg per min, running 50–70 km/week, who differ clinically and biologically from CD and pseudo-Cushing states, but who displayed for three of them, cortisol levels above 38 nmol/l after CRH stimulation, i.e. in the range of CD subjects. From a practical point of view, although the clinical appearances of trained athletes, no more than anorectic women, do not mimic Cushing's syndrome, it should be remembered that these situations are false positives of the Dex–CRH test (31).

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