Reduced Cortisol Potentiates the Exercise-Induced Increase in Corticotropin to a Greater Extent in Trained Compared With Untrained Men

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We examined the effect of acute exercise and reduced cortisol on pituitary and adrenal responsiveness and the impact of reduced plasma cortisol on maximal oxygen consumption ($\dot{V}O_2$max) in eight trained (T) and eight untrained (UT) males. Subjects completed two graded maximal exercise tests (GXT), each preceded by either overnight metyrapone (MET) or placebo (PLA) administration. Blood samples were collected before and after GXT. With PLA, resting corticotropin (ACTH) levels were higher in T versus UT men; however, cortisol and 11-deoxycortisol were similar between groups. Following GXT on PLA, cortisol was unchanged but 11-deoxycortisol increased in both groups; however, ACTH increased only in UT men. For both groups, cortisol, 11-deoxycortisol, and ACTH were different post-GXT with MET versus PLA. Furthermore, following GXT with MET, the ACTH response was greater in T versus UT subjects. $\dot{V}O_2$max was not altered by MET in either group. We conclude that (1) at rest, only ACTH levels differed between T and UT men; (2) individually, the GXT and MET provide a similar ACTH response in UT but not in T subjects; (3) when GXT and MET are superimposed, they provide a stronger stimulus to pituitary and adrenal reserve than either test alone; (4) the combination of MET and GXT elicits a greater ACTH response in T compared with UT men; and (5) an acute reduction in plasma cortisol does not alter $\dot{V}O_2$max.

THE ONSET OF HEAVY EXERCISE activates the hypothalamic-pituitary-adrenal (HPA) axis, and the repeated stress associated with regular physical training may result in alterations in the sensitivity of one or more of the components of the HPA axis.[1-7] Investigators have reported increased pituitary and/or adrenocortical sensitivity to exogenous corticotropin-releasing hormone (CRH) in trained subjects,[2,4] whereas others have reported decreased sensitivity.[5,6] Furthermore, overtrained athletes show a blunted HPA axis response to insulin-induced hypoglycemia,[1] which may be explained in part by the mild hypercortisolism resulting from training.[1,5,6] Although it has been shown that decreasing glucocorticoid negative feedback increases pituitary sensitivity to exogenous CRH,[8-10] it is unknown whether suppressing glucocorticoid negative feedback will increase the magnitude of exercise-induced corticotropin (ACTH) secretion.

The exercise-induced elevation of growth hormone and cortisol observed in a group of highly trained rowers may improve performance by creating favorable conditions for protein synthesis during the recovery period.[7] Chronic deficiency of cortisol is associated with fatigue, a common symptom of patients with Addison's disease,[11,12] and in the untreated state, these patients show reduced exercise tolerance that is restored by glucocorticoid administration.[12] However, an acute increase in glucocorticoid availability does not alter maximal oxygen uptake ($\dot{V}O_2$max) in trained or untrained healthy subjects.[13] It is unknown whether an acute reduction in cortisol will alter the work capacity in a manner similar to that observed with chronic cortisol deficiency.

Metyrapone (MET) is a pharmacologic agent that reversibly inhibits the synthesis of cortisol in the adrenal cortex by blocking the 11β-hydroxylation of 11-deoxycortisol to cortisol.[14] As a consequence of the blockade, 11-deoxycortisol increases, cortisol decreases, and ACTH release is stimulated.[15] The single-dose MET test (MET administered at midnight followed by a single blood sample at ~8 AM) is used to examine pituitary and/or adrenocortical function in subjects with suspected HPA axis abnormalities.[16,17] The MET test has not been used to identify any alterations that may exist between physically trained and untrained subjects.

Based on this information, we hypothesized that (1) reducing cortisol via MET administration will alter the ACTH response to a maximal graded exercise test (GXT); (2) pituitary sensitivity is altered by physical training and will result in differences in plasma ACTH in trained (T) versus untrained (UT) men following maximal exercise during a period of low cortisol (ie, MET administration); (3) the training state will alter pituitary sensitivity such that the resting ACTH response after a single-dose MET test will differ between T and UT subjects; and (4) an acute reduction in cortisol will alter $\dot{V}O_2$max. To test these hypotheses, both T and UT men were studied at rest and following maximal exercise under normal and low cortisol conditions.

SUBJECTS AND METHODS

Subjects

Eight T and eight UT healthy males volunteered to participate in this study. Each subject completed a health history questionnaire and signed an informed-consent form approved by The University of Tennessee-Knoxville Institutional Review Board. The age, height, and mass were 28.1 ± 3.3 versus 28.5 ± 3.2 years, 1.79 ± 0.02 versus 1.75 ± 0.03 m, and 74.9 ± 2.1 versus 74.4 ± 2.4 kg for T and UT subjects, respectively. The T group (five cyclists, one triathlete, one runner, and one weight lifter) reported training for 6.6 years (range, 2 to 32) at least 8 h/wk for 5 to 7 d/wk. The cyclists pedaled approximately 400 km/wk (~12 h/wk). The triathlete swam, cycled, and ran 8 to 20 h/wk depending on the season. The runner ran about 50 km/wk and lifted weights 5 d/wk, resulting in approximately 9 hours of total training per week. The weight lifter trained 6 d/wk for 60 to 90 minutes each session coupled with 90 to 120 min/wk of cycling or aerobics. UT subjects were a convenience sample recruited through word-of-mouth who had not

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participated in any form of systematic training for at least the previous 12 months. The subjects were not taking prescription medication known to alter HPA function and did not have any known psychosis or metabolic disorder. Additionally, subjects were asked to refrain from exercise and alcohol intake for 24 hours before reporting to the laboratory for testing. Although one UT subject reported taking fluoxetine to control depression, his physiological responses were similar to those of other UT subjects and his data were used in the analysis. Each subject reported to the laboratory on 2 separate days for a GXT. On the evening before testing, either placebo (PLA) or MET (30 $mg \cdot kg^{-1}$) was administered in a single-blind fashion with the test order balanced. Subjects were advised to take the treatment with a glass of milk or yogurt at midnight immediately prior to sleeping.[17] To allow sufficient time for washout of the drug, GXTs were separated by at least 4 days but no more than 21 days.

GXT

For each visit, subjects arrived at the laboratory at approximately 7:15 AM. Subjects assumed a recumbent position for the collection of a 5-mL blood sample. Following collection of the resting blood sample, the subject was transferred to a Monark 817E pendulum-style cycle ergometer (Monark, Varberg, Sweden). During the GXT, expired gas was analyzed continuously by previously calibrated O_2 (model S-3A/1; Applied Electrochemistry, Pittsburgh, PA) and CO_2 (model CD-3A; Applied Electrochemistry) analyzers. An Apple II+ computer (Apple Computer, Cupertino, CA) using REP-200C software (Rayfield Equipment, Waitsfield, VT) was interfaced with the gas analyzers and a dry-gas meter to calculate $\dot{V}O_2$ and $\dot{V}CO_2$. In an attempt to standardize the test duration, each subject pedaled the cycle ergometer for successive 3-minute stages starting at a work rate of 60 or 80 W depending on the subject's training status, with subsequent 60- or 80-W increments every 3 minutes until volitional fatigue. During the GXT, maximal power output was defined as the highest work rate achieved and maintained for at least 60 seconds. Immediately after the end of the GXT, the subject assumed a recumbent position, and at 3 minutes post-GXT, a 5-mL blood sample was collected. A three-lead electrode placement (ECG-MAC II/ST electrocardiograph; Marquette, Milwaukee, WI) was used to monitor heart rate (HR) and electrical activity of the heart. The rating of perceived exertion (RPE) was recorded at the end of every 3-minute stage. Systolic and diastolic blood pressure were measured and recorded at rest and at the end of every 3-minute stage by an automated system (STBP-780; Colin Medical Instruments, San Antonio, TX). If any clinical symptomatology indicated the presence of adrenal insufficiency (ie, hypotension), 100 mg hydrocortisone was to be infused and the test would be terminated. However, no subject developed hypotension at rest or during or after exercise.

Blood Collection and Analysis

The 5-mL blood samples at rest and 3 minutes post-GXT were collected by venipuncture into a chilled vacutainer tube containing disodium EDTA and centrifuged at 1,200 × *g* for 10 to 15 minutes at 2°C to obtain plasma. A 0.4-mL plasma sample was transferred to a chilled microcentrifuge tube containing 25 μL aprotinin (750 kallikrein inhibitor U/mL plasma) and frozen until analysis for ACTH. The remainder of the plasma was transferred to a microcentrifuge tube and stored frozen at −20°C until analysis for cortisol and 11-deoxycortisol. All samples from a given subject were analyzed concurrently in duplicate to reduce variability. Cortisol was determined by a solid-phase radioimmunoassay, and ACTH and 11-deoxycortisol levels were measured by a double-antibody radioimmunoassay. All kits were obtained from ICN Biomedicals (Costa Mesa, CA). The intraassay coefficient of variation was 8.1% for cortisol, 6.1% for 11-deoxycortisol, and 8.9% for ACTH. The cortisol antibody from the Corti-Cote Kit (ICN Biomedicals) had only 2.2% cross-reactivity with 11-deoxycortisol. Plasma total glucocorticoids were estimated by adding cortisol and 11-deoxycortisol.

Statistical Analysis

The data were analyzed as a two within-subject (time and treatment) and one between-subject (T and UT) repeated-measures ANOVA. SAS (SAS Institute, Cary, NC) General Linear Model procedures were used for data analysis. Various contrasts between time within group and treatment, between treatment within group and time, and between groups for time-treatment combinations were tested for significance, with a P level of .05. All data are presented as the mean ± SE.

RESULTS

Effect of Training Status on Resting Plasma Hormones

Before exercise under the PLA condition (PRE-PLA), plasma cortisol was similar in T (16.7 ± 2.3 μg/dL) and UT (13.5 ± 1.0 μg/dL) subjects. Similarly, there were no differences in PRE-PLA plasma 11-deoxycortisol (0.135 ± 0.011 *v* 0.164 ± 0.016 μg/dL) in T and UT subjects, respectively. However, PRE-PLA plasma ACTH was significantly higher (106.5 ± 8.4 pg/mL) in T compared with UT (81.5 ± 5.1 pg/mL) subjects ($P < .05$) (Fig 1).

Effect of GXT on the HPA

Figure 1 shows that after exercise in the PLA trial (POST-PLA), cortisol levels were not different than before the GXT, regardless of the training level of the subject. POST-PLA plasma 11-deoxycortisol increased compared with PRE-PLA in T and UT subjects ($P < .05$). The GXT was associated with a significant increase (3.8-fold) in plasma ACTH in UT ($P < .05$ *v* PRE-PLA) but not in T subjects.

Pituitary and Adrenal Response (effect of MET)

In general, the overnight single-dose MET test was well tolerated and no serious side effects were reported. One of 16 subjects reported feeling dizzy. This side effect started soon after MET ingestion and lasted approximately 15 minutes. None of the subjects presented evidence of adrenal (11-deoxycortisol < 7 μg/dL and cortisol < 5 μg/dL) or pituitary (ACTH < 150 pg/mL) insufficiency.[11,16] Figure 1 shows that at rest, MET decreased the cortisol concentration to 4.9 ± 0.8 and 3.2 ± 0.7 μg/dL in T and UT subjects, respectively ($P < .05$ *v* PRE-PLA). There were no differences noted for PRE-MET plasma cortisol suppression between groups. PRE-MET plasma 11-deoxycortisol increased 77- and 70-fold ($P < .05$ *v* PRE-PLA) in the T and UT group, respectively. PRE-MET plasma ACTH increased 3.5- and 3.8-fold in T and UT subjects compared with PRE-PLA ($P < .05$), with no differences between groups. Plasma ACTH was significantly higher ($P < .05$) at PRE-MET versus POST-PLA in T but not in UT subjects.

Pituitary and Adrenal Response (effect of GXT + MET)

POST-MET plasma cortisol tended to increase compared with PRE-MET in T and UT subjects, but failed to reach statistical significance ($P > .05$). Exercise induced a 40% and 26% increase in POST-MET 11-deoxycortisol ($P < .05$ *v* PRE-MET) in T and UT subjects, respectively. POST-MET plasma total glucocorticoids increased 40% and 32% versus

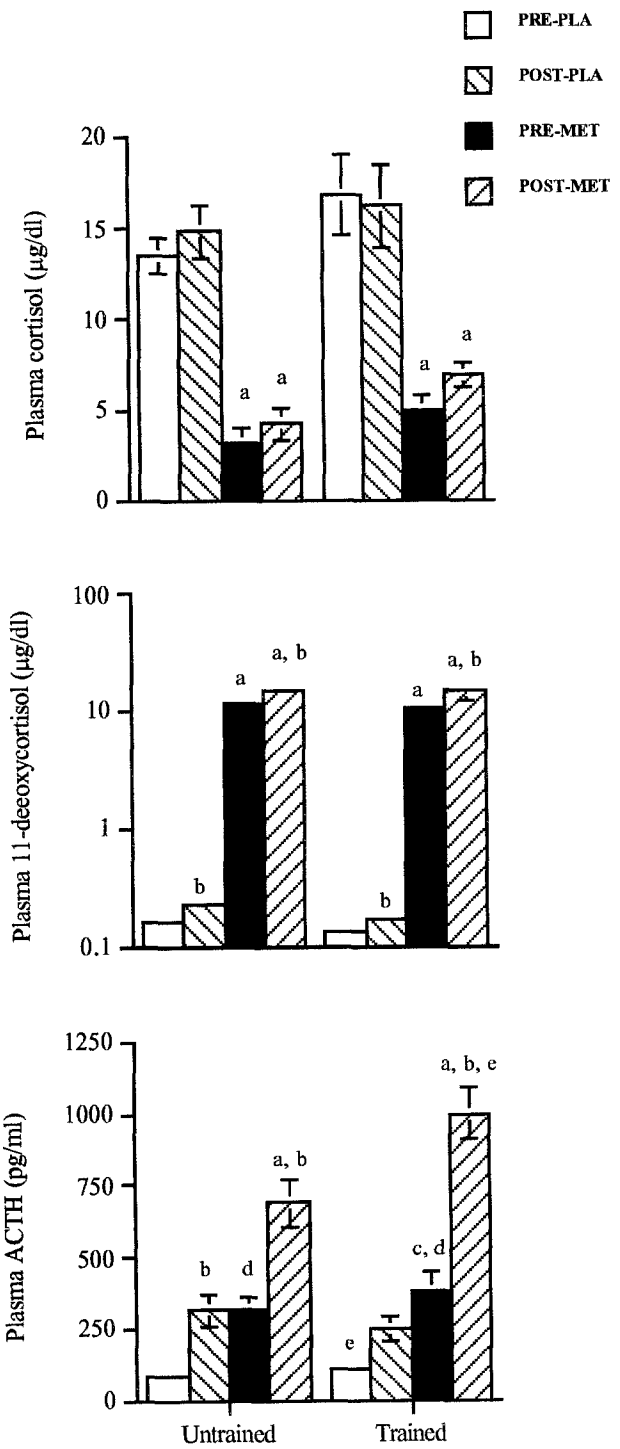

Fig 1. Plasma cortisol, 11-deoxycortisol, and ACTH before (PRE) and 3 minutes post-exercise (POST) in T and UT males. Plasma cortisol: a, significance *v* PRE-PLA and POST-PLA ($P < .05$). Plasma 11-deoxycortisol: ordinate is in logarithmic scale; a, significance *v* PRE-PLA and POST-PLA ($P < .05$); b, significance *v* PRE-PLA and PRE-MET ($P < .05$). Plasma ACTH: a, significance *v* POST-PLA within the same group ($P < .05$); b, significance *v* PRE-PLA ($P < .05$); c, significantly higher *v* POST-PLA in T subjects ($P < .05$); d, significantly higher *v* PRE-PLA ($P < .05$); e, significantly higher *v* the same time point in UT subjects ($P < .05$).

PRE-MET in T and UT subjects, respectively ($P < .05$). The GXT combined with MET treatment induced a higher ACTH level compared with PRE-MET (2.6- and 2.1-fold), POST-PLA (4.6- and 2.1-fold), and PRE-PLA (8.3- and 9.4-fold) in T and UT subjects, respectively ($P < .05$). Further, the T group showed a greater ACTH response compared with UT subjects ($P < .05$).

Effect of Hypocortisolemia on Work Capacity

With PLA, $\dot{V}O_2max$ was 55.6 ± 2.7 and 37.3 ± 1.7 $mL \cdot kg^{-1} \cdot min^{-1}$ in T and UT subjects, respectively. Table 1 shows that these values, the maximal power output (MPO), and the time to exhaustion were unaltered by MET treatment. However, MET resulted in an increased maximal heart rate and perceived exertion in both groups of subjects compared with PLA ($P < .05$).

DISCUSSION

The major findings of this investigation were (1) the pituitary and adrenal response to the single-dose MET test was similar for T and UT subjects; (2) for both T and UT subjects, MET administration combined with the GXT resulted in higher ACTH levels versus either test administered alone; (3) the combined MET challenge with the GXT revealed a greater pituitary sensitivity in T compared with UT subjects; and (4) the acute reduction in cortisol did not change $\dot{V}O_2max$ or time to exhaustion.

A critical aspect of this study is the combination of an exercise stress with the pharmacologic suppression of cortisol to challenge the HPA in T and UT subjects. Although some studies[2,18-20] have demonstrated that trained athletes show a normal degree of ACTH inhibition following administration of synthetic glucocorticoid (dexamethasone), it has been suggested that ACTH responsiveness is enhanced in athletes.[2,3,19,20] The similar pre-exercise values for ACTH, cortisol, and 11-deoxycortisol in our subjects challenged with MET suggest no differences in pituitary and adrenal responsiveness between T and UT subjects at rest. However, differences became apparent at the pituitary level when the subjects exercised under decreased glucocorticoid feedback. Although both groups showed an increase in the ACTH response to the GXT with MET treatment, the peak value was higher in the T versus UT group, suggesting alterations in corticotropic sensitivity due to train-

Table 1. Effect of Low Cortisol on Work Capacity for T and UT Subjects

Group	$\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	MPO (W)	Time (min)	Max HR (bpm)	RPE
T (n = 8)					
PLA	55.6 ± 2.7	380 ± 13.0	12.3 ± 0.5	175 ± 5.7	15.7 + 0.5
MET	54.6 ± 2.4	380 ± 13.0	12.3 ± 0.5	180 ± 6.9*	17.5 + 0.3*
UT (n = 8)					
PLA	37.3 ± 1.7	240 ± 11.3	10.5 ± 0.4	182 ± 5.1	15.6 + 0.4
MET	37.7 ± 1.3	240 ± 11.3	10.5 ± 0.4	188 ± 4.4*	16.1 + 0.5*

Abbreviations: time, time to exhaustion; Max HR, maximal heart rate; RPE, rating of perceived exertion.

*Significantly higher *v* PLA.

ing. Together, our findings and the results from Petrides et al[19,20] show that standardized endocrine tests (ie, single-dose MET test and dexamethasone suppression test) may not detect any differences between trained athletes and sedentary controls despite marked differences in physical activity patterns. However, dynamic tests involving the combination of a pharmacologic approach and vigorous exercise reveal alterations in the HPA axis that appear to be specific to physical training.

One of the aims of this study was to compare pituitary and adrenal responses to a GXT versus the MET challenge. When we diminished the glucocorticoid negative feedback by administering MET, resting plasma 11-deoxycortisol increased at least 70-fold in the T and UT group compared with the PLA trial. Additionally, in the MET trial, resting ACTH levels increased 3.5- and 3.8-fold in T and UT subjects compared with control conditions. These findings indicate proper compliance with the MET treatment and normal pituitary and adrenal function in these subjects. A comparison of the ACTH level following exercise in the PLA trial to the resting value in the MET condition suggests that the GXT and the MET test provide a similar stimulus to the pituitary corticotrope in UT subjects (~fourfold increase in ACTH). Interestingly in T subjects, the increase in ACTH induced by MET in the resting state (3.5-fold elevation) was significantly greater than the increase after GXT in the PLA trial (2.4-fold). This suggests that physical training attenuates the ACTH response to a "known" stimulus (exercise), whereas training does not alter the ACTH response to diminished cortisol negative feedback at rest compared with UT values.

The PLA trial yielded the results expected based on the literature. At rest, plasma ACTH was approximately 25% higher in T compared with UT subjects. This is in agreement with previous findings[3,6] and suggests an enhanced basal corticotropic tone. Although resting plasma cortisol was about 25% higher in T versus UT subjects, the values were not significantly different. Exercise caused a significant increase (3.8-fold) in plasma ACTH in UT but not in T subjects. The magnitude of the ACTH response to the GXT is similar to previous reports.[4,6] In response to exercise, plasma 11-deoxycortisol increased in both groups, whereas plasma cortisol was not altered. Whether these changes reflect an earlier spillover of the former versus the latter hormone or indicate an alteration in hormone kinetics is unknown. It is known that plasma cortisol levels are likely to peak 10 to 30 minutes after a GXT[21,22]; therefore, the timing of our blood sampling may not have been optimal to detect a cortisol increase. Our protocol was designed to maximize the likelihood of detecting increases in ACTH, because it peaks within the first 5 minutes after a GXT.[21,22]

T and UT subjects generated similar $\dot{V}O_2$max and MPO and had virtually identical times to exhaustion during MET compared with PLA. This is important for making appropriate hormonal comparisons between treatments, and suggests that an acute threefold to fourfold reduction in plasma cortisol has little bearing on $\dot{V}O_2$max and MPO. In contrast, chronic cortisol deficiency (ie, Addison's disease) is associated with reduced exercise tolerance.[12] It has been suggested that glucocorticoid deficiency attenuates $\dot{V}O_2$max and submaximal exercise tolerance by inducing cardiovascular instability (ie, hypotension), which is reversed by glucocorticoid administration.[12] The present findings, coupled with recent observations in our laboratory during prolonged exercise under a treatment similar to the present study, indicate that acute decreases in plasma cortisol do not alter the ability to complete maximal or submaximal exercise.[23] Similarly, an acute increase in glucocorticoid availability does not alter $\dot{V}O_2$max in T and UT subjects.[13] These findings suggest that acute alterations in plasma cortisol do not alter $\dot{V}O_2$max or the ability to complete a submaximal exercise bout in healthy men.

In summary, (1) pituitary and adrenal responses to the single-dose MET test are similar for T and UT men; (2) the MET test and the GXT generate similar ACTH responses in UT subjects, whereas T subjects show a higher ACTH response to MET versus the GXT; (3) when the MET test and the GXT are administered together, higher ACTH, 11-deoxycortisol, and total glucocorticoid responses are observed in both groups compared with either test alone; (4) the two tests combined (MET + GXT) show higher post-exercise ACTH in T compared with UT individuals; and (5) an acute decrease in plasma cortisol does not alter $\dot{V}O_2$max, MPO, or time to exhaustion during a GXT. These findings suggest that neither the GXT nor the MET test singularly are adequate to demonstrate differences in pituitary or adrenal responses between T and UT men; however, the combined MET + GXT reveals a greater pituitary sensitivity in T men.

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