Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids

M. DUCLOS,1 C. GOUARNE,1 AND D. BONNEMAISON2
1Laboratoire Neurogénétique et Stress, INSERM U471, Institut François Magendie, Université Bordeaux II, 33077 Bordeaux Cedex; and 2Laboratoire d’Immuno logie Moléculaire, Université Bordeaux II, 33076 Bordeaux Cedex, France

Submitted 11 February 2002; accepted in final form 1 October 2002

Duclos, M., C. Gouarne, and D. Bonnemaison. Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. J Appl Physiol 94: 869–875, 2003. First published October 25, 2002; 10.1152/japplphysiol.00108.2002.—The aim of this study was to address the effect of endurance training on tissue sensitivity to glucocorticoids (GC) in both resting and exercising conditions. In vitro dexamethasone inhibition of LPS-induced interleukin-6 secretion in cultures of peripheral monocytes was compared in untrained subjects (UT) and in endurance-trained men (ET) at the end of a 2-h run and during exercise recovery. We demonstrated an in vitro plasticity of sensitivity of monocytes to GC in ET men, superimposed to changes in systemic cortisol concentrations (plasma and saliva). Compared with sedentary men, similar resting cortisol levels in ET men were associated with decreased sensitivity of monocytes to GC 8 and 24 h after the end of the last training session (P < 0.05, ET vs. UT). Moreover, in these ET subjects, an acute bout of exercise increased the sensitivity of monocytes to GC (at 1000 and 1200; ET vs. UT, P > 0.05). This acute exercise-induced increase in tissue sensitivity to GC, which is synchronous with activation of the hypothalamo-pituitary adrenal axis, may act to shut off muscle inflammatory reaction and cytokine synthesis and then decrease exercise-induced muscle damage or inflammatory response. By contrast, the decreased sensitivity of monocytes to GC reported in ET men 24 h after the last bout of exercise may be related to the process of desensitization that may act to protect the body from prolonged, exercise-induced cortisol secretion. These acute and chronic effects of exercise on tissue sensitivity to GC demonstrate an adaptation of the hypothalamo-pituitary adrenal axis to repeated and prolonged exercise-induced increases in GC secretion.

endurance training; hypothalamo-pituitary adrenal axis; monocytes; immunoendocrine adaptations

EXERCISE REPRESENTS A POTENT physiological stimulus on the hypothalamo-pituitary adrenal (HPA) axis (17). Glucocorticoids (GC) exert many beneficial actions in exercising humans, increasing availability of metabolic substrates for the need of energy of muscles, maintaining normal vascular integrity and responsiveness, and protecting the organism from an overreaction of the immune system in the face of exercise-induced muscle damage (28). On the other hand, when an acute bout of endurance exercise is stopped, the hormonal profile is expected to converge toward anabolic processes. However, we have previously demonstrated that after a 2-h run, plasma cortisol levels remain significantly increased during almost 2 h after the end of the exercise (9). When training for a marathon race, subjects run an average of 120–180 km/wk. This implies daily sessions of prolonged and/or intense running and consequently prolonged phases of endogenous hypercortisolism (i.e., during exercise and during post-immediate exercise recovery). Given the antagonistic action of GC on muscle anabolic processes as well as their immunosuppressive effects, this has led us to hypothesize that endurance-trained (ET) men might develop adaptive mechanisms such as decreased sensitivity to cortisol to protect muscle and other GC-sensitive tissues against this increased postexercise cortisol secretion. Indeed, the response to GC is regulated not only by the concentration of GC but also by the sensitivity to GC of the target tissues. Changes in sensitivity to GC may explain the discrepancy between repeated and prolonged exercise-induced HPA axis activation and the lack of metabolic consequences of such increased cortisol secretion. The availability of an accurate measure of sensitivity to GC allows the evaluation of an additional level of GC action. It has been previously shown that the measure of in vitro dexamethasone (Dex) inhibition of LPS-induced interleukin (IL)-6 secretion in cultures of peripheral monocytes is an effective means of determining sensitivity to GC of one peripheral target of GC, i.e., the immune tissue (5).

The aim of this study was to address the effect of endurance training on tissue sensitivity to GC, both in resting and exercising conditions. For this purpose, in vitro Dex inhibition of LPS-induced IL-6 secretion in cultures of peripheral monocytes was compared in untrained (UT) subjects and in ET men 24 h after the end of the last session of exercise. Moreover, to determine the effect of an exercise-induced endogenous sustained...
increase in GC concentrations in ET men, tissue sensitivity to GC was further studied at the end of a 2-h run and during early and late recovery. To discard the potential effect of the circadian rhythm in regulating sensitivity to GC, a sedentary control group was also investigated in resting conditions.

**MATERIALS AND METHODS**

**Subjects.** Two groups of healthy male adults volunteered for this study: six UT men (<1 h/wk of physical activity for >3 yr) and six ET men [80–100 km run per week for at least 4 yr (range 4–8 yr), on a basis of 5–7 days/wk, 1–2 h/day, and having completed the marathon (42.125 km) in <3 h and 30 min]. All subjects were free of any medication, and none had a personal or family history of psychiatric disorders or diabetes mellitus or any endocrine disorder. The subjects did not smoke or consume alcohol abusively. Their mean ± SE age and body mass index were 26.7 ± 2.7 vs. 32.0 ± 2.8 yr and 21.9 ± 0.9 vs. 21.9 ± 0.7 kg/m², respectively (UT vs. ET men, respectively; P > 0.05 between both groups). The French short version of the Center for Epidemiological Studies Depression Scale was employed to detect depression (a score of ≥23 is consistent with depression) (25). Mean values were 13.3 ± 2.1 vs. 11.2 ± 1.5 (UT vs. ET men, respectively; P > 0.05).

All subjects underwent a screening laboratory examination, which included routine chemistry, differential blood cells count, and determination of basal thyroid (free triiodothyronine, thyreo-stimulating hormone) and testicular (testosterone) hormones concentrations. The study was approved by the Hospital Ethics Committee, and informed, written consent was obtained from all the subjects.

**Experimental design.** The subjects reported to the laboratory on two occasions: a screening visit and a test visit. The screening visit included physical examination, screening laboratory examination, and, in the case of ET men, progressive and exhaustive treadmill exercise to determine maximal oxygen uptake (V\(\text{O}_2\) max), ventilatory and metabolic parameters of intermediary graduated speeds, and maximal cardiac frequency. The treadmill started at 8 km/h and was increased by steps of 0.5 km/h at 2-min intervals until exhaustion. Subjects’ V\(\text{O}_2\) max was 63.0 ± 1.0 ml·kg\(^{-1}\)·min\(^{-1}\). During the 2 wk preceding the test visit, training was standardized for the ET group with four exercise sessions per week corresponding to 60–80 km run per week. Previous research has shown that a single session of daytime exercise increases urinary free cortisol (UFC) (3). For this reason, we chose to measure 24-h UFC during the resting day preceding the test visit.

For the test visit, subjects reported to the laboratory at the same hour (0730), having consumed no alcohol, chocolate, or caffeine, and having not exercised for 24 h. Two hours before beginning of the protocol (0600), subjects ingested a standardized breakfast (15% protein, 30% fat, 50% carbohydrate, 500 kcal = 2,090 kJ). From 0800 to 1800, all UT subjects and 60 min out of the laboratory, in a stadium (temperature range, 12–16°C). At 1000, they rested comfortably in a sitting posture in the laboratory until 1800. During the exercise period, ET men ingested only water (200 ml every 30 min to maintain optimal hydration and constant hematocrit) (24). During the rest period, both groups ingested only water, except at 1230, when a standardized meal was taken (15% protein, 30% fat, 50% carbohydrate, 800 kcal = 3,340 kJ). In all subjects, blood and saliva samples were drawn at 0800, 1000, 1200, and 1800.

**Hormones, glucose, and plasma volume.** Five-milliliter blood samples were collected in chilled tubes containing EDTA. After centrifugation at 4°C, plasma aliquots were stored at –20°C until assay. During blood collection, 2 ml of saliva samples (natural, unstimulated flow) were collected in a plastic test tube without any anticoagulant. Each saliva sample was collected 3 min before the blood sample. Saliva samples were stored at –20°C until assay. All samples were run in duplicate. Plasma cortisol concentrations were determined through a solid-phase RIA (coat-a-count cortisol kit, Diagnostics Products, Los Angeles, CA, distributed in France by Behring Diagnostic). The procedure had an intra-assay coefficient of variation between 3 and 5%; the interassay coefficient of variation ranged from 6 to 8% for plasma cortisol concentrations of ~130 and 650 nmol/L, respectively. The saliva samples were diluted 10-fold with human deuterated serum. The saliva cortisol was then extracted with dichloromethane (cortisol recovery of >95%) after evaporation and reuspension of the dried extract on human deuterated serum. CVs were similar to plasma assay CVs. The limits of detection of the assay were 29 and 1.7 nmol/L for plasma and saliva, respectively. UFC was determined with urine samples collected from 0800 to ~0800 (24-h UFC) during the resting day preceding the test visit. UFC was assayed by using a commercial kit (CORT-CT2, Cis Bio International). Urinary creatinine (UC) was determined with the same samples by the Jaffe method. Lastly, for each period of sampling, hemoglobin and hematocrit were measured for estimation of plasma volume changes (6). Plasma glucose was measured by the hexokinase method.

**Isolation of monocytes.** Fifty milliliters of heparinized venous blood were withdrawn at 0800, 1000, 1200, and 1800 and subjected to centrifugation on a Ficoll-Hyphaque gradient (Pharmacia Biotech, France) after 1:2 dilution with Hanks’ balanced salt solution (HBSS; Seromed, Noisy-le-Grand, France) without calcium and magnesium. Mononuclear cells were harvested from the interface Ficoll-plasma, washed once with 10 ml of HBSS, subjected to centrifugation (15 min at 250 g and 4°C to eliminate Ficoll), and further diluted with 10 ml of HBSS. Monocytes only were then counted and were >95% viable, as demonstrated by trypan blue exclusion. Finally, the cells were suspended with 80% RPMI-1640 medium (Seromed) supplemented with 2%, 200 mM L-glutamine and 20% heat-inactivated fetal calf serum (Seromed). Monocytes suspensions (3 × 10\(^5\) monocytes/ml) were cultured in 1-ml wells of culture plates for 48 h in a humidified, 5% CO\(_2\) atmosphere at 37°C. The plates were then washed two times in 1 ml of RPMI; nonadherent cells were aspirated (lymphocytes), and adherent cells (monocytes) were further incubated at 37°C in 5% CO\(_2\) atmosphere. The incubation was carried out for 24 h in 24-well dishes, each well containing 3 × 10\(^5\) monocytes suspended in 1 ml of culture medium in the presence or absence of Dex with or without LPS. After 24 h, the supernatants were collected, centrifuged, and stored at –80°C until further analysis.

**Stimulation and inhibition of IL-6 production by monocytes.** This assay was adapted from a previously reported protocol (10). Briefly, monocytes were incubated in the presence of bacterial LPS (Escherichia coli 0127: B8, Sigma Chemical, France) (final concentration of 0.3 µg/ml) or of no activator for control, for 24 h at 37°C in 5% CO\(_2\)-humidified air. After incubation, the supernatants were harvested by centrifugation and stored at –80°C until tested. In all experiments in which IL-6 production was inhibited with Dex; aliquots of 10 µl of Dex-21-phosphate (final concentration of 10\(^{-10}\), 10\(^{-9}\), 10\(^{-8}\) M in pyrogen-free saline;
Sigma Chemical, St. Louis, MO) were added to the culture of monocytes together with LPS (0.3 g/ml) for 24 h. After incubation, the supernatants were collected by centrifugation and stored at −110°C until tested. Dex sensitivity was expressed as percent inhibition of stimulated IL-6 production. The percent inhibition by Dex was calculated as the percentage of IL-6 produced in the presence of Dex relative to the production of IL-6 in the absence of Dex in the same individual at the dose of 0.3 g/ml LPS. Assays for each subject were realized in triplicate.

Cytokine assays. Levels of IL-6 were measured by ELISA according to the manufacturer’s instructions (Pelikine compact human IL-6 ELISA, CLB, The Netherlands). The lower limit of detection was 0.2 pg/ml for IL-6.

Statistics. The influence of the level of physical activity (ET vs. UT) was tested by a two- or three-way ANOVA, with sampling time and concentrations of Dex or LPS as repeated measures to detect differences in plasma and salivary cortisol concentrations and IL-6 production, followed by post hoc Newman-Keuls test. Associations between two variables were quantified by using the Pearson’s product-moment correlation coefficient. Data are presented as means ± SE. 

RESULTS

Plasma glucose concentrations and plasma and saliva cortisol concentrations. As previously reported (7, 9, 10), plasma volume did not change during exercise in ET men (data not shown), so no calculation adjustment was necessary.

At 0800, after a day without physical exercise, plasma and saliva cortisol concentrations were similar between UT and ET men (Fig. 1). The 24-h UFC and UFC/UC ratio measured 24 h after the last training session (during the resting day preceding the test visit) were also similar in UT and ET men: UFC 137.1 ± 9.3 vs. 121.8 ± 9.9 nmol/24 h and UFC/UC ratio 10.8 ± 1.0 vs. 10.9 ± 1.1 nmol/µmol (UT vs. ET men; P > 0.05 for both).

Compared with 0800 values, in UT men, plasma and saliva cortisol concentrations decreased along the day due to their nycthemeral rhythm [time effect (F) = 30.6 and 28.0, plasma and saliva cortisol, respectively; P < 0.001]. As previously described (7, 9, 10), 2 h of exercise induced a prolonged increase of cortisol objectively both at the end of exercise (1000) and 2 h after the end of exercise (1200). Consequently, plasma and saliva cortisol concentrations were significantly increased in ET compared with UT men at 1000 and 1200. At 1800, cortisol concentrations were similar in both groups.

At each time of sampling, blood glucose was not different between the two groups: at 0800: 5.9 ± 0.7 vs. 5.6 ± 0.5; at 1000: 4.6 ± 0.6 vs. 4.1 ± 0.3; at 1200: 4.1 ± 0.6 vs. 3.9 ± 0.4; at 1800: 4.6 ± 0.4 vs. 4.6 ± 0.6 nmol/l (UT vs. ET men; P > 0.05).

Unstimulated IL-6 secretion from monocytes. IL-6 levels in the supernatants of monocyte cultures obtained from UT and ET subjects are shown in Fig. 2. At 0800 and 1800, in the absence of stimulation by LPS, monocytes from ET men released significantly more IL-6 than did the monocytes from UT men. No effect of time sampling was observed in UT subjects. In ET, monocytes from blood collected immediately at the end of exercise (1000) and after 2 h of recovery (1200)
produced significantly less IL-6 than those collected before exercise (0800) and during late recovery (1800). The 1000 and 1200 IL-6 concentrations were similar to the concentrations of UT men at the same time.

**LPS-induced IL-6 secretion.** LPS (0.3 μg/ml) significantly increased IL-6 production in both groups \( F = 428.4, P = 10^{-6} \); Fig. 3A). When collected at 0800 and 1800, monocytes from ET men showed a higher sensitivity to LPS. By contrast, a similar LPS-induced IL-6 concentration was reached at 1000 and 1200 between ET and UT men. No effect of sampling time was observed in UT subjects. This was not the case for ET, because at 1000 and 1200, compared with preexercise values and late recovery values, postexercise IL-6 secretion was significantly lower when stimulated with 0.3 μg/ml LPS. Considering that at 0800 and 1800 unstimulated IL-6 values were significantly different between both groups and within the ET group with 1000 and 1200 values, we also calculated the percent of LPS-induced IL-6 increase. In these conditions, the LPS-induced IL-6 production was not significantly different between groups and within each group, according to the time of sampling (Fig. 3B).

**In vitro Dex inhibition of LPS-induced IL-6 secretion.** In both groups, administration of Dex \( 10^{-10} \)–\( 10^{-8} \) M significantly decreased LPS-induced IL-6 production compared with the absence of Dex \( F = 263, P = 10^{-7} \); Fig. 4). At 0800 and 1800, inhibition of IL-6 production was significantly lower in ET compared with UT subjects after Dex addition, regardless of the concentration of Dex used. Dex sensitivity was expressed as the percent inhibition of stimulated IL-6 production (see METHODS; Fig. 5). For each Dex concentration used, the percent inhibition was lower in ET subjects compared with UT subjects at 0800 and 1800 \( P < 0.05 \) ET vs. UT subjects. For example, at 0800, the percent inhibition by \( 10^{-10} \) M Dex of stimulated IL-6 production was...
37.9 ± 8.7 vs. 65.1 ± 4.7% (ET vs. UT, P < 0.05). No effect of sampling time was observed in UT subjects. This was not the case for ET subjects. Compared with preexercise values (0800) and late exercise recovery values (1800), for each Dex concentration used, a significant increase in the inhibition of LPS-induced IL-6 production (Fig. 4) and in the Dex sensitivity (Fig. 5) was noticed postexercise (1000 and 1200). Moreover, in these two postexercise sampling times (1000 and 1200), the inhibitory effect of Dex on LPS-induced IL-6 production was not significantly different from that obtained in UT subjects (Figs. 4 and 5).

DISCUSSION

The main finding of the present investigation is that, compared with sedentary men, similar resting cortisol levels are associated with a decreased sensitivity of monocytes to GC in ET men. Moreover, an acute bout of endurance exercise transiently increased the sensitivity of monocytes to GC in ET men. This exercise-induced increase of sensitivity of monocytes to GC may act to shut off muscle inflammatory reaction and cytokine synthesis and then decrease exercise-induced muscle damage or inflammatory response.

This study demonstrated that the 24-h cortisol secretion under nonexercising conditions is normal in ET men. Accordingly, 0800 plasma cortisol and 24-h UFC were normal and similar to those of age-matched, sedentary subjects. Because UFC represents an integrated measure of the 24-h cortisol secretion (4) and, therefore, is an integrated measure of the feedback loop set-point of the HPA axis, this is in accordance with the previously reported normal nycthemeral HPA axis rhythm in ET subjects, with similar plasma ACTH and cortisol concentrations between 0800 and 1700 in resting ET subjects compared with resting sedentary subjects (9).

As was previously reported, after a 2-h run, cortisol remains significantly increased for almost 2 h after the end of exercise (7, 10, 15). This suggests that a 2-h run induces an increase in cortisol concentrations for at least 3 h (the second hour of exercise and the 2 h of postexercise recovery) (9). When training for a marathon race, subjects run an average of 120–180 km/wk. This implies daily sessions of prolonged and/or intense running and, consequently, prolonged phases of endogenous hypercortisolism (i.e., during exercise and during post-immediate exercise recovery). Given the antagonistic action of GC on muscle anabolic processes, this has led us to hypothesize that ET men might develop adaptive mechanisms such as decreased sensitivity to cortisol to protect muscles against this increased, postexercise cortisol secretion.

Although plasma GC concentrations can be measured accurately, the biological effect of GC on the target tissues is uncertain. First, it depends on the free portion of the hormone, i.e., the free cortisol. Cortisol largely binds to plasma proteins and especially to the cortisol-binding globulin (CBG) (12). Thus plasma cortisol levels are modulated by variations of CBG and poorly correlate with cortisol production rates unless differences in CBG are corrected (4). Conversely, saliva cortisol concentrations are independent of CBG concentrations and thus closely reflect the free-active plasma cortisol (16, 27, 32). The response to GC also depends on the sensitivity to GC of the target tissues. The availability of an accurate measure of sensitivity to GC allows the evaluation of an additional level of GC action. It has been previously shown that in vitro Dex inhibition of LPS-induced IL-6 secretion in cultures of peripheral monocytes is an effective means of determining sensitivity to GC of one peripheral target of GC, i.e., the immune tissue (5).

IL-6 is produced by a variety of cells such as monocytes/macrophages, lymphocytes, endothelial cells, fibroblasts, and mast cells (31). Nonetheless, the major IL-6-producing cell line in whole blood is thought to be the monocytes (23). We have examined changes in functional activity of monocytes themselves, excluding changes in immune cell numbers and distribution between the blood and various immune compartments due to exercise. Indeed, prolonged, intensive exercise is associated with a sustained elevation in blood neutrophils and monocytes and a drop in lymphocytes (21, 22). Because of the importance of the leukocyte redistribution/traffic during and after exercise, we have chosen to study only the production of IL-6 by monocytes instead of by whole blood or peripheral blood mononuclear cells by using a constant number of monocytes in each experimental situation.

At 0800 and 1800, the basal secretion of IL-6 by monocytes is higher in ET men than in UT men. This is in agreement with two previous studies demonstrating that the IL-6 levels in plasma (30) and in the supernatants of monocytes cultures (10), respectively, were elevated in resting, long-distance runners compared with those of UT subjects. Basal levels of IL-6 can be viewed as an interplay between natural exogenous antigenic stimulation and inhibition by cortisol. The two factors being identical between ET and UT subjects (similar plasma cortisol concentration at 0800 and 1800 and no clinical or biological infection) suggests that long-term training increases IL-6 production by monocytes. This can also be viewed as an index of reduced sensitivity of GC receptors (GR) in ET men and, therefore, a reduced inhibitory tone of GC on monocyte function.

In agreement with previous studies, the LPS-induced IL-6 response was inhibited by Dex. As previously reported, at 0800, monocytes of ET men were less sensitive to Dex than those from UT men (10). This decreased sensitivity to GC cannot be attributed to the effect of prior muscular exercise itself since the last exercise session went back >24 h. This impaired suppressibility by Dex is consistent with two previous studies using in vivo inhibition by Dex of the overall HPA axis (8, 13). Dex exerts a strong feedback signal at the pituitary level (18). Therefore, the degree of Dex-induced suppression of plasma cortisol levels is viewed as another index of GC tissue sensitivity (i.e., pituitary sensitivity to GC). Heuser et al. (13) demonstrated that
a chronic exposure to frequent periods of HPA activation due to physical endurance training leads to alterations of the response capacity of the HPA axis in nonexercise circumstances. The originality of the present study is to demonstrate another site of decreased tissue sensitivity to GC (i.e., the immune system) in ET men.

The sensitivity to GC in UT men is similar at every time sampling between 0800 and 1800 despite different plasma cortisol levels. This absence of regulation of sensitivity to GC by the cortisol circadian rhythm has been previously reported (5). Acute exercise increased the sensitivity of monocytes to GC in ET men. Results of previous studies are scarce and conflicting. Using a similar in vitro technique of Dex suppression of LPS-induced IL-6 production, DeRijk et al. (5) have subjected trained men to a graded exercise of short duration (20 min) and high intensity (70 and 90% \( \dot{V}O_2 \max \)) and demonstrated an exercise-induced decrease in sensitivity to GC in peripheral lymphocytes 20 min after the end of exercise. Although the authors stated that the relative amount of monocytes did not change during exercise, it has been previously demonstrated that exercise induces a significant change in specific leukocyte subsets (19, 21). Because DeRijk et al. used peripheral whole blood cells, it is difficult to discard a role of putative variations in specific lymphocyte subsets. Moreover, in a later study, Smits et al. (29) used an intermittent, high-intensity exercise (total duration: 15 min at \( \sim 135\% \dot{V}O_2 \max \)), but specific lymphocyte subsets were studied as well as monocytes. The results show that exercise differentially affects sensitivity of monocytes and T cells to GC. Nevertheless, when expressed per monocyte, the decrease in IL-6 secretion was significant after exercise. This transient, exercise-induced GC resistance contrasts with our present demonstration of increased sensitivity to GC after exercise.

However, one study supports the present results. A similar exercise-induced increase in sensitivity of monocytes to GC was reported in ET men 2 h after the completion of a 2-h run (10). This discrepancy between Smits et al.’s study and our studies is likely to be related to the differences in the protocols, the type of exercise, and the timing of blood sampling. Comparing the effects of different duration and intensity of exercise and the kinetics of recovery will be necessary to decipher the regulation of sensitivity to GC in ET men.

Taken together, our findings and the findings of others support the existence of a plasticity of sensitivity to GC in ET men. Although changes in sensitivity to GC have mainly been described under pathological conditions (33), this is the first report indicating the kinetics of such rapid and transient changes in healthy subjects. Interestingly, in UT subjects, a recent paper reported that a psychological stress increased salivary cortisol and sensitivity of monocytes to GC 1 h after stress in men (26). Because running for 120 min at 65–75% \( \dot{V}O_2 \max \) may represent in sedentary subjects an intense psychological stress among other stress (energetic, metabolic, etc.), we have not submitted our sedentary group to an acute bout of exercise. Although stress has not been evaluated rigorously after exercise, all of our six trained men reported increased feelings of well-being after exercise. Therefore, the hypothesis of a psychological stress-induced increase in GC sensitivity is unlikely. By contrast, these results suggest that different conditions that lead to increased free cortisol concentrations [exercise in ET men (present study) and psychological stress in sedentary men (26)] can be associated with increased sensitivity of monocytes to GC. Therefore, this phenomenon of plasticity of GC sensitivity reported in the present study is not exclusive to ET men.

Several mechanisms may explain these transient changes in sensitivity to GC reported in the present study: 1) variations in the amount of GR (decreased at rest and increased during exercise), 2) alteration of the ligand-binding capacity in peripheral monocytes, 3) changes in direction of GR trafficking, and 4) different expression of \( \alpha \)- and \( \beta \)-isoforms of GR (1). An alternative explanation for the rapid changes reported is that acute exercise results in a differential migration of subsets of monocytes from the circulating pool, resulting in the depletion of the subset less sensitive to GC from the circulation. To our knowledge, subsets of monocytes that differ in their sensitivity to GC have not been described. Tissue-specific concentrations of cytokines are other potential sources of dissociation. IL-2, IL-4, IL-6, IL-10, and tumor necrosis factor-\( \alpha \) can lead to regional modulation in the sensitivity of immune cells to GC (11, 14, 20).

The present study provides evidence that the sensitivity of monocytes to GC action is reduced when individuals are submitted to repeated stimulations of the HPA axis due to endurance training. Moreover, in these ET subjects, an acute bout of exercise increased the sensitivity of monocytes to the levels assayed in control UT men. These exercise-induced changes are synchronous with activation of the HPA axis, as indicated by the increase in plasma and saliva cortisol. Taken together, these findings support the existence of a plasticity of sensitivity to GC in ET men, superimposed to systemic cortisol concentrations (plasma and saliva). The transient, exercise-induced increase of sensitivity of monocytes to GC may act to shut off inflammatory reaction and cytokine synthesis (28). Nevertheless, although such a restrained inflammatory response may, on one hand, decrease exercise-induced muscle damage or muscle inflammatory reactions, on the other hand, it may lead to increased susceptibility for bacterial and viral infections in immediate, postexercise recovery. Inversely, and although hypothetical, the decreased sensitivity of monocytes to GC reported in ET men 24 h after the last bout of exercise may be related to the process of desensitization that may act to protect the body from prolonged, exercise-induced cortisol secretion. Indeed, evidence has accumulated that increased, prolonged cortisol secretion resulted in severe metabolic consequences when repeated and prolonged (28).

In conclusion, the present results of acute and chronic effects of exercise on tissue sensitivity to GC in
ET men add important insight into the role of the adaptation of the HPA axis to repeated and prolonged exercise-induced increases in cortisol secretion. Further studies will be necessary to elucidate the mechanisms of these changes in sensitivity to GC and to determine whether these changes in immune sensitivity to GC may be associated with susceptibility to infections and/or inflammatory disorders, particularly in the case of overtraining-associated HPA axis dysfunction.

REFERENCES


