

Chapter 2

Exercise, Training, and the Hypothalamo–Pituitary–Adrenal Axis

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Activation of the HPA Axis During an Acute Bout of Exercise

During exercise, the HPA axis responds to numerous stimuli demonstrating the regulatory and integrative functions of the HPA axis: neuronal homeostatic signals (chemoreceptors, baroreceptors, and osmoreceptors stimulation), circulating homeostatic signals (glucose, leptin, atrial natriuretic peptide), and inflammatory signals (IL1, IL6, TNF α) [1]. In humans, the dynamics of the HPA axis activation during exercise associate stimulation of hypothalamic corticotropin-releasing hormone (CRH) and arginin-vasopressin (AVP) secretion (with a prominent role of CRH), and synthesis and release of ACTH from pituitary corticotroph cells preceding the increase of cortisol [2].

Two major factors modulate the HPA axis response to exercise: intensity and duration of exercise [3]. The minimum intensity of exercise (i.e., threshold) necessary to produce a cortisol response from the HPA axis is 60% of VO_2 max. Above 60% VO_2 max, a linear increase between the intensity of exercise and the increase in plasma cortisol concentrations is observed [4–6]. Below this intensity threshold, i.e., during light and prolonged exercise (<60% VO_2 max), ACTH and cortisol concentration may increase, with a duration threshold around 90 min of exercise at 40% VO_2 max [4]. These thresholds are independent of training. Indeed, when exercise is realized at similar relative intensity (% VO_2 max) between sedentary and trained men, the thresholds of intensity and duration for exercise-induced cortisol secretion are similar between the two groups as also the magnitude and duration of cortisol increase [4, 7–9].

Other factors can modulate the cortisol response to exercise such as hypohydration, meals, and time of day. Independently of external thermal stress, hypohydration (up to 4.8% body mass loss) potently amplifies the exercise-induced responses of cortisol to exercise. This enhancement of exercise-induced stress probably results from an increased core temperature and cardiovascular demand consecutive to decreased plasma volume [10]. Meals also stimulate cortisol release in humans. Exercise

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performed immediately after food ingestion results in a blunted cortisol response to the exercise stimulus, and conversely, the postprandial increase in serum cortisol concentrations is attenuated by prior exercise [11]. Finally, as the cortisol response to exercise is significantly modulated by time of day, neglecting the circadian cortisol variations may introduce errors into conclusion about the hormone responses to exercise and training [12, 13]. More specifically, the incremental response of cortisol to exercise is enhanced during the evening compared to morning exercise.

When repeated daily bouts of exercise are performed, the recovery time between bouts may also influence the HPA response to exercise. In male elite endurance athletes, the repetition of a prolonged strenuous exercise (bout of 75 min of exercise at 75% VO_2 max) induces a more pronounced increase in ACTH and cortisol when the previous bout of exercise was performed 3 h as opposed to 6 h earlier. This enhancement of the HPA axis activity during repetition of exercise occurs despite completely normalized plasma concentrations of cortisol and ACTH between the two exercise sessions. Thus, the duration of rest between the first and second sessions of exercise is a significant determinant of the magnitude of the cortisol response during reactivation of the HPA axis by the second bout of exercise [14]. These data must be considered in the light of the role of cortisol in consolidating glycogen reserve in muscle tissue, shutting off muscle inflammatory reaction and preparing the organism for the next bout of exercise [1]. Finally, whatever the type and the duration of exercise, plasma cortisol levels decrease to preexercise values within 120 min after the end of exercise [4, 7, 8, 12, 15, 16].

Adaptation of the HPA Axis to Endurance-Training

According to the data mentioned above, an exercise such as 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) (Fig. 2.1) [7]. When training for a marathon race, subjects run an average of 120–180 km/week. This implies daily sessions of prolonged and/or intense running and consequently prolonged phases of endogenous hypercortisolism (i.e., during exercise and during postimmediate exercise recovery). These periods of hypercortisolism are mandatory for fuel mobilization that is needed to achieve prolonged and/or intense exercise. However, given the antagonistic action of GC on muscle anabolic processes and their immunosuppressive effects, we have hypothesized that endurance-trained men may develop adaptive mechanisms such as decreased sensitivity to cortisol to protect muscle against this cortisol oversecretion. Through these adaptive processes, the HPA axis may cope with repeated stimulations, allowing, on the one hand, the ability of the organism to respond adequately to repeated stimulations and, on the other hand, protecting some GC sensitive tissues from high cortisol levels.

Since the last decade, several studies have shown that in endurance-trained subjects, 24 h cortisol secretion is not increased *under nonexercising conditions*. Accordingly, 800 h plasma cortisol, nycthemeral cortisol rhythm, overnight and 24 h urinary free

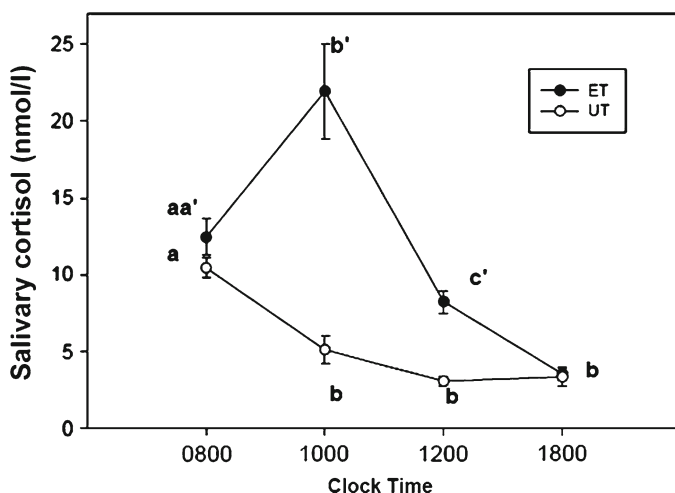


Fig. 2.1 Saliva cortisol concentrations across time during the experimental day in endurance-trained (ET) men (exercise and resting sessions) and untrained (UT) men (resting session). ET men realized a 2-h run between 800 and 1,000 h. Bars not sharing a common letter are significantly different from each others. Results are means \pm sem. From Duclos et al. [8]. At 800 h, saliva cortisol concentrations were similar between UT and ET men. Two hours of exercise induced an increase of cortisol at the end of exercise (1,000 h) and 2 h after the end of exercise (1,200 h) (ET)

cortisol (UFC), seasonal rhythmicity of cortisol excretion, and cortisol response to dexamethasone suppression test in resting endurance-trained subjects are similar to those of age-matched sedentary subjects [4, 9, 12, 15]. Altogether, these results probe the functional integrity of the HPA axis in endurance-trained subjects. The overactivity of the HPA axis reported by some authors [5, 17] may represent a further step in the intensity of physical activity strain, leading to overreaching and/or overtraining and pathological adaptations of the HPA axis. As suggested by Luger et al. [5], the highly trained group of people that they studied and who presented with mild evening hypercortisolism may have included subjects whose personalities had anorectic or depressive components, all conditions associated with chronic activation of the HPA axis. In women, alterations of the HPA axis in amenorrheic runners have been reported, with UFC levels elevated to levels observed in anorexia nervosa [17]. However, the physiopathology of this increased cortisol secretion has been extensively explained by De Souza and Loucks [18, 19], who repeatedly demonstrated that it is the stress of chronic energy deficiency (negative energy balance) that induces this chronic hypercortisolism and not the stress of exercise by itself.

Contrary to their apparently similar resting HPA axis activity, endurance-trained subjects differ from sedentary subjects when their HPA axis is challenged. These differences are highlighted when the HPA axis function is evaluated during the immediate postexercise recovery period (when plasma cortisol is still increased) and can be summarized as follows (Fig. 2.1). During this critical period and despite postexercise increased plasma cortisol concentrations, the HPA axis of trained subjects is still able to respond to subsequent physiological (food intake [4],

exercise [4, 14]) or pharmacological challenges (ACTH 250 μ g [20], CRF/LVP test [20]). This ability to respond to a second stimulation during this critical period is not observed in sedentary subjects. These results suggest a decreased pituitary sensitivity to the early GC negative feedback in endurance-trained athletes. The cortisol response to food intake illustrates this difference. In sedentary men, Brandenberger et al. [11] have shown that the daily cortisol pattern results from the interactions between the meal-related peaks, especially the major midday cortisol peak, and the exercise-induced cortisol increases, both of which inhibit the responses to subsequent stimulation. It explains why in conditions of exercise-induced marked cortisol increase, the subsequent stimulation exerted by meal taken 1 h after a 2-h run did not elicit a rise of cortisol levels in sedentary men [4]. By contrast, endurance-trained men, despite similar increased cortisol concentrations, are able to escape to the blunting effect of the preceding exercise-induced cortisol increase (GC feedback), and therefore, to respond to subsequent stimulation with a significant cortisol increase to noon meal [4].

Different mechanisms can be involved in this adaptation. At the level of the central nervous system, neuropeptides and corticosteroid receptors (GR, MR) in the brain and anterior pituitary play a major role in the regulation of circulating cortisol levels. The influence of exercise on these central regulators in humans is largely unexplored for evident methodological reasons. In animals, studies investigating the mechanisms underlying the potential influence of exercise training on the central regulation of HPA axis activity have used forced exercise protocols (treadmill training or swimming) [21]. In rats and mice, forced exercise induces different regulatory changes in the HPA axis compared to voluntary exercise (allowing access to a running wheel in the cage) and must be regarded as a chronic stress paradigm. Using voluntary access to a running wheel, Droste et al. [21] have shown that long-term (4 weeks) exercising mice showed unchanged GR levels, whereas MR levels were decreased in hippocampus of exercising animals. CRH mRNA levels in the paraventricular nucleus were also lower in exercising mice. Thus, voluntary exercise in rodents resulted in complex adaptive changes at various levels within the HPA axis and limbic/neocortical efferent control mechanisms.

At the peripheral level, tissular sensitivity to GC may also be different between endurance-trained and sedentary subjects. Changes in availability and/or sensitivity to GC may explain the apparent discrepancy between repeated and prolonged exercise-induced HPA axis activation (during exercise and 1–2 h postexercise) and the lack of metabolic consequences of such increased cortisol secretion. Duclos et al. [8] have reported an *in vitro* plasticity of monocytes sensitivity to GC in endurance-trained men, superimposed to changes in systemic cortisol concentrations. Despite similar resting cortisol levels, the sensitivity of monocytes to GC in endurance-trained men is decreased 8 and 24 h after the end of the last training session compared to sedentary men (Fig. 2.2). However, an acute bout of exercise increased the sensitivity of monocytes to GC of such endurance-trained subjects to the level observed in untrained men (Fig. 2.2). This transient decreased sensitivity of monocytes to GC in endurance-trained men may be related to a process of desensitization, which is supposed to protect the body from long-lasting exercise-induced

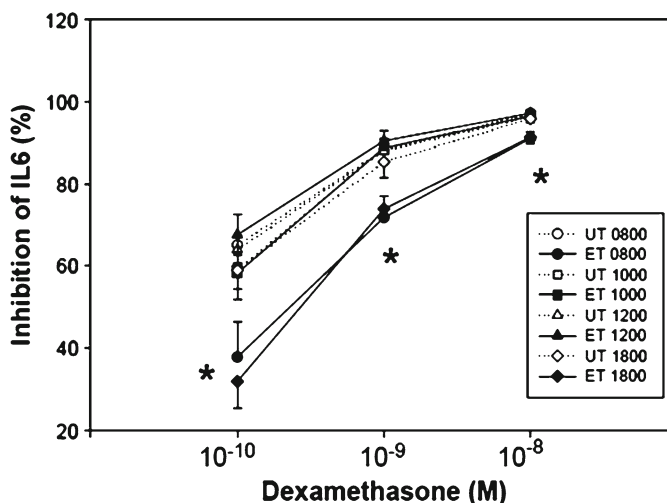


Fig. 2.2 Percentage inhibition of lipopolysaccharide (LPS) (0.3 $\mu\text{g/ml}$)-stimulated IL-6 production in cultures of peripheral monocytes in ET (solid lines) and UT men (dotted lines). Asterisk: The percent values of dexamethasone-induced IL-6 inhibition are significantly lower in ET at 800 and 1,800 h as compared with their values at 1,000 and 1,200 h, and as compared with the values of UT men at 800, 1,000, 1,200, and 1,800 h ($p < 0.05$). From Duclos et al. [8]. The sensitivity to glucocorticoids (GC) in UT men is similar at every time sampling between 800 and 1,800 h, despite different plasma cortisol levels (Fig. 2.1). At 800 h, monocytes of ET men were less sensitive to dexamethasone than those from UT men. An acute exercise (between 800 and 1,000 h) increased the sensitivity of monocytes to GC in ET men to the levels observed in control ET men

cortisol secretion. However, this observation should not be generalized to the whole organism since differences in GC sensitivity across tissues (immune system, cardiovascular system, and the HPA axis) have been shown in healthy subjects [22].

Upstream these cellular mechanisms, the extracellular and/or the intracellular availability of cortisol could also be modified. Extracellular bioavailability depends on the free fraction of cortisol. Cortisol largely binds to plasma proteins and especially to the cortisol-binding globulin (CBG). Thus, plasma cortisol levels are modulated by variations of CBG and poorly correlate with cortisol production rates unless differences in CBG are corrected [3]. Saliva cortisol concentrations closely reflect the free – active – plasma cortisol [3]. Measuring simultaneously plasma and saliva cortisol concentrations, we did not find differences in endurance-trained men vs. sedentary men, in resting conditions as well as during exercise [7–9, 23]. In addition to CBG which modulates the extracellular availability of cortisol, the access of cortisol to target cells is controlled by prereceptor metabolism of cortisol. Tissue-specific enzymes 11β hydroxysteroid dehydrogenases (11β -HSD), which interconvert hormonally active cortisol and inactive cortisone, have been shown to modulate cortisol hormone action in several peripheral tissues [24]. The crucial physiological principle illuminated by the action of 11β -HSD is that cortisol action on target cells is determined by enzyme activity within the cells, rather than circulating

cortisol levels alone. Interestingly, the 24-h urinary cortisol/cortisone ratio (an index of whole body 11β -HSD activity [25]) was reported to be negatively related to the total training load in a population of swimmers [26]. This suggests that any significant increase in 24-h cortisol secretion is balanced by its parallel inactivation into cortisone. Elsewhere, the nocturnal period is essential for exercise recovery. Gouarne et al. [9] have studied the overnight GC output to assess the delicate balance between cumulative fatigue resulting from exercise training and its recovery period over a 10-month season in triathletes. To dissociate the effects of training from those of seasonal hormonal variations, endurance-trained men were compared to sedentary men [9]. Gouarne et al. reported similar overnight urinary cortisol output in both groups during the 10-month follow-up. Moreover, whereas overnight urinary cortisol excretion showed seasonal variations (November > June) in both groups, urinary cortisol/cortisone excretion remained stable in both groups during the follow-up period, suggesting again that any significant increase in cortisol secretion (seasonal-induced increased cortisol secretion) is balanced by its parallel inactivation into cortisone. The importance of this mechanism is also highlighted in the two triathletes of this study who developed an overtraining syndrome (decreased performance, high score of fatigue, and inability to maintain the training load) during the follow-up: both presented a sharp decrease of inactivation of cortisol into cortisone with increased cortisol/cortisone ratio compared to their basal (pretraining values) and compared to the values of the other triathletes at the same period.

In conclusion, endurance-training subjects have similar HPA axis activity in resting condition than healthy sedentary subjects. However, when the HPA axis is challenged, endurance-trained subjects demonstrate a decreased pituitary (and probably hypothalamic and/or suprahypothalamic) sensitivity to the negative feedback of GC that explain their capacity to achieve successfully a second bout of exercise separated by a short rest period. Successful adaptation to exercise-induced repeated and prolonged cortisol secretion also includes decreased peripheral tissue sensitivity to GC that is supposed to protect the body from the severe metabolic and immune consequences of increased cortisol levels. A great diversity of mechanisms is involved in such adaptation, acting at potentially all levels in the cascade leading to the biological effects of cortisol.

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