Learning Objectives:

- Identify patterns of cortisol and growth hormone (GH) release in response to exercise.
- Recall how hormone release in response to exercise is affected by age, gender, body composition, time of day, and exercise training.
- Describe the influence of cortisol or GH deficiency on the ability to exercise; the meaning of an impaired GH response to exercise in obese persons; and the significance of an excessive cortisol response to exercise.

Introduction

Exercise is one of the most physiologically relevant and potent stimuli that can be presented to the body and results in dramatic changes in the hormonal milieu. The degree of provocation of the hypothalamic-pituitary axis by exercise is dependent on a myriad of factors, which include the intensity, duration, and mode of exercise, previous meals, training level of the subject, aerobic versus resistance exercise, and body composition. Two hormones under hypothalamic-pituitary control that have been studied extensively are growth hormone (GH) and cortisol. Considerable interest in these hormones stems not only from their potential role in exercise metabolism but also from their pulsatile secretory patterns and circadian/idiurnal rhythms.

Cortisol and GH levels increase dramatically in response to an exercise stimulus of sufficient intensity and may take a few hours to recover back to baseline levels. Despite their significant increases in response to exercise, these hormones play a secondary role to catecholamines and insulin in regulating glucose and fat metabolism. However, these hormones have been proposed to be important during exercise as well as during the postexercise period. This review discusses the pattern of hormone release for cortisol and GH in...
humans, the factors affecting the exercise-induced hormone response, the possible mechanisms of hormone release, and potential clinical implications of these physiological observations.

Cortisol

At rest, cortisol secretion is pulsatile and the secretory pulses are modulated by a circadian rhythm [1]. Cortisol concentrations peak in the early morning hours just before awakening because of increases in secretory pulse amplitude and frequency. After the early morning peak, cortisol levels decrease throughout the day, with the lowest levels seen in the evening hours. This rhythm is independent of sleep, although an inhibitory effect of nocturnal sleep on cortisol levels has been reported in humans [2]. Corticotrophin-releasing hormone (CRH), released from the hypothalamus, is the major substance that stimulates adrenocorticotropin (ACTH) release from the pituitary [3]. The ACTH, in turn, stimulates cortisol release from the adrenal gland. This is regulated by negative feedback.

Cortisol Response to Exercise

The first studies on the cortisol response to exercise were conducted in the early 1970s. These studies indicated that aerobic exercise increases cortisol levels [4]. Further research using [3H] cortisol found that intensities greater than 65% of maximal oxygen consumption (VO2 max) increased plasma cortisol levels, whereas exercise at lower intensities resulted in variable results, with cortisol concentrations usually decreased or diminished in comparison with baseline concentrations [4, 5]. The increase in plasma cortisol levels during heavy exercise is caused by the net effect of increases in the rate of secretion and the rate of removal from the plasma. These early studies, however, did not compare cortisol release during exercise with a no-exercise control day, so the study designs did not control for the effects of the circadian rhythm on the cortisol response to exercise. Dependent on the exercise intensity, peak cortisol values of 550 nmol/L have been reported with aerobic exercise at 70% VO2 max [6] as compared with normal resting values of 110 to 520 nmol/L at 8:00 AM.

The cortisol responses to aerobic and resistance exercise have been shown to stimulate the hypothalamic-pituitary-adrenal axis (HPA) and elicit neuroendocrine responses proportional to relative intensity and duration [7–9]. Greater cortisol responses to higher-intensity exercise are likely related to the higher ACTH levels observed with increasing exercise intensity. Gender and training do not affect the ACTH and cortisol concentrations when expressed as relative exercise intensities [10, 11], but when these responses were expressed as absolute workload, these responses were attenuated in trained subjects [11].

Early research [12] in humans documented that physical exercise affected the normal diurnal pattern of cortisol release by blunting the decrease in cortisol concentrations during the day. When exercise and meals were used to stimulate a cortisol response, the exercise- and meal-induced increases in cortisol were not additive. The exercise-induced increase in cortisol suppressed a subsequent meal-related increase, and no marked cortisol increase occurred when the exercise coincided with the postprandial cortisol peak. Subsequent research [13] demonstrated that exercise performed during different periods of cortisol secretory quiescence produced similar increases in plasma cortisol, despite the general downward trend in basal levels. Lower peak exercise values were observed in the evening because of lower basal levels, resulting in a brief plateau of cortisol concentrations, which interrupted the decrease in cortisol secretion because of the diurnal rhythm. Similarly, the meal-related peaks were reduced when preceded by an exercise-induced cortisol increase. Thus, the daily pattern of cortisol release is affected by the interactions of meals and exercise, both of which can overcome the diurnal rhythm to stimulate cortisol secretion but can also inhibit the response to subsequent stimulation of cortisol release [13].

In recent years, there has been a considerable amount of interest in the effect of time of day on the cortisol response to exercise, because of the strong circadian rhythm underlying cortisol secretion. Some studies reported that the morning and evening exercise responses were similar [13–15]. Another study that used low-intensity exercise observed an increase in cortisol concentrations in the afternoon but not in the morning or evening [16]. Early studies did not include a nonexercise control day and simply compared cortisol concentrations during exercise with the pre-exercise levels on the same day [4, 5, 13, 14]. This approach does not take into account the changing cortisol concentrations over the course of the day caused by the circadian rhythm. Thuma et al. [15] compared the area under the curve of cortisol concentrations on an exercise day with a no-exercise control day. This analysis revealed that morning-integrated (8:00 AM) and evening-integrated (8:00 PM) cortisol responses to exercise were similar when moderately intense exercise was used (70% VO2 max for 40 min). However, this method does not detect the change in response pattern over time. Using a statistical method that enables differences in hormone levels between exercise and control conditions to be assessed at each time point with 95% confidence limits, Kanaley et al. [6] reported that for short periods of time (approximately 40–130 min), the time of day did modulate the
exercise-induced cortisol response. The study design controlled for the confounding factors of meals, previous exercise, and sleep. The increase in cortisol levels during control-day conditions was greatest at midnight, intermediate during the early morning (7:00 AM), and least during the early evening (7:00 PM). Peak cortisol concentrations in response to exercise were highest at 7:00 AM, followed by 12:00 AM, and 7:00 PM, in that order (Fig. 1). Thus, assessing the cortisol response to exercise in relation to nonexercise control conditions is important, particularly if different times of day are used.

Effect of Training on the Cortisol Response to Exercise

The repeated stress associated with regular physical training is linked with alterations in the sensitivity of the components of the HPA axis [11, 17–19]. In some studies, trained subjects have increased pituitary and/or adrenocortical sensitivity to exogenous CRH, whereas others have reported decreased sensitivity [11, 18]. Highly trained runners demonstrate a diminished response of ACTH and cortisol to ovine CRH, consistent with sustained hypercortisolism [11]. Although some studies have reported ACTH responsiveness to be enhanced in athletes [17, 20, 21], Del Corral et al. [22] found no differences in pituitary and adrenal responsiveness between trained and untrained subjects at rest. Metyrapone, which inhibits cortisol synthesis, has been used to identify alterations in the HPA axis in trained and untrained men. Using metyrapone to induce a state of diminished glucocorticoid feedback, Del Corral showed that the ACTH response to exercise was greater in trained than in untrained subjects, which suggests that training enhances corticotroph sensitivity [22].

Long-term overtraining in elite athletes may modify cortisol release at rest and in response to an exercise bout. In anorexic people and amenorrheic athletes, hypercortisolism has been observed [23–25]. In anorexic people, the increased cortisol levels are believed to be a defect at or above the level of the hypothalamus. Even though the pituitaries in anorexic people respond appropriately to exogenous CRH, the response is restrained by the chronically increased levels of cortisol [24]. It has also been proposed that these individuals have decreased peripheral metabolism of cortisol. Soon after the correction of the weight loss, there is a return to euthyroidism, indicating resolution of this central defect despite persistence of abnormalities in adrenal function [24]. Some studies have shown that runners with eumenorrhea and runners with amenorrhea have higher cortisol levels compared with those of controls [26]; however, other studies have reported that only the amenorrheic women have higher levels [23, 25]. Unlike anorexic women, runners have higher basal cortisol levels because of increased ACTH secretion; therefore, they probably do not have decreased peripheral metabolism that is seen in anorexic people [26]. Increases in either central CRH or peripheral cortisol levels disrupts LH pulsatility, suggesting that both of these alterations in the HPA axis may be involved in the mechanism of athletic amenorrhea [18, 27]. Others have found that amenorrheic athletes who did not have increased cortisol levels would spontaneously regain their menstrual cycles within 6 months, whereas those athletes with increased cortisol levels continued to have amenorrhea [23].

The impact of overtraining on the HPA axis can be relatively acute, with dramatic increases in ACTH and cortisol. In one study of multiple consecutive days of strenuous exercise, ACTH and cortisol levels were increased for the first 3 days but remained unchanged for the remaining days of exercise or reverted to pre-exercise day values. It was hypothesized that the fatigue induced by previous exercise may have modified the hormone responses to subsequent exercise [28]. In the laboratory setting, continuous, prolonged, aerobic exercise for 2 hours has been used as a means of inducing fatigue [29]. Comparison of the hormonal responses to acute exercise before and after this prolonged bout demonstrated that pronounced increases in the cortisol concentrations were seen before the fatiguing exercise, but no increase in cortisol levels was seen after the fatiguing exercise. By stratifying the data into those individuals who had increased cortisol release to the second exercise bout and to those who did not, they noted that the former group had impaired feedback suppression of cortisol release [29]. They speculated that in such individuals, there is a resetting of the regulation of pituitary adrenocortical activity, which may be related to the hypothesized serotonergic mechanisms of central fatigue in humans [29].

Figure 1. Cortisol response to 30 minutes of exercise (70% VO2 peak) at three different times of day in eight young men (adapted from reference 6).
Mechanisms of Cortisol Release

Activation of the HPA axis during and after incremental exercise lags behind that of the response of the sympathetic nervous system. In particular, the sympathetic nervous system activation of the HPA axis is primarily triggered by the fuel demands of the muscles, signaled by decreasing blood glucose levels [30]. In contrast, during psychological stress, the response of the HPA axis is not delayed because the higher brain centers are more involved, and these centers operate independently of physiological demands [31]. These situations produce immediate activation of the HPA axis.

The mechanism of cortisol release during exercise appears to be different when compared with other stimuli. The peak response to pharmacological tests of cortisol secretory reserve is not influenced by time of day, whereas the incremental response is. The peak cortisol response 30 minutes after an ACTH intravenous bolus is similar in the morning (8:00AM) and afternoon (4:00PM), with the cortisol concentrations increasing more rapidly after ACTH administration in the afternoon than in the morning [32]. Insulin-induced hypoglycemia and ovine CRH provoke a greater incremental cortisol response in the afternoon than in the morning, although peak cortisol concentrations do not differ by time of day [33]. When assessing adrenal cortical reserve, the peak response to ACTH has been found to be more valuable than the incremental cortisol response. A peak cortisol response exceeding 550 nmol/L (20 μg/dL) is considered a normal response to ACTH [32]. In response to exercise, we have shown that peak cortisol response will exceed this threshold at 7:00AM and 12:00AM but not at 7:00PM, suggesting that the cortisol response to exercise is regulated by more complex mechanisms that differ from those in response to hypoglycemia, CRH, or ACTH. One limitation, however, is that the time of day that the exercise testing was performed [6] differed from previous pharmacological studies; thus, a direct comparison of the results is not possible. Other authors have found similar peak cortisol values during exercise [14]. High-intensity intermittent exercise has been shown to increase ACTH concentrations to values greater than what is seen with an infusion of CRH [34]. Because the infusion was believed to saturate the CRH receptors, these findings indicate that additional factors other than CRH stimulate ACTH release during exercise.

Recently, Di Luigi et al. [35] reported that acetylsalicylic acid (ASA) treatment is able to modify the pituitary response to exercise-related stress in humans. The ASA decreased the observed ACTH, cortisol, and GH concentrations before exercise and was associated with reduced mean cortisol concentrations after exercise; ASA had no effect on the GH response to exercise. Because ASA inhibits prostaglandin production, these researchers speculated that there is involvement of a prostaglandins pathway in the control of endocrine response to exercise-related stress [35].

Growth Hormone

The release of GH is characterized by a pulsatile pattern and has a diurnal rhythm, with peak values occurring at night [36, 37]. The increase in GH secretion at night is in close association with slow-wave sleep [2, 37, 38]; however, GH levels still remain maximal at night if subjects are kept awake [37]. In addition to the diurnal rhythms, GH secretion at rest and during exercise is influenced by numerous factors, such as age, nutrition, sleep, body composition, fitness level, gender, and sex steroid hormones [39].

Growth Hormone Response to Exercise

Continuous and intermittent exercise result in an increase in GH concentrations [40], with a lag in the GH increase of approximately 15 minutes [40, 41]. During an incremental exercise test, plasma GH concentrations remain low at low-work intensities and increase with increasing exercise intensity [42–45]. Prolonged submaximal exercise (50%–60% VO₂ max, 90–120 min) also produces a significant increase in GH concentrations, which then plateau and may even decrease somewhat [46, 47]. The GH levels during exercise can increase 300% to 500% during a nonexercise day depending on the exercise intensity, and it is not uncommon to see values of 13 to 20 μg/L [6]. The peak GH response to exercise can be attenuated in response to a high-fat pre-exercise meal, whereas a high-glucose meal before exercise had a lesser effect on the GH response [48]. These data suggest that the composition of the pre-exercise meal can alter the hormonal response to exercise and, moreover, may play a role in modulating the protein–anabolic and lipolytic effects of exercise.

Considerable controversy has occurred regarding the appropriate exercise intensity to elicit a GH response. Felsing et al. [42] observed that during low-intensity exercise (10 min at 50% of lactate threshold [LT]), GH levels did not increase significantly from pre-exercise baseline values, whereas 10 minutes of high-intensity exercise (50% between LT and VO₂ max) significantly increased GH levels [42]. Others have reported that the minimal exercise intensity to elicit a GH response is 50% of VO₂ max, with a maximal response at 70% VO₂ max, and no further effect at 90% VO₂ max [44]. Pritzlaff et al. [45] studied the GH secretory response to 30 minutes of exercise at five different intensities: 25% and 75% of the difference between LT and...
rest; at LT; and at 25% and 75% of the difference between LT and VO2 max. A linear relationship between exercise intensity and the integrated GH response was observed in men and women [45, 49]. Low-intensity exercise (below the LT) resulted in stimulation of GH release, which was questioned in previous work.

Women have higher resting GH levels than men, regardless of training status [50–52]. The 24-hour integrated GH concentrations are also higher in women than in men [53, 54]. This is the result of a greater mass of GH secreted per pulse in women compared with that in men, with no gender differences in the number of GH pulses [54]. Although some studies have reported that maximal GH responses to exercise are similar in men and women [55], a recent detailed assessment across multiple exercise intensities demonstrated that for each incremental increase in exercise intensity, the fractional stimulation of GH secretion was greater in women than in men [49]. Compared with men, women had greater basal (nonpulsatile) GH secretion across all conditions, more frequent GH secretory pulses, greater GH secretory pulse amplitude, greater production rate, and a trend for a greater mass of GH secreted per pulse [49].

During the late follicular phase of the menstrual cycle, GH pulse amplitudes and integrated GH concentrations are increased (approximately doubled) compared with the early follicular and mid luteal phases. The GH pulse amplitudes are positively correlated with serum estradiol and negatively correlated with progesterone concentrations, suggesting that changes in gonadal steroid concentrations during the menstrual cycle likely regulate GH secretion to a significant degree [56]. Some authors report that the mean GH response to aerobic exercise at ovulation is higher than when measured in the early follicular phase, whereas others [47, 57] find no difference in the integrated GH response to exercise in women tested during the follicular and luteal phases. In women using oral contraceptives, greater exercise-induced increases in GH secretion are reported during the oral-contraceptive phase than during the phase of nonoral-contraceptive use [58]. This is consistent with observations in postmenopausal women in whom oral-estrogen use enhances GH secretion [59]. Paradoxically, GH responses to exercise are reported to be as high [47] or higher [60] in amenorrheic female athletes with chronically decreased estrogen levels similar to eumenorrheic levels.

In addition to gender and exercise intensity impacting the GH response, time of day of exercise must also be considered. The magnitude of the exercise-induced GH response is independent of the time of day. In our study, the increase in GH concentrations over nonexercise control day conditions was similar at 7:00AM, 7:00PM, and 12:00AM when the confounding factors of meals, previous exercise, and sleep were controlled [6]. A transient suppression (approximately 55–90 min) of GH release occurred after 30 minutes of exercise at 7:00AM and 7:00PM but not after 12:00AM. Similarly, Gallivén et al. [14] and Scheen et al. [16] found no diurnal difference in the magnitude of the GH response with morning, afternoon, or evening exercise. Aerobic exercise appears to override the diurnal rhythm underlying the GH release.

Body composition is also related to serum GH concentrations. A high body fat percentage is associated with decreased GH levels. In particular, higher amounts of abdominal visceral fat are associated with lower 24-hour GH release. Clasey et al. [53] reported that the amount of abdominal visceral fat was a stronger predictor of 24-hour integrated GH concentrations than age, gender, percent body fat, body fat mass, or aerobic fitness (peak VO2). In response to exercise, the GH levels in obese women were found to be attenuated compared with age-matched nonobese women [61] (Fig. 2). During a 6-hour study period, the integrated GH concentrations in obese women were only 31% of those found in the nonobese women. This diminished response was accounted for by a decreased GH production rate, but no difference in the GH half-life between groups [61]. Sixteen weeks of exercise training in the obese subjects improved aerobic fitness, but the GH response to exercise did not change and there were no changes in body composition. Although regional distribution of body fat was only calculated by waist and hip measurements, the estimated amount of abdominal visceral fat was higher in obese women with mainly upper body fat than in obese women with mainly lower body fat and in nonobese women. There was no relationship between the

![Figure 2. Mean serum GH concentrations for nonobese (n = 8), lower-body obese (n = 12), and upper-body obese (n = 12) women before, during (30-minute bout), and after exercise at 70% VO2 peak (adapted from reference 61).](image)
estimated visceral fat adjusted for total body fat and the exercise-induced GH response [61]. Thus, contrary to findings of 24-hour spontaneous GH release, the total body fat percentage may be a more important determinant of the GH response to exercise than is regional fat distribution [61]. In contrast, Holt et al. [62] recently reported that aging, and not adiposity, is a regulator of GH secretion during exercise.

Aging is associated with a decrease in resting and exercise-induced GH secretion. The GH levels peak in the second decade of life and remain increased for a short period of time; however, levels decrease in the second decade of life so that by the age of 40, very low levels of GH are found [63]. Because of these low levels in middle-aged and older adults, there is controversy whether exercise or exercise training can increase serum GH concentrations. Studies using an acute bout of exercise to stimulate GH release have shown either no increase [64, 65] or only a very slight increase in GH levels [65–67]. Any increases observed were dramatically lower than those seen in young individuals [65]. The GH area under the curve was blunted in older men (age: 66 y) compared with young men (age: 20 y) in short-duration maximal exercise or prolonged submaximal exercise [67]. Secretion of GH was stimulated to a greater degree by aerobic exercise in aerobically fit compared with sedentary older men [66]. Acute resistance exercise also increases GH concentrations, regardless of age, but the GH response in elderly men is less than that observed in young men [64, 68]. Pyridostigmine (which indirectly suppresses somatostatin secretion) administration increased total GH secretion during exercise in young and old men but did not eliminate age-related differences in GH levels. Possible mechanisms for the age-related differences were increased somatostatin tone with age, decreased cholinergic inhibition of somatostatin, decreased adrenergic drive stimulating growth–hormone-releasing hormone (GHRH), or possibly a decreased sensitivity of the pituitary to GHRH stimulation [67].

Effect of Training on the Growth Hormone Response to Exercise

The effect of exercise training on GH secretion has been somewhat controversial. Endurance-running training was found to increase the 24-hour release of GH in eu-menorrheic untrained women [69]. Exercise training for 1 year amplified the pulsatile release of GH when training was above the LT [69], but not when it was below the LT. Differences in pulsatile GH release after 1 year of training were seen for maximal peak height, incremental peak amplitude, peak area, nadir GH concentration, and 24-hour integrated concentration of GH. In contrast, a short duration (6 wk), high-intensity exercise training program decreased the exercise-induced GH response when the same absolute workload was used after training [70]. This suggests that the GH response to exercise is determined by the relative workload (the intensity relative to VO2 max or the LT) rather than the absolute workload. Unlike cortisol, there are few studies to document that overtraining alters the patterns of GH release. There is some evidence that GH pulse frequency is accelerated in amenorrheic athletes [71, 72]. One study reported that during 8 hours of nocturnal blood sampling, the greater number of GH pulses was accompanied by an increase in half-life of GH and a decrease in the mass of GH secreted per pulse [72]. During exercise, the amenorrheic athletes also showed a substantial blunting of stimulated peak and integrated GH secretion [72].

Comparison of healthy middle-aged (age = 42 y) and young (age = 21 y) men before and after 4 months of intensive endurance training [73] showed that the peak GH response to an incremental maximal exercise test was lower in middle-aged men (P < 0.01) than in young men. After training, the groups showed similar training-related increases in VO2 max, and neither group demonstrated any effect on the GH peak responses to exercise, confirming the blunted GH response in the middle-aged and older men cannot be modified with training [73]. Another recent study conducted in men and women older than age 60 observed no increase in 24-hour integrated GH concentrations after 1 year of moderate aerobic exercise training [74].

Mechanisms of Growth Hormone Release

At rest, GH release is stimulated by GHRH and is inhibited by somatostatin. The mechanisms responsible for exercise-induced GH release have not been elucidated. Enhanced cholinergic tone potentiates the GH response to moderate intensity exercise, possibly by suppressing hypothalamic secretion of somatostatin and enhancing the response to GHRH [75, 76]. During high-intensity exercise, augmented hypothalamic secretion of GHRH may occur in addition to suppression of hypothalamic somatostatin activity. It is also possible that secretion of an endogenous ligand for the GH secretagogue receptor may be increased during exercise [77]. Peripheral concentrations of ghrelin, which is one such ligand, are not altered with submaximal aerobic exercise (personal communication, Dall et al.).

Weltman et al. [78] have provided evidence suggesting that during exercise α2 adrenergic pathways may limit...
somatostatin release and stimulate GHRH release, thus triggering GH secretion. Conversely, β2-adrenergic agonists are likely to block GH secretion by eliciting somatostatin release [79]. Weltman et al. [78] have demonstrated that peripheral markers of heightened adrenergic outflow precede and are quantitative physiological correlates of exercise intensity-dependent GH release in humans.

In other efforts to establish how exercise perturbs the GH axis, several investigators have used multiple bouts of exercise. The GH response to exercise of moderate intensity (20 min at 100 W) may be attenuated by previous administration of a bolus of GHRH (100 μg) [80]. Thus, a pulse of GH secretion may induce negative feedback on the GH axis such that the GH response to a subsequent stimulus is reduced. In contrast, the GH response was not attenuated by repeated bouts of exercise separated by as little as 1 hour when a sufficient intensity (≈70% VO₂ max) and duration of exercise (30 min) were used. When repeated bouts of exercise were separated by a longer time interval (3.5 h), the GH response to exercise was augmented with successive periods of exercise [81]. These data suggest that exercise of appropriate intensity is a powerful stimulus of GH release that is able to override GH auto-negative feedback. This may involve stimulation of hypothalamic GHRH secretion and/or suppression of hypothalamic somatostatin release. Because GH auto-negative feedback is thought to involve the opposite mechanism, it is hypothesized that the exercise stimulus is more potent than the inhibitory feedback of GH on these hypothalamic neurons. In addition, the pituitary stores of GH do not limit the GH response and desensitization to this repeated stimulus does not occur. Similarly, Rosen et al. [82] observed more pronounced increases in ACTH, cortisol, and GH concentrations with two bouts of exercise than with one exercise bout. In contrast, Galassetti et al. [83] found GH, cortisol, and other hormones were blunted during a second exercise bout in men, but these hormone responses were preserved or increased in women. Differences in results between these studies may be because of methodological differences. In the latter study, subjects consumed carbohydrates in the second exercise bout to prevent hypoglycemia, which may have suppressed GH secretion.

Water balance may also influence the GH response to exercise. In male subjects performing cycling exercise with and without water intake (≈500 mL) to account for the water lost during the exercise session [84], the total GH response was lower with no water replacement than it was with water replacement. These authors concluded that the GH response to exercise decreases when exercise is performed without fluid intake, and they speculated that osmoreceptors and baroreceptors provide negative feedback to GH secretion.

Clinical Implications

Impact of Cortisol and Growth Hormone Deficiency on Exercise Performance

Patients with adrenal insufficiency require glucocorticoid replacement to avoid nausea, vomiting, dehydration, muscle weakness, hypotension, and death. Thus, exercise performance is dramatically affected by chronic cortisol deficiency [85]. In normal subjects, administration of metyrapone during the evening before morning exercise did not alter maximal oxygen uptake (VO₂ max) despite a significant reduction in plasma cortisol concentrations and increased 11-deoxycortisol and ACTH concentrations. However, the subjects reported a higher rating of perceived exertion and maximal heart rates were greater after metyrapone administration [22]. Thus, reductions of plasma cortisol concentrations for less than 1 day does not have major effects on exercise performance, but prolonged cortisol deficiency results in an impaired ability to exercise.

The impact of GH deficiency on exercise performance has only been appreciated during the past 10 to 15 years. Adults with GH deficiency (GHD) caused by hypothalamic or pituitary disease have alterations in their body composition, with marked reductions in lean body mass and excess body fat when compared with their peers without GHD [86]. This reduction in muscle mass is considered to be one of the causes of the reduced exercise capacity in this group of individuals. In adults with GHD, VO₂ max was reduced by 20% using cycle ergometry when compared with the values predicted for age, sex, and height. Six months of GH replacement therapy in these patients increased VO₂ max by 17% compared with the placebo group [87], and the improvement was attributable to the increase in lean body mass associated with GH treatment. Thigh muscle cross-sectional area and strength of the hip flexors and limb girdle muscles were also increased by GH therapy in these patients [88]. In a second study [89], adults with GHD treated for 6 months with GH had an increase in VO₂ max of 14% compared with those administered treatment with placebo, achieving levels that were within those predicted for age, sex, and weight. Maximal power output increased by 15% in the GH-treated patients compared with those who received placebo. Exercise time, anaerobic threshold, maximal ventilation and the product of power output, and operating time also increased significantly in this study [89]. Similar results were reported in a 6-month placebo controlled study of adult patients with childhood-onset GHD. This study also reported that the beneficial effect of GH on exercise performance persisted for 36 months during open-label therapy, but VO₂ max...
reported fatigue, but VO₂ max and muscle strength did not increase the oxygen cost of walking and the patients’ self-reported fatigue, but VO₂ max and muscle strength did not improve in this study, perhaps because of the shorter duration of therapy [91]. In contrast, 2 years of GH therapy in adults with GHD has been reported to improve muscle strength [92]. Finally, GHD in adults is associated with impaired sweating and thermoregulation, which places these patients at risk for hyperthermia during physical activity in hot environments [93].

Thus, cortisol and GH are necessary for optimal exercise performance. The importance of these hormones for exercise performance is most evident in chronic severe hormone deficiency states. Replacement therapy for cortisol or GH deficiency restores normal exercise performance. It is more difficult to demonstrate an essential role for GH in exercise performance in states of partial GH deficiency, such as normal aging. For example, two research groups have demonstrated that administration of GH to healthy elderly subjects does not enhance the response to resistance training programs of 16 to 24 weeks in duration [94, 95].

Significance of Impaired Growth Hormone Response to Exercise in Obese Subjects

The attenuation of the GH response to exercise in obese subjects is similar to that observed in response to pharmacological stimuli of GH secretion, including insulin-induced hypoglycemia, GHRH, arginine, l-dopa, clonidine, pyridostigmine, GH-releasing peptide, and various combinations of these pharmacological agents [96–99]. The exercise-induced GH response in obese subjects is greater than the response of l-dopa, and the clonidine [98, 99] response is similar to that observed with GHRH, pyridostigmine, and arginine [96–99] and lesser than the response to GH-releasing peptide and tests using combinations of agents [98, 99]. The reduced GH secretion with obesity is not an absolute or permanent defect. Prolonged fasting or significant weight loss [96, 97] will restore GH levels similar to those observed in fed nonobese subjects. With weight loss, the GH responses to other provocative stimuli are also improved [97, 100, 101]. Massive weight loss in obese individuals will restore 24-hour GH release to normal levels [102], suggesting that the metabolic milieu associated with obesity results in negative feedback on the neuroendocrine mechanisms controlling GH secretion. In obese individuals, exercise of sufficient intensity and duration can stimulate GH release despite these metabolic negative feedback signals [61]; however, the response is diminished, as it is with other known stimuli for GH secretion.

These findings suggest that decreased GH secretion is not a primary cause of obesity in patients without hypothalamic or pituitary disease. However, it is possible that diminished GH secretion associated with obesity may contribute to continued body fat gain. In support of this latter hypothesis, 9 months of GH treatment of abdominally obese men without hypothalamic or pituitary disease resulted in a reduction of abdominal fat, improved insulin sensitivity, and favorable effects on lipoprotein metabolism and diastolic blood pressure [103]. These preliminary findings should be confirmed in larger clinical trials including women before such therapy is used in clinical practice.

Significance of Excessive Cortisol Response to Exercise

The cortisol pattern of response to exercise has been considered to be predictive of an individual’s adaptation to other forms of stress. Differential sensitivity of the HPA axis to glucocorticoid suppression is a normal feature of human physiology, and the frequency of glucocorticoid resistance among the normal population is higher when exercise is used as a criterion [20]. Within a normal healthy population, there is a differential metabolic and neuroendocrine reactivity to exercise stress. In response to exercise stress, Petrides et al. [20] observed that one group of men and women exhibited high reactivity as indicated by exaggerated exercise-induced increases in plasma lactate, glucose, arginine vasopressin (AVP), ACTH, and cortisol. The other group demonstrated low to moderate reactivity [20]. With dexamethasone (DEX) suppression (4-mg orally), high-intensity exercise resulted in escape of ACTH and cortisol in high responders but not in low or moderate responders [20]. The exaggerated HPA responsiveness in the high responders seems to reflect a confluence of possible relative type II glucocorticoid resistance, enhanced CRH secretion during the stress of exercise, and a glucocorticoid-mediated facilitation of stress-induced plasma AVP secretion [21]. Petrides et al. propose that the response of the HPA axis to glucocorticoid pretreatment combined with strenuous exercise may be useful to determine susceptibility to disorders characterized by hyperactivation and hypoactivation of the HPA axis.

The escape of pituitary ACTH release from DEX suppression (4-mg orally) is dependent on exercise intensity. An exercise intensity of 90% VO₂ max resulted in an escape of ACTH, but an intensity of 100% VO₂ max resulted in a greater escape of ACTH and cortisol release.
The stronger exercise stimulus also further increased plasma concentrations of AVP. Thus, high-intensity exercise can overcome glucocorticoid negative feedback, and this occurs to a greater extent in women than in men [104]. The magnitude of the ACTH and cortisol response may reflect the degree of hypothalamic drive for AVP and CRH secretion and the sensitivity of the glucocorticoid negative feedback system at the time of the stress [104].

The differences between low and high responders are also apparent with low-dose DEX (1-mg orally) suppression, the usual dose used clinically to screen for Cushing’s syndrome. This dose of DEX suppressed the response of the HPA axis to exercise in the low-responding subjects but not in the high-responding subjects. Basal concentrations of cortisol were also higher in the high responders [105]. These data provide further support for differential sensitivity of the HPA axis to stress and to glucocorticoid negative feedback among individuals. The relationship between these differences in HPA reactivity and sensitivity to negative feedback and short-term function or long-term health remains to be established. It is known, however, that men who are high responders to exercise stress are also high responders to psychological stress [106] (Fig. 3). This generalized response suggests a nonspecific tendency for greater stress reactivity. Additional studies need to determine whether high- or low-stress responsiveness in healthy individuals is a transitional state caused by some underlying perceived stress or is an inherent genetic characteristic [106].

Conclusions

Exercise is a physiologically relevant and reproducible stimulus for GH and cortisol secretion. The degree of perturbation of the HPA depends on many factors and can be substantially altered with prolonged stress or overtraining. Deficiencies of GH and/or cortisol may contribute to abnormalities in body composition, metabolism, and exercise performance. The clinical importance of impaired GH response to exercise in obese subjects and the exaggerated reactivity of the HPA axis in response to exercise in some individuals requires further investigation. Because cortisol and GH respond to stressful stimuli, more research is needed on the interaction of these two axes. Although no studies have examined the interaction between these two axes during exercise stress, hourly administration of low doses of ACTH and CRH increased the number of GH pulses and the amount of GH released during the daytime [107]. Furthermore, GH administration can prevent the protein catabolic effects of glucocorticoid excess [108]. Thus, further research should investigate the interactions of GH and cortisol from secretory and metabolic perspectives. Exercise may once again prove to be a useful model for these future studies.

References

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