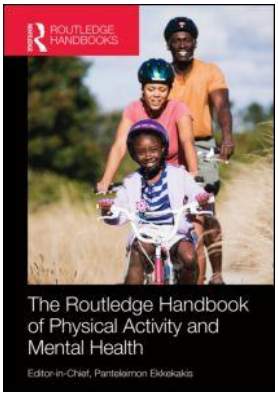

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22

PHYSICAL ACTIVITY AND STRESS

Peripheral physiological adaptations

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Stress constitutes a sophisticated physiological response coordinated by the activation of the hypothalamic pituitary adrenal (HPA) axis and sympathetic nervous system (SNS). These primary mediators of the stress response act on peripheral tissues (liver, muscle, and adipose tissue) to mobilize energy stores and prepare the body for a "fight or flight" action. In today's society, stressors are more likely to be psychological than physical in nature, and are comprised of a variety of adverse forces including emotional, social, or professional. Psychological stress is viewed as a prolonged or chronic type of stress as the origin and termination of the stressor is most likely unclear. On the other hand, physical activity, a stressor in and of itself, provides beneficial adaptations rather than deleterious effects to the body in animals (Campbell et al., 2010) and in humans (Luger et al., 1987). Activation of both the HPA axis and SNS has profound effects on metabolism, cardiovascular function, immune function, and reproduction. Chronic stress is associated with a number of metabolic disturbances including heart disease, insulin resistance, and central obesity (De Kloet, Vreugdenhil, Oitzl, & Joels, 1998; Habib, Gold, & Chrousos, 2001; Miller & O'Callaghan, 2002; Seckl, Morton, Chapman, & Walker, 2004). In contrast, physical activity also increases mobilization of energy but reverses undesirable metabolic effects associated with chronic stress (Schmidt, Wijga, Von Zur Muhlen, Brabant, & Wagner, 1997). This chapter will highlight the dynamic physiological adaptations that occur in peripheral tissues in response to both physical activity and chronic psychological stress.

Glucocorticoid activation during stress

Central stress response: activation of the HPA axis and SNS

The stress response first begins by recognition of a threat and excitatory signals stimulate the parvocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus to secrete corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP) into hypophyseal portal circulation. In brief, both CRH and AVP travel to the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH) and its precursor proopiomelancortin (POMC) (Tsigos & Chrousos, 2002). AVP is secreted along with CRH as it functions to exaggerate the stimulatory effect of CRH and binds to similar receptors on the pituitary to facilitate the entry of calcium into the cells. However, alone AVP does not affect ACTH levels as it does not induce POMC

transcription (Antoni, 1993). ACTH, released from the pituitary gland, binds to the melanocortin 2 receptors localized within the zona fasciculate of the adrenal cortex (Gallo-Payet, Cote, Chorvatova, Guillon, & Payet, 1999). This process is critical as it stimulates the release of glucocorticoids (GCs) into circulation from the adrenal in the active form of either cortisol or corticosterone in humans or rodents, respectively. Secretion of GCs occurs in response to stressful stimuli and as a result of a regular diurnal pattern of release. GCs that are released in the systemic circulation bind to GC receptors (GRs), which are ubiquitously expressed throughout the body and brain.

Overexposure of stress hormones in the tissues is prevented by a negative feedback system in which GCs bind to their respective receptors in the hypothalamus and anterior pituitary to decrease HPA activation and GC production (Reul & de Kloet, 1985). As lipid-soluble hormones, GCs are capable of freely diffusing through the blood–brain barrier to bind to mineralocorticoid receptors (MRs) or GRs located in the hippocampus, anterior pituitary, or PVN of the hypothalamus. In the hippocampus, GCs have a 10-fold higher binding affinity for MRs in the brain, thus at lower concentrations GCs primarily bind to MRs (Yao & Denver, 2007). Therefore, MRs are involved in the maintenance of basal HPA activity, while GRs are responsible for shutting off HPA activity when GCs increase (i.e., during the peak of the diurnal rhythm or during a stress response). The negative feedback effects of GCs are exerted directly on the anterior pituitary to inhibit the synthesis and secretion of ACTH and centrally to block CRH production. Activation of the PVN neurons occurs in combination with the central catecholaminergic neurons in the brainstem. Both the HPA axis and SNS work together to coordinate a stress response that is initiated in the CNS but is concluded in peripheral target tissues.

Peripheral stress response: activation of GR and 11βHSD1

The peripheral actions of GCs are mediated primarily via their binding to their receptor, although non-receptor-mediated, non-genomic actions have recently been described. As such, the tissue-specific response is determined by the concentration of hormone, the expression and activity of the enzymes responsible for pre-receptor metabolism, and the density of GR (Seckl et al., 2004). GCs are known for their transcriptional control and are capable of up-regulating or inhibiting transcription of hundreds of diverse genes (Revollo & Cidlowski, 2009).

GC action in peripheral tissues is further regulated by the pre-receptor enzyme activity of 11 β hydroxysteroid dehyodrogenase (11βHSD). These intracellular NADPH-dependent enzymes regulate pre-receptor metabolism of GCs (Albiston, Obeyesekere, Smith, & Krozowski, 1994). They exist in two isoforms: 11βHSD1 and 11βHSD2. The predominant isoform outside of the kidney, 11βHSD1, is distributed in adipose, liver, and muscle tissue and is involved in the interconversion of inert GCs (e.g., cortisone) into their active form (e.g., cortisol), thus enabling increased GC action. 11βHSD1 activity/expression can amplify levels of active GCs by 10- to 15-fold over that found in plasma, thereby potentially contributing to a host of deleterious metabolic consequences (Masuzaki et al., 2001).

Types of stress

The term "stressor" may be considered any threat to homeostasis. This may be difficult to define any further since the perception of stress differs from organism to organism. In rodent models, stress research incorporates a number of modalities including exercise, physical restraint, electric shock, near drowning, exposure to cold, and an introduction of a socially dominant member of

the same species (Rosmond, 2005). In humans, the definition of a stressor becomes even more complex and may include adversity endured in a number of social and emotional situations and remains difficult to simulate within the laboratory setting. In a laboratory or clinical setting, a stress response in humans is often provoked by manipulation of the environment (cold temperature), perceived uncontrollability, and through a social-evaluative threat typically referred to as the Trier Social Stress Test. This test may be the most useful and appropriate standardized protocol for studies of stress hormone reactivity as the test combines a social component of a psychological stress where task performance could be negatively judged by others and uncontrollability of the immediate situation (Birkett, 2011).

Chronic stress

A tight regulation of GC release via the circadian rhythm and negative feedback of the HPA axis is required to protect against the deleterious effects of chronically elevated GC levels. These deleterious effects are highlighted in spontaneous conditions of excess GC production, as occurs in Cushing's syndrome, in which patients experience central adiposity, impaired glucose tolerance, and attenuated muscle mass. Similarly, individuals with type 2 diabetes mellitus (T2DM) or insulin resistance and cardiometabolic disease often have elevated basal plasma GC levels, suggesting a link between altered GC concentrations and development of metabolic disease (Andrews & Walker, 1999). Altered GC release may also occur in response to chronic psychological stress that includes emotional, social, or professional stress, which can negatively impact the rhythmic release of GCs.

Tissue actions of glucocorticoids

Whole body metabolism

GCs facilitate the delivery of substrates to specific tissues (e.g., muscle, heart), ideally in situations of increased metabolic rate. Within adipose tissue, elevations in GCs are associated with increased lipolysis, liberating free fatty acids into circulation where they may be taken up and oxidized by other tissues, although the acute lipolytic effect of GCs on adipose tissue has recently been challenged (Peckett, Wright, & Riddell, 2011). Evidence is emerging that the hormone may actually inhibit lipolysis through non-genomic mechanisms (Campbell, Peckett, D'souza, Hawke, & Riddell, 2011), although further clarification is needed. In the liver, GCs drive the increase in glucose production from non-glucose substrates (i.e., gluconeogenesis), by escalating the expression of the rate-limiting enzymes phosphoenopyruvate carboxykinase (PEPCK) and glucose 6 phosphatase (G6Pase). Other sources of non-glucose substrates may be derived from other tissues including skeletal muscle, in which GCs promote liberation of amino acids. The negative consequences of elevated GCs are demonstrated in transgenic mice with 11βHSD1 adipocyte over-expression, which causes hyperglycemia, insulin resistance, dyslipidemia, and hypertension (Masuzaki et al., 2001; Rask et al., 2001). 11βHSD1 knockout mice have much healthier fat partitioning, which helps to protect against the development of the metabolic syndrome (Wamil et al., 2011).

Visceral adiposity

Numerous epidemiological studies have linked elevated stress levels with the development of cardiac and metabolic conditions, which may be driven by the potent adipogenic effects of these

hormones, particularly in central adipose depots (Bjorntorp, 2001). GCs regulate adipose tissue differentiation and distribution, and in excess clearly induce visceral obesity (Peckett et al., 2011; van Raalte, Ouwens, & Diamant, 2009). The location of excess adiposity is extremely important as visceral adiposity is particularly associated with development of insulin resistance, T2DM, and other metabolic conditions (Kahn, Hull, & Utzschneider, 2006). Clinical studies have demonstrated a positive correlation between hypercortisolemia, as seen in Cushing's syndrome patients, and visceral fat accumulation (Chandola, Brunner, & Marmot, 2006). The mechanism behind this increased central adiposity is believed to be due to the elevated concentration of GR and 11βHSD1 in adipose depots, indicating increased sensitivity to GC action. Moreover, in male Sprague-Dawley rats elevated exogenous GC treatment (400mg corticosterone pellets for 14 days) (Shpilberg et al., 2012) significantly increased mRNA expressions of 11βHSD1 and GR compared to placebo animals (those administered wax pellets) in both epididymal and subcutaneous adipose depots. As well, GC treated animals had significantly more epididymal fat depots representing visceral adiposity than placebo animals. These findings suggest that a high level of GCs, perhaps indicative of chronic stress, promotes increases in GR and 11βHSD1 expression that lead to increased adipogenesis rather than elevated lipolysis, at least in the central adipose depots. Moreover, in the presence of insulin, cortisol has a greater stimulatory effect on lipoprotein lipase activity, which hydrolyzes triglycerides from the lipid droplet in human adipose tissue *in vitro*, resulting in increased lipolysis of adipose tissue. It is likely due to the elevated insulin levels as well as other factors associated with obesity that contribute to the accumulation of visceral adiposity (Peckett et al., 2011). However, these mechanisms still remain unclear and further investigations are required.

Insulin sensitivity

T2DM is caused by a combination of insulin deficiency and insulin resistance. GCs and catecholamines (also released from the adrenals) are known to oppose the effects of insulin. Elevated cortisol secretion or a decrease in diurnal variability is associated with glucose intolerance and insulin resistance (Buren & Eriksson, 2005). GCs *in vivo* appear to impair insulin-dependent glucose uptake in peripheral tissues (Shpilberg et al., 2012) and stimulate gluconeogenesis in the liver (D'souza et al., 2012; Rizza, Mandarino, & Gerich, 1982). In skeletal muscle, GCs decrease GLUT4 translocation and inhibit glycogen synthesis, thus increasing glucose availability for the brain (Dimitriadis et al., 1997; Nielsen et al., 2004).

Elevated GC levels are a hallmark feature of experimental models of diabetes (Chan, Inouye, Riddell, Vranic, & Matthews, 2003). Zucker Diabetic Fatty (ZDF) rats gradually develop hypercortisolemia after 5 weeks of age as well as hyperinsulinemia (Campbell et al., 2010). These elevated GC levels may also mediate the observed hyperglycemia that occurs in this and other models of obesity/T2DM (Shimomura, Bray, & Lee, 1987). Moreover, clinical studies have also provided compelling evidence of a relationship between chronic stress or elevated GC levels and impaired glucose tolerance (Hoes et al., 2011; van Raalte et al., 2010; van Raalte et al., 2011).

Physical inactivity: the exercise-deficient phenotype

Currently, there is considerable research available that draws the association between sedentary individuals and the prevalence of "cardiometabolic-based diseases" (LaMonte & Blair, 2006). Unfortunately, increasing psychological stress is associated with a decline in physical activity – a behavior that protects against disease (Geulayov, Goral, Muhsen, Lipsitz, & Gross, 2010).

Adaptive effects of exercise

Exercise as a "stressor"

In the general sense, a "stress" implies a disturbance to the "normal" physiological equilibrium, and thus is often associated with a negative connotation. However, not all "stressors" have adverse effects. Physical activity and exercise have the capacity to disturb the normal homeostasis, and can be considered a "stressor" by definition (Hackney, 2006; Steadman & Sharkey, 1969). Exercise in this context is considered to be a period of purposeful physical activity in which the metabolic rate significantly rises above rest for a period of time. Exercise can be acute (30 minutes of brisk walking at a significantly elevated heart rate) or chronic (e.g., several weeks of an exercise training program). Selye (1976) was the first to acknowledge the systemic effects of physical exercise as being different from those produced by other stress stimuli – he termed exercise a "eustressor." These differences are related to the fact that training, or repeated bouts of the same exercise, results in an attenuated HPA axis response. However, it should be noted that the type and duration of training are critical determinants of whether or not there is an attenuated stress response (Garcia, Mari, Valles, Dal-Zotto, & Armario, 2000).

Forms of exercise stress

Exercise training and the adaptations to the initial stress of exercise are unique compared to chronic psychological stress in that exercise promotes an adaptive response that reduces the stress response over time. Resting or basal levels of GCs have been found to rise initially but eventually return to pre-training levels during the course of exercise training, at least in rodents (Coutinho, Campbell, Fediuc, & Riddell, 2006; Park et al., 2005). Paradoxically, non-exercise forms of acute stress may also be advantageous to the body as well. Exposure to intermittent restraint stress or swimming stress in a rodent model of T2DM (ZDF rats) delayed development of hyperglycemia due to adaptation of feedback sensitivity of the HPA axis and adaptation to pancreatic β-cells (Bates et al., 2007; Bates, Sirek, Kiraly, Yue, Goche Montes et al., 2008; Bates, Sirek, Kiraly, Yue, Riddell, et al., 2008). ZDF rats that were subjected to intermittent stress (restraint) had lower baseline GC levels as well as higher insulin levels and better glucose control. Moreover, other forms of strenuous stress such as forced swimming have been investigated on diabetes development. Kiraly et al. (2007) examined male ZDF rats after a series of non-volitional exercise bouts and showed improved glycemic control compared to sedentary controls in just 5 weeks of daily forced swimming exercise.

Benefits of exercise – peripheral adaptations

The central stress response can cause debilitating effects to the brain that can induce hippocampal remodeling, suppression of gonadal and growth hormones, as well as lead to other comorbidities such as hypertension, cardiovascular disease, and diabetes. On the other hand, regular exercise alters tissue sensitivity to stress not only through the central system but through peripheral tissue adaptations such as the adrenal glands, adipose, and skeletal muscle (Campbell, Fediuc, Hawke, & Riddell, 2009). These benefits include improvements in metabolic function, insulin sensitivity, and increasing fuel supplies for oxidation rather than for storage. Therefore, it is now well established that in the presence of chronic social stress, regular exercise is imperative (Tsatsoulis & Fountoulakis, 2006).

Glucocorticoid sensitivity

Adaptations in GC sensitivity as a result of exercise training are tissue specific and are largely due to altered expression of GR and 11βHSD1. For example, endurance swim training in rodents results in decreases in hepatic and thymus GR content (Peijie, Zicai, Haowen, & Renbao, 2004). This lowering of GR content has also been demonstrated in rodent muscle and liver following 4 weeks of voluntary wheel running in hamsters (Coutinho et al., 2006). Normal sedentary males who undergo 6 weeks of training experienced reduced basal cortisol levels, significant reductions in mRNA levels of GR, and reduced pro-inflammatory cytokine expression including NFKB1 and IkB kinase A levels (Sousa e Silva et al., 2010). Another study demonstrated that exercise training led to a decrease in GR in human peripheral blood cells and cultured monocytes of trained male adult athletes (Peijie et al., 2004). This down-regulation of monocyte GC sensitivity suggests an adaptation of the HPA axis to repeated, prolonged exercise that induces increases in GC secretion to protect the body from detrimental effects of chronic stress (Duclos, Gouarne, & Bonnemaison, 2003). Even low-grade exercise in obese youth (ages 9–15) has been shown to induce reductions in GC sensitivity after 3 months (Faria et al., 2010).

Skeletal muscle

Evidence shows that exercise training improves glucose transport via an insulin-independent mechanism within skeletal muscle. Training results in a rapid increase in the expression of GLUT4 content translocation to the plasma membrane in skeletal muscle (Kraniou, Cameron-Smith, & Hargreaves, 2006). Other mechanisms of improved skeletal muscle insulin sensitivity may include modulations to peripheral GC action. Following 4 weeks of voluntary wheel running, rodents had decreased GR and 11βHSD1 content in skeletal muscle, which would be expected to improve insulin sensitivity (Coutinho et al., 2006). At the very least, regular exercise should help offset the insulin resistance in skeletal muscle caused by elevated GCs, although surprisingly few studies have investigated this in human or animal models of Cushing's Syndrome.

Visceral adiposity and body composition

Voluntary wheel running in rodents promotes a reduction in body weight and improves body composition (Narath, Skalicky, & Viidik, 2001). In contrast to what is observed in liver and muscle tissue, GR and 11βHSD1 content in adipose tissue increase in animals undergoing voluntary training (Campbell, Rakhshani, Fediuc, Bruni, & Riddell, 2009). This increase in GC activity and content is believed to facilitate increased lipolysis when insulin levels are low, but may set the stage for adiposity rebound if the animal stops exercising and insulin levels rise. These findings suggest that GC-mediated central obesity is avoided with training because training lowers circulating insulin levels and increases adipose tissue lipase activity (Campbell et al., 2010). A summary of the abovementioned peripheral adaptations to GC secretion and exercise training can be found in Figure 22.1.

Exercise type influences adaptations to GC sensitivity

Changes to GC sensitivity occur after a single bout of exercise and are tissue specific. For example, GR expression in peripheral blood cells is down-regulated in response to a single bout of exercise (Smits, Grunberg, Derijk, Sterk, & Hiemstra, 1998) while GR expression paradoxically increases in muscle following a single exercise bout of strenuous eccentric exercise (Willoughby, Taylor,

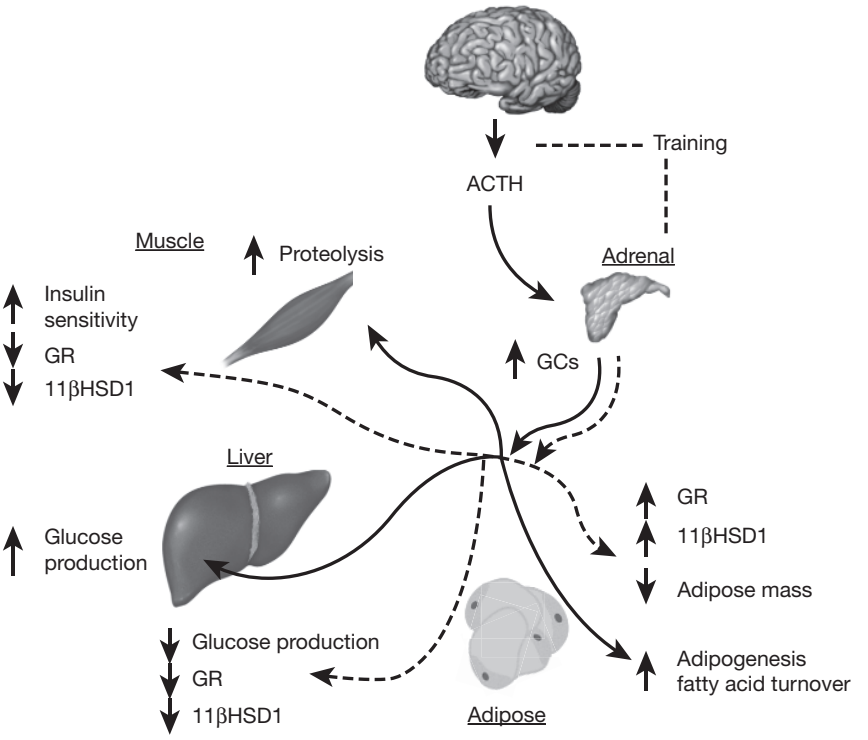

Figure 22.1 Glucocorticoid (GC) action in peripheral tissues (skeletal muscle, liver, and adipose tissue) in the presence and absence of exercise training. Perceived stress activates ACTH release from the pituitary gland in the brain, which stimulates GC release from the adrenal gland. Solid black lines indicate GCs actions. Dashed lines indicate inhibitory actions of training. GCs stimulate adipogenesis and increased fatty acid turnover in the adipose tissue. In the liver, GCs increase glucose production through mechanisms of gluconeogenesis and glycogenolysis. In skeletal muscle, GCs up-regulate proteolysis. In the presence of exercise training, the brain adapts to exercise as a stress and decreases ACTH release into circulation. This lowers GC release from the adrenal gland and contributes to reduced amounts of GC in the plasma. Dashed line indicates GC action as a result of exercise training in peripheral tissues. Overall, regular exercise lowers basal (resting) GC levels in the circulation. With regular exercise, GR and 11βHSD1 mRNA expression may be decreased in skeletal muscle and liver, while expression in adipose tissue increases. Adipose mass decreases and insulin sensitivity increases in liver and muscle. The functional significance of increased GC exposure in adipose tissue with training, via increased GR and 11βHSD1 expression, is unclear but may help to promote lipolysis and adiposity rebound if regular exercise ceases.

& Taylor, 2003). Elevations in GC levels typically return to normal within 24 hours after a single bout of exercise (Duclos, Corcuff, Rashedi, Fougere, & Manier, 1997). However, men undergoing a single bout of rowing exercise have a decrease in peripheral blood lymphocyte GC sensitivity and GC-induced cytokine (IL-6, TNF-alpha) release (DeRijk, Petrides, Deuster, Gold, & Sternberg, 1996; Smits et al., 1998). These findings demonstrate that even acute physical activity has the potential to temporarily alter the sensitivity to stress hormones in peripheral tissues.

A number of animal studies have demonstrated that basal (i.e., resting, unstimulated) GCs are lowered with regular exercise, after a period of brief elevation. In one study, obese ZDF rats that were exercise trained 5 days per week for 14 weeks demonstrated lower basal GC levels after exercise training (Martin-Cordero, Garcia, Hinchado, & Ortega, 2011). However, after a single bout of exercise, the obese ZDF animals had higher GC levels than untrained animals in the

post-exercise period. These data suggest exercise training adapts to chronic stimulation of the HPA axis; however, a single bout of exercise still can promote increases in GC levels, perhaps to increase fuel utilization and recovery.

Research methodology: issues worth considering

Challenges in the investigation of the physiological adaptations that occur with exercise and stress include the variability of the stressors used, difficulty in quantifying the stress response, and a lack of uniformity in techniques employed to assess the stress response. Physical activity involves a number of variables that regulate the amount of energy expenditure or rate of energy expenditure that occurs, including the type, intensity, regularity, and duration of the activity. In addition to the variability in the types of activity performed are the ways in which stress is quantified to reflect adaptations by the stress system.

Models of exercise

Animal models of exercise are commonly used to study the stress response to exercise as these experimental designs provide a controlled dose and timing of exercise, but at a cost. Forced exercise models are considered a form of anticipatory stress because they elicit a physiological and psychological response (e.g., anxiety) (Pacak & Palkovits, 2001). Animal models employ the use of foot shock and cold water stimulus, and despite providing beneficial effects to metabolism by increasing mitochondrial capacity and reducing weight gain, they also result in adverse effects, including adrenal hypertrophy and suppressed immune function, which make them difficult to relate to human models of exercise (Moraska, Deak, Spencer, Roth, & Fleshner, 2000). Also, these forms of exercise are typically employed during daylight hours—the normal sleep period for rodents. Alternatively, the use of voluntary wheel running in rodent models of stress and exercise is regarded as the most "natural" model of exercise training, as it generates a stress response similar to human exercise (Stranahan, Lee, & Mattson, 2008). However, voluntary exercise is not without its own limitations. Of primary concern is the inability to regulate exercise quantity, quality, timing, and intensity among individual animals. For example, young hamsters may run 17–20 kilometers per night, while rats typically will run between 2 and 15 kilometers. Similarly, the age of rodents used may also influence the exercise outcome. Older C57BL/6J mice (19–22 months) experienced a decline in the number of wheel revolutions per day and decrease in activity duration in comparison to adult (6–9 months) mice (Valentinuzzi, Scarbrough, Takahashi, & Turek, 1997). These studies demonstrate the variability of exercise response that occurs as a result of the strain and age of animals, and suggest that a more streamlined methodology should be employed to allow for an easier comparison between exercise studies examining the stress response.

Measuring the peripheral response

Methods employed to assess the peripheral stress response usually involve quantification of hormone levels released during the stressor/exercise. These methods range from salivary, urine, fecal material and/or plasma samples for cortisol, corticosterone, or their metabolites. The testing of hormones from saliva offers a non-invasive, stress-free alternative to serum that is commonly employed in human studies of stress and exercise. Measurements of cortisol in saliva are a useful tool to analyze stress response; however, the concentrations in the saliva differ from those in serum as salivary glands have the capacity to metabolize steroids into their inactive forms (Shimojo

et al., 1997). The uniformity with which salivary hormone samples are collected must also be taken into consideration as confounders including type of exercise, time of day, and method of collecting sample can all influence hormone values (Gatti & De Palo, 2011). Similarly, cortisol sampling via urine collection has a wide variation in the response to stress. As recently reported, a case study in healthy women for 65 days in 12-hour intervals provided evidence that the appearance of cortisol in the urine was extremely dependent on the perceived stress that was either categorized as positive or negative, as well as the emotional level of the stressful event (Schubert et al., 2012).

Future directions

The field of stress physiology has grown tremendously since Dr. Selye first acknowledged the stress response in the late 1930s. However, there still remains a great deal of refinement of techniques and additional information that is required to better understand the peripheral physiological adaptations to stress and exercise. Topics requiring further research include (a) examining the intermediate to long-term benefits of exercise on the stress system by conducting extended term follow up studies; (b) utilizing both animal and human models of various ages of development and use of disease models to determine the influence of stress adaptations that occur with exercise; (c) characterizing features of physical activity to distinguish between the effects of voluntary and involuntary exercise, intensity, duration, and frequency on the peripheral stress system; and (d) streamlining physiological measures, which will help determine the appropriate method of stress hormone measurement (salivary GCs, plasma GCs) that provides the most accurate reflection of the stress response and ensure little technical variability in data collection.

Conclusion

It has long been established that exercise has a positive influence on energy balance and other aspects of fitness. However, additional benefits to exercise exist with respect to its influence on stress hormone levels, behavior, mood, and immune function. The study of the physiological adaptations that occur with regular physical activity is important to determine how it can be utilized to mitigate the effects of chronic stress. The mechanisms behind these protective and adaptive effects are multiple and tissue specific. Understanding the integrative response of the stress system to physical activity will lead to valuable clues about the potential benefits of exercise in protecting against development of chronic diseases including obesity, diabetes, and cardiovascular disease.

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