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Stress and obesity: the role of the hypothalamic–pituitary–adrenal axis in metabolic disease

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Abstract

Purpose of review—Chronic stress, combined with positive energy balance, may be a contributor to the increased risk for obesity, especially upper body obesity, and other metabolic diseases. This association may be mediated by alterations in the hypothalamic–pituitary–adrenal (HPA) axis. In this review, we summarize the major research that has been conducted on the role of the HPA axis in obesity and metabolic disease.

Recent findings—Dysregulation in the HPA axis has been associated with upper body obesity, but data are inconsistent, possibly due to methodological differences across studies. In addition to systemic effects, changes in local cortisol metabolism in adipose tissue may also influence the risk for obesity. HPA axis dysregulation may be the causal link between conditions such as maternal malnutrition and sleep deprivation with metabolic disease.

Summary—The present review provides evidence for the relationship between chronic stress, alterations in HPA activity, and obesity. Understanding these associations and its interactions with other factors will be important in developing effective treatments for obesity and related metabolic diseases.

Keywords

cortisol; hypothalamic-pituitary-adrenal axis; metabolic syndrome; obesity

Introduction and background

The prevalence of obesity has increased dramatically in the USA in the last several decades. Obesity, particularly upper body obesity (UBO), is associated with type 2 diabetes (T2DM), dyslipidemia, and hypertension. These associations describe the metabolic syndrome, a clustering of symptoms with insulin resistance as a core cause [1,2]. Currently, the prevalence of obesity and metabolic syndrome in the USA is 33 [3] and 24% [4], respectively, deeming both conditions important public health issues, requiring immediate efforts to understand these diseases and reduce their occurrence.

Elements of modern society, including western diet, sedentary lifestyle, and environmental stress may contribute to positive energy balance and the development of obesity and metabolic diseases, possibly through dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis.

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Stress response: role of hypothalamic–pituitary–adrenal axis

Stress is a challenge to the natural homeostasis of an organism [5]. Animals react to stress by producing a physiological stress response to regain equilibrium lost by the stressor. The stress response is characterized by acute behavioral and physical adaptations, including increased cognition, analgesia, gluconeogenesis, lipolysis, and inhibition of reproduction [6]. There are two major components of the stress response: the autonomic nervous system (ANS), which encompasses the sympathetic and parasympathetic nervous system, and the HPA axis. These systems work centrally and peripherally to produce several responses. The 'fight or flight response' is an active reaction to either confront the stressor or escape confrontation. The 'defeat response' is when the individual does not engage in either the fight or flight response and ultimately 'loses' the confrontation; this is the primary stress response in modern society and is associated with HPA axis changes [7]. Although the ANS is a key element of the stress response, the purpose of this review is to discuss the role of the HPA axis in obesity and metabolic disease.

Stress can be caused by external stressors such as employment or social strains or by intrinsic stressors such as sleep deprivation. Although an acute short-term stress response is necessary for homeostasis recovery, chronic or prolonged stress responses can be harmful and may cause several disease states [5]. A study on women [8] reported that history of depression was associated with hyperactivity of the HPA axis and decreased bone mineral density. In the past 30 years, numerous studies have shown that obesity and other metabolic risk factors are associated with lower socioeconomic status, job strain, sleep deprivation, and depression [9–14].

Elegant studies on stress and risk for obesity and metabolic disease in nonhuman primates [15,16] were previously reported. In female cynomologus monkeys fed an atherogenic diet and housed in social groups, subordinate animals (more likely to receive aggression) showed higher visceral adipose tissue (VAT) to subcutaneous adipose tissue (SAT) ratio (suggesting UBO), incidence of atherosclerosis, and ovarian dysfunction compared with non-subordinate animals [17••].

Hypothalamic–pituitary–adrenal axis

The HPA axis is one of two major neuroendocrine systems associated with the stress response. Corticotropin-releasing hormone (CRH), secreted from the para-ventricular nucleus (PVN) of the hypothalamus, stimulates the synthesis of adrenocorticotropin (ACTH) from the anterior pituitary gland. Other hypothalamic ACTH secretagogues are arginine vasopressin and oxytocin, also produced in the PVN [18,19]. Physical stressors such as hypoglycemia, hemorrhage, and immune stimuli activate PVN neurons expressing arginine vasopressin and CRH [20]. ACTH stimulates cortisol production from the adrenal cortex. In addition to these mechanisms of HPA axis activation, studies in the past 15 years have demonstrated that cytokines produced by immune cells or adipocytes can also stimulate the HPA axis, at the level of the hypothalamus, anterior pituitary gland, and the adrenal cortex [6,21]. Cortisol is transported in circulation bound to corticosteroid-binding globulin (CBG) and directed to peripheral target tissues, where its availability is dependent on the activity of 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme. The 11β-HSD1 isoform converts the inactive cortisone into active cortisol, and the 11β-HSD2 isoform converts cortisol to the inactive cortisone [22]. Cortisol binds to the glucocorticoid receptor; this complex homodimerizes and translocates to the nucleus, binding to glucocorticoid response elements and modulating transcription of cortisol-responsive genes [6].

The first evidence that cortisol levels may be related to obesity and metabolic disease was based on clinical observations of Cushing's syndrome; the pathological hypercortisolemia in

Cushing's syndrome is associated with UBO, glucose intolerance [impaired glucose tolerance (IGT)], and hypertension. Adrenalectomy in Cushing's syndrome patients reverses IGT and obesity [22,23].

Studies in the field of obesity research in the past 10 years have demonstrated that obesity and metabolic syndrome are characterized by chronic inflammation [24]. Pro-inflammatory cytokines can stimulate the HPA axis; conversely, cortisol decreases the production of cytokines and other inflammatory mediators [25,26]. Therefore, it is evident that there exists some crosstalk between the HPA axis and the inflammatory response; this may relate to the role of HPA axis alterations in the development of obesity. A recent study [27•] reported that a higher BMI was associated with decreased anti-inflammatory action of glucocorticoids. Nevertheless, the nature of these relationships remains to be determined.

Clinical assessment of hypothalamic–pituitary–adrenal axis

Of the various methods to assess HPA axis activity, 24-h urinary-free cortisol (UFC) or salivary cortisol, measured at different times of the day (to assess diurnal patterns of cortisol), are preferred to plasma measurements as these are not associated with stress of venipuncture and can be performed in a home setting at various times [28]. In the dexamethasone (a glucocorticoid receptor agonist) suppression test (DST), used to evaluate feedback inhibition of cortisol, 1 mg dexamethasone is given at midnight and plasma cortisol is measured 8 h later [29]. The accuracy of the DST in the determination of HPA axis alterations can be compromised by several conditions. Medications such as phenytoin, phenobarbitone, carbamazepine, and rifampicin increase the hepatic clearance of dexamethasone. Hormone therapy, pregnancy, and oral contraception, by increasing CBG levels, can result in a false-positive DST. Renal and hepatic dysfunction may reduce dexamethasone clearance, and psychiatric conditions such as depression, obesity, alcoholism, and anorexia nervosa may exhibit hypercortisolemia, which may confound dexamethasone suppression [30,31].

Cortisol response in obese patients

HPA axis assessment in common obesity is not performed routinely unless Cushing's syndrome is suspected. However, there is extensive clinical research on the role of the HPA axis in common obesity. Early studies were inconsistent and showed increased [32] or unchanged [33] 24-h UFC, and no or slight decrease in circulating cortisol levels [23]. More consistent data emerged when comparing patients with UBO with either lean individuals or patients with lower body obesity (LBO). Pasquali *et al.* [34] demonstrated increased 24-h UFC in women with UBO compared with women with LBO. Similarly, Rosmond *et al.* [35] reported a significant correlation between postprandial salivary cortisol and BMI, waist-to-hip ratio (WHR), fasting glucose, insulin, triglycerides, cholesterol, and blood pressure in men; similar correlations were demonstrated in morning salivary cortisol levels, BMI, and WHR [36]. Others also reported an increased postprandial salivary cortisol response in women with UBO compared with those with LBO, but no difference in dexamethasone suppression between groups [37]. One study, however, did not find an association of UBO with cortisol levels [38•].

Twenty-four-hour UFC is increased in obese women who gained weight as a result of a stressful event (stress-related obesity, SRO) compared with age-matched and weight-matched obese women without SRO (NSRO) or lean control women [39••], suggesting overactive HPA activity in SRO.

Genetic polymorphisms of hypothalamic–pituitary–adrenal axis in obesity

Currently, there are few genetic polymorphisms that present with both functional alterations in the HPA axis and obesity. Several polymorphisms at the level of ACTH synthesis [40], and in genes associated with glucocorticoid receptor [41,42] or local cortisol metabolism (11β-HSD1 and 11β-HSD2) [22,23,43–45], which may predict UBO, have been described. The variability in the heritability of obesity makes it difficult to determine the role of these polymorphisms in common obesity.

Tissue-specific cortisol metabolism: role of 11β-hydroxysteroid dehydrogenase 1 in adipose tissue

The enzyme 11β-HSD1, expressed in several peripheral tissues, including liver and adipose tissue [46], is important in HPA axis activity, regenerating active cortisol from its inactive forms intracellularly. Adipose tissue expression of 11β-HSD1 and regulation of local cortisol levels may play a role in the development of obesity and metabolic disease. Masuzaki *et al.* [47] found that overexpression of 11β-HSD1 in adipose tissue resulted in visceral obesity and metabolic syndrome in mice when fed a high-fat diet. Furthermore, adipose tissue overexpression of 11β-HSD2, the enzyme that inactivates cortisol, in obesity-prone mice, protected these mice from high-fat diet-induced obesity and IGT [48].

In humans, adipose tissue depot-specific alterations in 11β-HSD1 expression have been reported in obesity, with increased expression of 11β-HSD1 in SAT in obese individuals compared with lean individuals [49,50••]; studies on VAT have been less consistent [51–53]. Simonyte *et al.* [54••] found that SAT 11β-HSD1 expression was significantly higher than in VAT in obese patients. 11β-HSD1 enzyme activity in SAT was positively correlated with waist size, SAT and VAT area, and total adipose tissue area. The depot-specific alterations may be related to the regulation of 11β-HSD1. TNF-α and leptin, adipokines that may be expressed differentially across adipose tissue depots [55,56], have shown to stimulate 11β-HSD1 expression [57,58].

Recently, an elegant study by Stimson *et al.* [50••] measured cortisol release from different adipose tissue depots and from the liver in men. They found that cortisol release from SAT was substantial, but was undetectable in VAT. The authors concluded that due to feedback control of the HPA axis, this cortisol release from SAT was unlikely to produce systemic effects (which were mainly attributable to liver 11β-HSD1 activity) but rather autocrine and paracrine activities on adipose and surrounding tissues. Nevertheless, its effects on adipose tissue as an endocrine organ remain to be determined.

Interactions with diet and other appetite-regulating hormones

The pathology of obesity is multifactorial, and therefore, it is necessary to understand the various signals and their interactions that contribute to obesity. Leptin, a key adipokine secreted by adipocytes in proportion to fat mass, signals to the central nervous system regarding the status of fat stores to control food intake [59]. Adrenalectomy reduces body weight of obese leptin-deficient *ob/ob* mice [60], suggesting a role of glucocorticoids in leptin metabolism. Administration of dexamethasone in both lean and obese patients increases serum leptin levels [61–63], suggesting that glucocorticoids play a role in the control of hyperleptinemia characteristic of obesity. However, this effect of dexamethasone on leptin levels is seen only under fed conditions [62] or after administration of glucose and insulin [61], demonstrating an interaction of cortisol, insulin, and positive energy balance on leptin regulation.

Leptin levels show a circadian rhythm, with low values during the day and a rise during sleep [64]. It is speculated that the nocturnal rise in leptin serves to suppress appetite. Leptin

levels are robustly decreased by sleep deprivation [65]; this reduction may stimulate food intake and ultimately increase the risk for obesity and metabolic disease. Glucocorticoid agonists modulate leptin levels [61–63,66], and one study has shown that the decrease in leptin levels after 6 days of sleep restriction (compared with 6-day sleep recovery period) is inversely correlated to 24-h plasma cortisol levels [67].

Ghrelin is a gastric hormone that plays a role in long-term and short-term energy balance and acts centrally to increase food intake. There is a nocturnal increase in ghrelin during sleep deprivation [68] and an inverse relationship between serum ghrelin and serum cortisol levels during 84 h of fasting [69], suggesting that weight gain due to sleep deprivation may be mediated by cortisol and its effects on ghrelin, or vice versa. More studies are necessary to define the relationship between sleep deprivation, cortisol metabolism, appetite-regulating hormones and the development of obesity.

Several studies have examined a potential link between chronic stress and food intake. HPA axis dysregulation has been associated with other eating disorders such as binge eating disorder, bulimia, and anorexia nervosa [70–73]. Changes in insulin or neuropeptide Y (NPY) levels, peptides implicated in food intake regulation [74], occur as a result of altered cortisol metabolism [75,76]. Administration of the glucocorticoid prednisone has shown to stimulate food intake in healthy men [77]. Conversely, diet may influence cortisol metabolism. In obese men, cortisol levels increased after weight loss with low calorie high-fat diet, but not after an isocaloric low-fat diet [78]. There are also studies that describe the role of the HPA axis and its effects on food addiction and reward circuitry for palatable foods [22,79,80]. Although not discussed in this review, these are also important areas of research.

Interaction with sex hormones

Body fat distribution is often sex-specific, and UBO is more prevalent in men than women. In women with UBO, the risk for T2DM is significantly greater than in men with UBO [81]. It is possible that sex hormones play a role in HPA axis activity and in the pathology of metabolic disease. A negative association between 24-h mean plasma cortisol levels and body weight in obese women was not seen in obese men. Obese women showed higher CRH-stimulated plasma cortisol levels compared with obese men and cortisol levels were positively correlated with testosterone levels in UBO women, but not UBO men [82]. Estradiol stimulated 11β-HSD1 expression in VAT of women in one study [58] but not in another [83]. Whether the sex-associated differences in cortisol metabolism are related to its depot-specific differences in 11β-HSD1 expression and subsequent local cortisol generation remains to be determined.

Fetal programming, stress, and obesity

Stress experienced in early life may also be a risk factor in the development of obesity and metabolic syndrome. A recent study on nonhuman primates reported that juvenile bonnet macaque monkeys exhibit greater weight, BMI, waist circumference, and insulin resistance if their mothers are exposed to food insecurity when the monkeys are young (age 3–5 months) [84]. An emerging hypothesis in the last several years is that of ‘fetal programming’ that growth and development *in utero* may predict BMI and adiposity in adulthood. This hypothesis suggests that stress adaptation due to maternal malnutrition during pregnancy, resulting in low birth weight, may increase the risk for obesity and metabolic disease in adulthood [85]. The Dutch famine of 1944 has been extensively studied for evaluation of this hypothesis. Analyses of birth weight and susceptibility for metabolic disease found that *in utero* exposure to famine resulted in increased incidence of obesity [86,87] and diabetes [88] in adulthood. Recently, another study [89] found an association between postnatal

weight gain in preterm babies and glucose-stimulated insulin secretion in adulthood, although there was no relationship between birth weight or gestational age and adult insulin sensitivity.

Animal studies [90–92] have shown that dietary restriction *in utero* results in altered HPA activity and increased glucocorticoid levels as adults. Prenatal exposure to glucocorticoids impairs glucose tolerance in adult rats [93–95]. Clinical studies showed increased CRH levels in umbilical cord plasma from growth-retarded children [96]. Birth weight was associated with stress-induced salivary cortisol in 7–9-year-old boys, but not in girls [97]. This association, however, was demonstrated in both middle-aged men and women [98]. Shorter stature, smaller head circumference at birth, and lower BMI at 7 years of age were associated with increased WHR and increased morning salivary cortisol levels in adult men and women [99]. These studies suggest that there may be a relationship with intrauterine growth restriction, HPA activity, and the risk for metabolic disease later in life, although sex and stage of life in which the outcome measure is taken may influence the association.

Sleep deprivation and obesity

In the past 30 years, the average nightly sleep duration has decreased from 8–9 to 7 h per night. Currently, 30% of all adults in the USA sleep less than 6 h per night. Sleep deprivation has been linked to both increased risk for obesity and T2DM [65]. Epidemiological studies have reported a negative association between BMI and sleep duration in adults [100–102] and children [103,104]. In laboratory studies, insulin sensitivity was reduced in sleep-restricted individuals [105,106]. Sleep deprivation is suggested to be a chronic stressor that may contribute to increased risk for obesity and metabolic diseases, possibly in part through HPA axis dysregulation, although the data are inconsistent. Sleep deprivation resulted in decreased night-time [107] and morning [108] plasma cortisol levels, or increased night-time plasma cortisol levels in other studies [67,109]. To date, there have been no reported studies on the effect of sleep deprivation on salivary cortisol or UFC.

Conclusion

The present review provides basic support for the relationship between chronic stress, alterations in HPA activity, and obesity. Although animal models provide evidence of the association of stress, HPA axis, and metabolic diseases, human studies have proven to be more challenging, with more understated changes in the HPA axis.

In modern society, where overnutrition, sedentary lifestyle, and sleep deprivation are typical traits, chronic exposure to environmental stress potentially contributes to the development of obesity. This may be at least partially mediated through the HPA axis, although this relationship is complex and many factors, including genetic polymorphisms, tissue-specific cortisol metabolism, chronic inflammation, leptin, ghrelin, and sex hormones, influence the strength of this association. Future studies should address the mechanisms that HPA activity dysregulation contributes to obesity and other metabolic complications. Changes in food intake appear to be a primary target. These actions may be related to effects of leptin and other central signals such as NPY and insulin.

HPA axis dysregulation in obesity is subtle and difficult to assess clinically. Continued research in this field is imperative to define a causal role for chronic stress and obesity, and ultimately develop effective treatment or preventive interventions.

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•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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