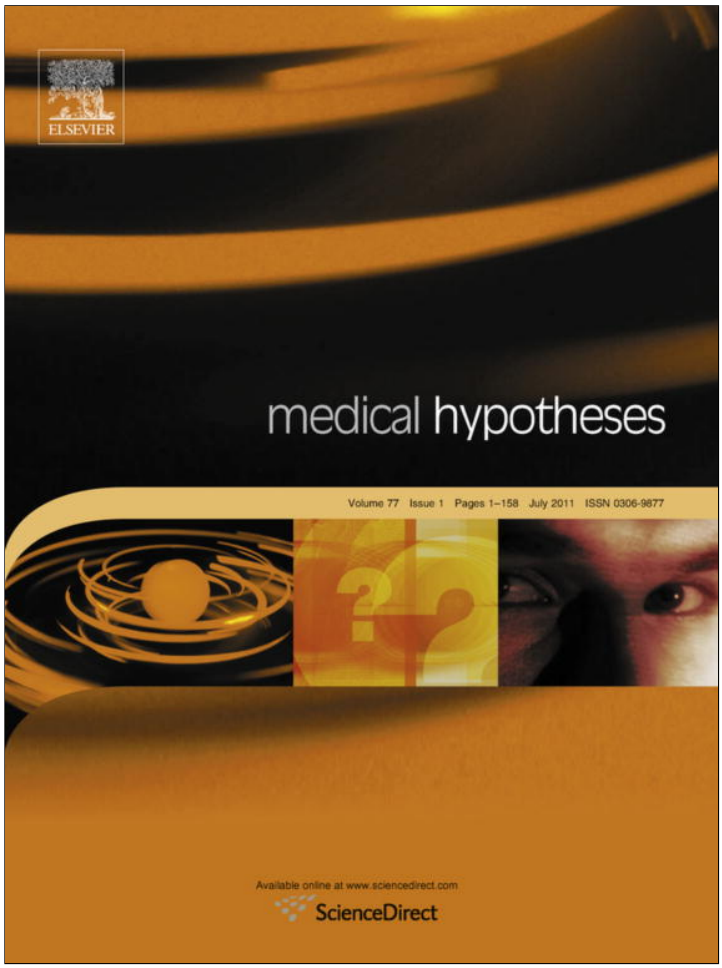

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Stress in obesity: Cause or consequence?

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ABSTRACT

Obesity is a global public health challenge that increases the risk of various diseases including type 2 diabetes mellitus, hypertension and cancer, and will in the future cause further increases in the incidence of chronic disease. Understanding the mechanisms of obesity is critical if we are to prevent and treat this pandemic challenge. Diet and physical activity have traditionally been the major tasks in preventing and treating obesity. However, other mechanisms are now also being considered in the quest for knowledge and understanding of obesity, including the body's stress system and cortisol release. While it seems evident that stress is a cause of obesity, whether stress is also a consequence of obesity has up to now only briefly been discussed. The aim of this article is to elucidate how stress and obesity might be linked and discuss the cause/consequence relationship between the stress response and obesity. Our hypothesis is that stress and obesity interfere by positive feedback. This may be an important issue in both our understanding and coping of obesity.

Introduction

Through the various mechanisms of homeostasis regulation, the body aims to maintain the organism's delicate and dynamic equilibrium. Internal as well as external changes and challenges are at all times compensated for in order to maintain or re-establish the body's homeostasis. Stress is defined as a "state of threatened or perceived as threatened homeostasis" [1]. Stressors, including injury, noise, extreme cold, loss of work and low social standing may activate the stress system [2] and cause a direct or perceived threat of homeostasis. The stress system (Fig. 1) consists of two major parts: (i) the sympathetic nervous system, which by itself and via the adrenal medulla releases noradrenaline and adrenaline and triggers the fight-or-flight mechanism; and (ii) the hypothalamic–pituitary–adrenal (HPA) axis, which releases cortisol, an adrenal cortex-derived hormone that plays a central role in the physiology of stress responses [2] as well as illness [3]. Persistent exposure to stressors may induce overactivity of the stress system and may ultimately lead to development of various pathological conditions of, e.g., reproduction, growth, immune function, and mental disorders [1,2]. Previous reviews have confirmed clear associations between altered stress/HPA axis activity and metabolic disturbance, including both metabolic syndrome and obesity [2,4,5].

Obesity is a global public health challenge that will cause an increase in chronic diseases, and is thus characterized as a global health crisis [6]. Diet and physical activity have been the major tasks concerning prevention and treatment of obesity; however, other factors are now being more closely considered including the role of the HPA axis [7]. Morning rise in cortisol levels has been found to be increased with increased body mass index (BMI) [8], and obese women with binge eating disorder have higher morning cortisol levels than women without this disorder [9]. On the other hand, lower morning cortisol but increased salivary cortisol responsiveness to lunch has been found in overweight women with abdominal fat distribution compared with overweight women with peripheral fat distribution [10]. However, whether the altered HPA axis and cortisol levels are a result or a trigger of obesity is not clear [11,12]. To handle the challenges of obesity, more knowledge of the physiological interactions between stress and weight gain is crucial. The aim of this article is to bring into focus how stress and obesity might be linked and discuss the cause/consequence relationship between stress response and obesity.

Stress – a cause of obesity?

One indication of cortisol's involvement in weight regulation is the similarity seen between hypercortisolism and obesity [11]. In Cushing's syndrome, which is characterized by hypercortisolism, weight gain with abdominal fat distribution, among other obesity symptoms, is common [13]. Direct observations of cortisol's involvement in weight gain were recently presented in a case–con-

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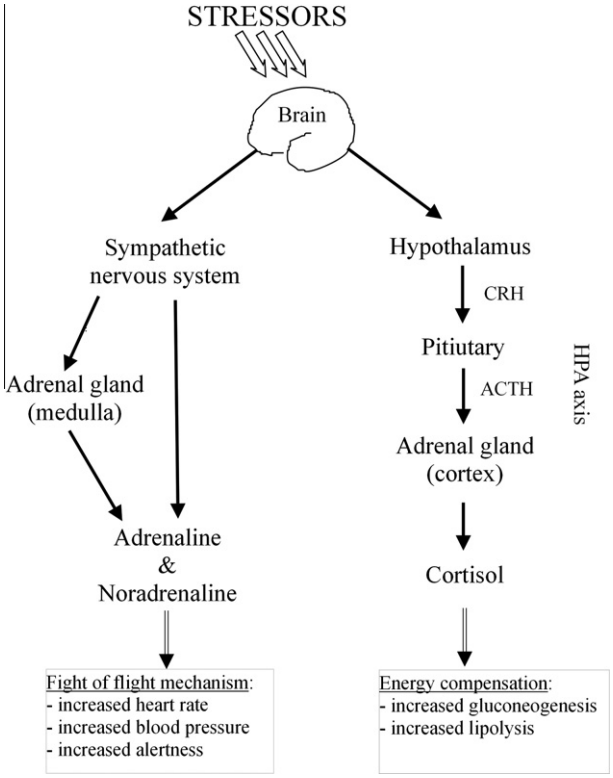

Fig. 1. The stress system: stressors, including social, psychological and biological factors of both internal and external origin activate the stress system. The command center is the brain that activates (i) the sympathetic nervous system and the fight or flight mechanism, and (ii) the hypothalamic–pituitary–adrenal (HPA) axis that stimulates cortisol release by the adrenal cortex and thereby mobilizes energy as stress compensation. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropin hormone. The figure is based on De Vriendt et al. [2].

trol study. This study compared women who gained weight after a stressful event to women whose obesity development was not stress related, and women in a normal weight control group. There were no differences in free urinary cortisol between the normal weight control group and the non-stress-related obesity group, but, cortisol was significantly increased in the stress-related obesity group. Importantly, the stress-related obesity group's weight gain was greater and happened in a significantly shorter time span [14]. These results suggest that increased cortisol levels are involved in the development of obesity, rather than the other way around. If obesity was the cause of increased cortisol levels, elevated cortisol levels would also be detected in the non-stress-related obesity group as well. This was not the case.

In a study of depressed adolescents, depression was significantly associated with BMI [15]. For the girls in this study, the link between depression and BMI was mediated by cortisol reactivity, and cortisol was thus concluded to be the biological connection between depression and obesity development. These results were based on the changes in salivary cortisol levels (cortisol reactivity) following the Trier Social Stress Test for Children. The significance for the girls only underlines the complexity of cortisol's role in obesity and suggests that obesity involves additional factors [16] not examined in this study. Explanations of gender differences may include the choice of food during stress, and that girls are more likely to consume high calorie foods [15].

Several studies have characterized the role of stress and cortisol in food intake. In a questionnaire survey of male Japanese workers, obesity was associated with eating behavior, which was related to high job demands, fatigue, depression and anxiety [16]. Increased as well as decreased eating responses are also related to activation of the HPA axis, possibly depending on the stressors, gender and individual differences [13,17]. In a recent study, healthy adults were given corticotropin-releasing hormone (CRH, see Fig. 1). This caused cortisol secretion to increase, which resulted in increased food consumption and calorie intake in the participants [18]. These results support the observation that stress, in the form of hassles, increases snack intake in persons with high levels of cortisol [19], and thus links the stress system to food intake regulation. Cortisol may act on food intake and food selection via different mechanisms, including: (i) inducing leptin resistance and thereby blocking the food intake suppressive effects of leptin [13], and/or (ii) increasing the release of neuropeptide Y (NPY) which stimulates fat tissue production [13]. The NPY release has been characterized in an animal model in which induced stress increased both the release of NPY and the growth of abdominal fat [20]. Interestingly, this effect of NPY seemed to be at least partly dependent on glucocorticoids (i.e. cortisol in humans). Since stress normally leads to an increase in energy expenditure, these cortisol mechanisms (via leptin and NPY) may contribute in a physiological manner to keep the total body energy content relatively constant.

All together, the studies described above all point in the same direction. Using different approaches and methods, they show that the stress system and cortisol release can be a cause of obesity, thus representing a mechanism that is initiated in advance of weight gain. This is supported by the idea that visceral obesity may be looked upon as a physiological adaption to stress [12].

Stress – a consequence of obesity?

Obesity is associated with development of various diseases including diabetes type 2, hypertension, dyslipidemia and cancer [2,5]. Obviously, obesity represents disruption of homeostasis. It is therefore reasonable to consider obesity as a potential stress inducer on the body.

In an experiment from the early 70's, men intentionally increased their body fat mass, which resulted in increased levels of cortisol [21]. These observations are recently corroborated by a study of middle-aged and older men, which found that cortisol increase seemed to be dependent on weight gain [22]. These two studies directly show that cortisol increase can be secondary to weight gain. In addition, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), an enzyme that converts cortisone into cortisol in humans, has increased activity in adipose tissue of obese persons [23]. This means that even though elevated cortisol levels by 11β-HSD1 activity may be mainly local, it is still possible that increased adipose tissue in the obese can affect total body cortisol levels. By 11β-HSD1, the adipose tissue expansion occurs prior to increased cortisol release, which is then secondary to weight gain.

One of the hallmarks of obesity is chronic low-grade inflammation [24], in which adipose tissues releases various inflammatory mediators including interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNFα) [25]. These three pro-inflammatory cytokines can activate the HPA axis either independently or in concert, thereby increasing the release of cortisol in an attempt to limit the inflammation reaction [26]. Thus, there is a pathophysiological link between obesity, inflammation activation and cortisol release that might be relevant in the regulation of the stress response in obese persons.

Another characteristic feature in obesity is the increased secretion and high levels of leptin, a hormone that might play a key role in the development of, as well therapy for, obesity [27]. Interestingly, leptin secretion and the HPA axis seem to be functionally connected under physiological conditions in humans in a time-regulated positive and negative fashion. In experiments on healthy individuals, cortisol was found to increase leptin levels, and the

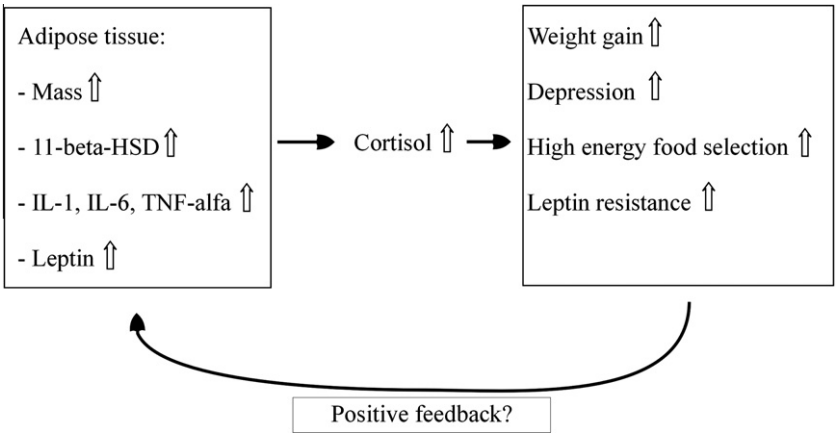

Fig. 2. Interaction between obesity and cortisol release (i.e. the stress system): various factors related to increased adipose tissue can trigger cortisol release. On the other hand, cortisol release can trigger weight gain directly or via mechanisms that indirectly lead to weight gain. This bidirectional interaction may act as a positive feedback loop.

rise in leptin levels increased the cortisol levels [28]. Thus, increased levels of leptin, as seen in obesity [29], may trigger increased release of cortisol.

Stress and obesity – positive feedback interactions?

It seems evident that stress can be a cause of obesity. This is shown by different observations including (i) similarities between hypercortisolism and obesity characteristics [11], (ii) differences seen between stress-induced and non-stress-induced weight gain [14], (iii) weight gain in depressed persons [15] and (iv) changes in food intake as a result of stress and cortisol [16,18]. Together, these observations suggest that stress induces weight gain as thoroughly reviewed [2,4,5,13]. On the other hand, it may not be equally obvious that obesity activates the stress response. Two independent observations suggest that cortisol release increases secondary to weight gain [21,22]. However, the limitations of these two observations must be considered. First, studies reporting increased cortisol secondary to weight gain are limited. One of the two studies is based on experiments of intentional increased body mass, which may not accurately represent spontaneous development of obesity [11]. The other study should be greeted with caution due to the observation that age-related weight loss, and not weight gain, was associated with increased cortisol levels [22]. Interestingly, energy restriction in obese persons has also been shown to increase cortisol secretion [30], further underlining the complexity between obesity and the stress response, but also supporting that increased cortisol release and stress can be secondary to obesity [11], e.g. during strict diets. Second, the differences observed between stress-induced obesity and non-stress-induced obesity [14] appear to argue against obesity-induced stress since cortisol levels did not increase in the women whose obesity was not stress-induced. However, this finding may be explained by different mechanisms. One explanation may be normal biological variance: the simple fact that different persons have different reaction patterns. Combined with the relatively low number of participants (stress-induced obesity, $n = 14$, non-stress-induced obesity, $n = 21$) may have affected the outcome. Another possible, and interesting, explanation is gender. In the stress-induced and non-stress-induced obesity study [14] only women were observed, while the studies that showed cortisol increase being secondary to weight gain included only men [21,22]. Gender differences were also found in the study of depressed adolescents, in which a link between depression and BMI mediated by cortisol reactivity was significant for girls only [15]. Gender differences in HPA axis activity in obesity is well known and seems to involve an imbalance in the sex hormones [31]. Thus, gender differences in obesity are likely. In addition, increased 11β-HSD1 activity [23], inflammation activation [25] as well as increased leptin secretion [27] may indirectly affect the activation of the stress system in obese persons. Thus, various mechanisms have the potential to affect the stress system in obese persons.

All together, the studies presented here show that (i) stress as a cause of obesity seems well established, and (ii) stress as a consequence of obesity is less documented but is still likely and possibly gender dependent. Thus, it seems possible that stress is potentially both a cause and a consequence of obesity, interacting in a bidirectional pattern. This means that weight gain has the potential to trigger the stress response which again may increase weight gain, and so forth. In this way the interactions between stress and obesity could create a positive feedback loop interaction (Fig. 2). In fact, even losing weight, which can also trigger the cortisol release, could trigger the stress response and thus oppose further weight loss, suggesting that the stress system may be involved in the challenges of losing weight. This model of positive feedback loop interaction between stress and obesity means that treatment of obesity should focus not only on energy balance, but on the stress system and its stressors as well. In order to break the stress-obesity spiral, it may be important to identify and remove possible stressors. This would not only be a positive factor for weight reduction, but would by itself also improve life quality. Further studies involving the interaction between obesity and stress are needed to fully understand the causes behind obesity.

Conflicts of interest statement

The authors have no relevant conflict of interest.

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