The hypothalamic-pituitary-adrenal-axis in the regulation of energy balance

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Abstract

Human (visceral) obesity is associated with alterations hypothalamus–pituitary–adrenal (HPA) axis functioning. It is however not completely clear whether the HPA axis is causally or co-incidentally related to (visceral) obesity. This review summarizes supporting data of an involvement of the HPA axis in the development of (visceral) obesity. First, several DNA polymorphisms related to HPA axis functioning are correlated to the development of obesity. Second, chronic elevation of circulatory glucocorticoid concentrations, as in Cushing’s disease, results in increased abdominal adiposity. Third, (visceral) obesity is associated with a diminished capacity of cortisol to suppress its own secretion. HPA axis functioning might affect energy balance through affecting energy intake. Both CRH and cortisol influence physiological, central mechanisms involved in the regulation of food intake. Still, general activation of the HPA axis has shown to have inconsistent effects on food intake in humans. This inconsistency may partially be explained by gender differences, individual differences in the functioning of the HPA axis, as well as differences in attitude towards eating. In particular, women with high scores on dietary restraint are prone to stress-induced hyperphagia. Dietary restraint scores, in turn, are positively correlated to basal and dexamethasone-suppressed cortisol levels, indicating a complex dual relationship between stress, HPA axis functioning, attitude towards eating and the risk for stress-induced hyperphagia. In the Western society, with chronically high ambient levels of stress and the availability of high caloric foods, this relationship may imply a risk for the development of (visceral) obesity and the metabolic syndrome.

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1. Introduction

Evidence suggests that the HPA axis is involved in the pathogenesis of human obesity, in particular characterized by visceral fat distribution. The HPA axis functioning plays an important role in the regulation of energy balance and body weight; it is, however, not completely clear whether the HPA axis is causally or co-incidentally related to the development of (visceral) obesity.

The hypothalamus–pituitary–adrenal (HPA) axis is a neuroendocrine system involved in the stress-response, by regulating the secretion of cortisol [1]. The cascade of the HPA axis beholds that first the hypothalamus produces and releases corticotropin-releasing hormone (CRH), which subsequently stimulates the synthesis and release of adrenocorticotropic (ACTH) from the anterior pituitary. ACTH is produced from a larger precursor namely the proopiomelanocortin (POMC) protein, and stimulates the synthesis and release of cortisol by the adrenal cortex. In the circulation, cortisol is bound to corticosteroid-binding globulin (CBG) with high affinity, facilitating transport of cortisol in blood, followed by conversion of cortisol at the peripheral level by 11b-hydroxysteroid dehydrogenase (11b-HSD) 1 and 11b-HSD 11. The 11b-HSD 1 enzyme, converts cortisone into the active form, and 11b-HSD 11 inactivates cortisol by conversion into cortisone. Cortisol exerts his actions through binding to and activation of two types of intracellular receptors, the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). The GR initiates or represses gene transcription, and induces negative feedback of the HPA axis through GR on the hypothalamus and pituitary level. The MR regulates basal activity of the HPA axis. Physiological cortisol levels follow a circadian rhythm; an early morning peak
after awakening, a rapid decrease over the next few hours, and then a more gradual decline over the course of the day, to very low levels by bedtime [2].

Addison’s disease and Cushing’s syndrome represent two extremes of plasma cortisolism in human pathology. Addison’s disease shows hypocortisolism, which causes symptoms like fatigue, muscle weakness, changes in mood, and weight loss [3]. Also hypocortisolism caused by adrenalectomy will induce body weight loss in humans [4]. In animals, adrenalectomy will even prevent genetic as well as diet-induced form of obesity [5]. Cushing’s syndrome is characterized by hypercortisolism, which causes symptoms like hypertension, insulin resistance, hyperglycemia and rapid weight gain, particularly of the trunk and face with sparing of the limbs [6]. In the adipose tissue the glucocorticoids promote differentiation of pre-adipocytes into mature adipocytes and increase lipoprotein lipase activity, thus promoting adipose tissue increase and weight gain [7]. The clinical observations in Addison’s disease and Cushing’s syndrome clearly demonstrate a role for the HPA axis in the regulation of energy balance [8].

The pathology of visceral obesity shows a marked resemblance with Cushing’s syndrome, including a central fat distribution of excess body-fat mass, elevated blood pressure, insulin resistance, and dyslipidemia. This form of obesity is associated with hypercortisolism, which becomes more pronounced when the HPA axis is stimulated (physiological or psychological) [9–11] and is associated with a diminished capacity of a low-dose (0.5 mg) dexamethasone (a GR agonist) to suppress plasma cortisol concentrations [12]. The latter finding suggest that the negative feedback loop, with cortisol activity on GR in both the hypothalamus and pituitary to inhibit HPA axis activity, is impaired in visceral obese subjects. This might explain (partially) the HPA hyperactivity and hypercortisolism of visceral obesity. In contrast, obese with a more peripheral body fat distribution do not show health risk markers, hypercortisolism, and diminished feedback capacity.

This review summarizes supporting data of an involvement of HPA axis hyperactivity in the development of (visceral) obesity. We start by describing physiological consequences of polymorphisms related to HPA axis functioning and the development of obesity. This will be followed by description of pathways through which the HPA axis might affect energy balance, and ultimately body weight, which will lead to a proposal of a model on the relationship between alterations in HPA axis functioning and (visceral) obesity.

2. Physiological consequences of polymorphisms related to HPA axis functioning

Visceral obesity shows considerable heritability, which results from contributions from many genes, so it is plausible that genetic variation in the cascade of the HPA axis may be involved in visceral obesity development [13]. Several polymorphisms in the cascade of the HPA axis have been described in the literature, which cause differences in HPA functioning and/or are involved in obesity development. In Table 1 the polymorphisms, the functional variation in HPA axis functioning caused by the mutations, and the possible association to obesity have been described.

Regarding the initial step of the HPA axis cascade, a variant in the 5’-flanking region of the corticotropin-releasing hormone (CRH) gene (T255G) the of (CRH) has been found. This polymorphism has been associated with increased cortisol levels during physiological stress and total diurnal cortisol secretion, when combined with a variant in the gene of the GR. Still, no association between the T255G mutation and obesity has been shown yet [14].

With respect to functional variations of the POMC gene related to ACTH production, a rare mutation in exon 2 (C3804A) of the POMC gene, that causes ACTH insufficiency, has been associated with early-onset obesity [15].

Several polymorphisms have been described that can be linked to glucocorticoid action and may be related to specific aspects of obesity. Thus, a (GTTT)_h repeat in intron 1 of the corticosteroid-binding globulin (CBG) has been associated with increased proliferation/differentiation of pre-adipocytes, higher salivary cortisol after dexamethasone suppression test, higher waist-to-hip ratio and a higher risk on obesity development [16,17].

At the level of cortisol conversion, the ns4436A polymorphism of the 11b-hydroxysteroid dehydrogenase (11b-HSD) 1 gene has been associated with increased waist-to-hip ratio in women and pediatric obesity. No functional variation in HPA axis functioning caused by the ns4436A polymorphism has been described yet [18]. Additionally, a polymorphism at (CA)_h repeat in the first intron of the 11b-HSD 11 gene has been associated with

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>Obesity</th>
<th>Functional genetic variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>T255G</td>
<td>No</td>
<td>Increase cortisol levels</td>
</tr>
<tr>
<td>Proopiomelanocortin (POMC)</td>
<td>Exon 3 (AAC)(AGC)_d(GGC)</td>
<td>No</td>
<td>No influence</td>
</tr>
<tr>
<td>Proopiomelanocortin (POMC)</td>
<td>C3804A</td>
<td>Yes</td>
<td>ACTH insufficiency</td>
</tr>
<tr>
<td>Corticosteroid binding globulin (CBG)</td>
<td>Intron 1 (GTTT)_h repeat</td>
<td>Yes</td>
<td>Decrease feedback functioning</td>
</tr>
<tr>
<td>11b-HSD 1</td>
<td>ns4436A</td>
<td>Yes</td>
<td>No influence</td>
</tr>
<tr>
<td>11b-HSD 11</td>
<td>Intron 1 (CA)_h repeat</td>
<td>Yes</td>
<td>Increase local cortisol levels</td>
</tr>
<tr>
<td>Glucocorticoid receptor (GR)</td>
<td>N363S</td>
<td>Yes</td>
<td>Increase cortisol sensitivity</td>
</tr>
<tr>
<td>Glucocorticoid receptor (GR)</td>
<td>ER22/23EK</td>
<td>Yes</td>
<td>Decrease cortisol sensitivity</td>
</tr>
<tr>
<td>Glucocorticoid receptor (GR)</td>
<td>Bell</td>
<td>Yes</td>
<td>Increase cortisol sensitivity</td>
</tr>
<tr>
<td>Mineralocorticoid receptor (MR)</td>
<td>M180V</td>
<td>No</td>
<td>Increase cortisol secretion</td>
</tr>
</tbody>
</table>
increased activity of the 11b-HSD 11 enzyme in vitro, which was observed in the subcutaneous adipose tissue of obese men. This results in higher local cortisol levels in adipose tissue and an increase in the ratio of urinary free cortisol/urinary free cortisol [19].

At the level of cortisol binding by the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) several polymorphisms have been described [20]. Three of the most prominent polymorphisms in the GR gene are the N363S, ER22/23EK and BclI polymorphisms, which all have been associated to obesity. The N363S polymorphism has been associated with increased glucocorticoid sensitivity, increased BMI, increased waist-hip ratio, and increased cholesterol levels [21,22]. Secondly, the ER22/23EK polymorphism, which has been associated with decreased glucocorticoid sensitivity, decreased cholesterol levels, decreased insulin levels, and increased fat free mass [23]. Thirdly, the BclI polymorphism which has been associated with increased glucocorticoid sensitivity, increased insulin levels, increased blood pressure, increased abdominal visceral fat, and increased cholesterol levels [14,24–26]. The most common described polymorphism in the MR gene is the MR180V polymorphism, which has been shown to enhance responses in cortisol secretion to a psychological stressor. In vitro studies showed a mild loss of function of the MR180V polymorphism, when cortisol was used as a ligand [27]. No associations have been found between the MR180V allele and the prevalence of obesity.

One can conclude that genetic variation in the cascade of the HPA axis does not only influence HPA axis functioning, but is also frequently related to differences in body composition and metabolic parameters. These findings stress that the HPA axis plays an essential role in the regulation of body weight, body composition and energy balance. The next paragraphs will extend on the physiological role of the HPA axis in the regulation of energy balance.

3. HPA axis functioning and energy balance

In the literature several possible mechanisms have been described through which the HPA axis might affect energy balance, which is composed of energy intake and energy expenditure. Obesity results from a chronic deregulation of energy balance, with energy intake exceeding energy expenditure, which leads to the storage of the excessive energy as fat.

3.1. HPA axis functioning and energy intake

The literature consists of ample human data on the effects of stress on food intake [28]; however, these data are difficult to interpret with respect to the role of the HPA axis for various reasons. First of all, a wide variation in the type of stressor is used, resulting in different outcomes. Thus, stress in the workplace has been associated with higher energy intake [29,30] while examination stress and surgical stress have produced mixed results [31,32]. Secondly, there is a large inter-individual variance in HPA axis responses, i.e., plasma ACTH and cortisol production, to stress [8,33]. A few studies on the effects of stress on food intake included measurements of plasma cortisol levels [34,35]. Both studies showed a higher increase in stress-induced food intake in women who showed high cortisol responses to the stressor, suggesting a relationship between cortisol responses and food intake.

Most of the data directly indicating a crucial role of the HPA axis in the regulation of food intake are derived from animal studies, showing that the anorectic effects of adrenalectomy can be reversed by glucocorticoid (corticosterone) replacement [36,37]. Human studies on the effects of glucocorticoids on food intake are limited, but generally support the findings in laboratory animals of an orexigenic effect of glucocorticoids [7,33]. The stimulation of food intake by glucocorticoids seems to be macronutrient specific: when rats had a free choice for different chow compositions, corticosterone withdrawal (adrenalectomy) and subsequent replacement principally affected carbohydrate intake [38,39]. In another paradigm, where adrenalectomized rats were offered a choice between chow and lard, corticosterone replacement dose-dependently increased intake of the more palatable lard, but only in the presence of insulin [37]. These actions of glucocorticoids may underlie the preference for certain macronutrients and kinds of foods in humans after stress, in particular high saturated fat and sweet food items [30,34,40,41]. Additionally, studies have shown that snack consumption may be more susceptible to stress-induced eating than meals [42]. Such foods may be preferred during stressful conditions, through learning that small energy-dense snacks are more easily ingested and digested when gut activity is suppressed by sympathetic arousal [43]. Several homeostatic and non-homeostatic mechanisms have been proposed through which HPA axis functioning may regulate food intake, and they will be discussed below.

3.2. HPA axis functioning and homeostatic regulation of food intake

The HPA axis seems to have many cross-links with the neuroendocrine pathways that control the homeostatic regulation of food intake [44]. First of all, the CRH containing neurons, which comprise the initial component of the HPA axis, are located in the paraventricular nucleus (PVN) of the hypothalamus, which is also considered to be a major centre in the control of feeding behavior [45]. Central (intraventricular) administration of CRH inhibits feeding in rats [45,46], and CRH is suggested to be an important intermediate in the anorectic effects of leptin [46–48]. The hypophagic effect of central CRH may (in part) result from inhibitory control of the orexigenic neural pathways involving neuropeptide Y (NPY), as paraventricular administration of the CRH-antagonist, alpha-helical CRF9-41, potentiated NPY-induced food intake [49]. CRH may be involved in the pathogenesis of obesity, at least in specific animal models: in the obese fa/fa Zucker rat a reduced level of CRH mRNA expression has been found [50]. Whether CRH is also involved in the pathogenesis of human obesity is unknown, but when subcutaneous fat cells from humans were incubated in vitro with CRH, it decreased 11b-HSD 11 enzyme activity, thereby reducing local cortisol production and reducing adiposity [48].
Thus, CRH exerts an opposite effect on appetite when compared to glucocorticoids. Physiologically, the (later) orexigenic effect of glucocorticoids, following the anorectic effect of CRH at the beginning of the stress response, may play a role in the recovery stage for the replacement of the replenishment of energy required during the ‘fight of flight response’. The inhibitory effects of glucocorticoids on hypothalamic CRH release [46] may be involved in the stimulatory effect of glucocorticoids on food intake.

The opposite effects of CRH and glucocorticoids on food intake also emerge at a mechanistic level: where CRH exerts inhibitory control on NPY-induced food intake [49], (central) glucocorticoids potentiate the orexigenic actions of NPY. Additionally, dexamethasone stimulated NPY release in the mediobasal hypothalamus of female rats, and NPY production of cultured hypothalamic neurons [47]. In addition, recent research shows that cortisol up-regulates the NPY Y2 receptor in the abdominal fat. Release of NPY and activation of the NPY Y2 receptor stimulates fatangiogenesis, proliferation and differentiation of new adipocytes, thereby linking HPA axis activation, NPY and increased abdominal fat storage [51].

The HPA axis interferes with leptin release, in that glucocorticoids stimulate secretion of leptin by (rat) adipocytes [52]. This stimulatory effect of cortisol on leptin secretion has also been shown in vivo [53,54]. On the other hand, glucocorticoids may reduce the efficacy of leptin to suppress food intake, hence, induce leptin resistance. In rats, adrenalectomy has shown to increase the anorectic potency of leptin, while this effect was reversed by glucocorticoid replacement [55]. Leptin exerts its anorectic actions in part through activation of the central melanocortin system [56]. Similar to the results on leptin, the anorectic response to the melanocortin agonist, melanotan II, in rats is enhanced by adrenalectomy, which can be reversed by glucocorticoid replacement [39]. These data suggest that glucocorticoids potentially decrease leptin sensitivity, partially through inducing insensitivity to central melanocortins. Induction of leptin resistance may also explain why glucocorticoid administration in humans results in elevated leptin concentrations on the one hand, and an increased food intake on the other [7]. Indeed, HPA axis hyperactivity, and a subsequent elevation of glucocorticoid concentrations, has been hypothesized to be involved in the leptin resistance of human obesity [57,58].

Glucocorticoids also interact with the action and secretion of insulin, another endocrine adiposity signal. In vitro, glucocorticoids interfere with insulin-induced glucose uptake and metabolism in both cultured myocytes and adipocytes [59–62]. In vivo, dexamethasone administration to humans decreases whole body insulin sensitivity [63,64]. This is associated with a compensatory increase in plasma insulin concentrations [65]. Since intraventricular administration of insulin has shown to suppress food intake [66], one might speculate that insulin (or insulin resistance) is involved in the effects of glucocorticoids on energy intake. Still, studies in glucocorticoid-treated adrenalectomized, streptozotocin-diabetic rats showed that total energy intake was not affected by insulin supplementation [36,37], although insulin did dose-dependently increase the relative contribution of palatable high-fat food to total energy consumption [37]. Thus, insulin is likely to be involved in the effects of glucocorticoids on feeding behavior through modulation of food choice, rather than energy intake. Furthermore, through its anabolic actions on adipocytes, the hyperinsulinemia caused by glucocorticoids may facilitate fat deposition. Remarkably, dexamethasone and insulin synergistically stimulate lipoprotein lipase activity in human adipose tissues, thereby facilitating free fatty acid uptake and lipogenesis [67].

### 3.3. HPA axis functioning and non-homeostatic regulation of food intake

In addition to the hypothalamic homeostatic pathways involved in food intake regulation, cortico-limbic brain areas are important structures for determining non-homeostatic regulation of food intake. These brain areas are involved in processes such as cognition, reward, memory and cognition, which are able to override the above-mentioned homeostatic regulatory mechanisms [44].

To a certain extent, humans show tendencies to cognitively moderate their food intake, a phenomenon that has been called “dietary restraint”. Under some conditions, however, some subjects loose their cognitive control of caloric intake, which is called “disinhibition”. The level of dietary restraint and disinhibition can be assessed by using specific questionnaires, such as the Three Factor Eating Questionnaire (TFEQ) [68]. We previously showed [Rutters, submitted] that the level of dietary restraint was positively correlated to 5-hour plasma cortisol patterns, and negatively correlated to the ability of the GR-agonist, dexamethasone, to suppress cortisol release under a strenuous exercise protocol. Accordingly, three studies reported that salivary cortisol at one time point (time point not specified) and 24-hour cortisol excretion were significantly higher in restrained women compared to unrestrained women [69–71]. Notably, some other studies did not find this relationship [72–74], possibly because cortisol concentrations where only measured at one time point or during the night.

One can speculate about the causality of this relationship. Although it cannot be excluded that high ambient cortisol levels increase cognitive awareness of caloric intake, the opposite (i.e., high level of dietary stress causes HPA axis activity) seems a somewhat more tempting hypothesis. Dietary restraint is positively correlated with body fat percentage [73,75,76], and the load of continuously restrained eating behavior is reportedly perceived as stressful [77]. Still, dietary restraint may be a risk factor for stress-induced hyperphagia, as studies showed that restrained eaters experiencing psychological stress increased their food intake, while unrestrained eaters decreased food intake [30,78–80]. Also, women with high disinhibition scores showed an increase in food intake following psychological stress [81,82].

In the concept of non-homeostatic regulation of food intake, as lined out by Berthoud [44], food reward plays an important role. Like addictive drugs, palatable foods may act as a reinforcer, thereby influencing their own intake. Berridge and Robinson defined two distinct psychological processes determining the reinforcing value: “liking” and “wanting” [83].
These processes are regulated by different neural networks and mediated by different neurotransmitters [84].

In the process of “liking”, mu-opioid systems in the nucleus accumbens seem to play an important role [85,86]. Thus, local administration of the opioid agonist, morphine, or the mu-opioid agonist, (d-Ala2, N-Me-Phe4, Gly(5)-enkephalin (DAMGO), into the nucleus accumbens of rats increased food intake [85,87]. In humans, the opioid antagonist, naltrexone, results in a reduction of both the intake and the reported pleasantness of food [88–90]. The expression of the mu-opioid receptor, and, hence, opioid sensitivity, is modulated by glucocorticoids: its expression is diminished in CRH-deficient mice and increased by corticosterone administration [91]. Indeed, activation of the endogenous opioid system has been suggested to be involved in stress-induced eating [92].

The endogenous opioid system may exert its effects in interaction with the endocannabinoid system, which has also been shown to be involved in the regulation of feeding behavior [93] and reward [94]. Endocannabinoid receptors of the CB1 type are abundantly expressed in the nucleus accumbens [95], and combined administration of the opioid antagonist, naloxone, and the CB1 receptor antagonist SR141716 decrease food intake in rats in a synergistic fashion [96]. Direct evidence for a role of endocannabinoids in the orexigenic effects of glucocorticoids is lacking at present, but it is noteworthy that the endocannabinoid antagonist, AM281, antagonizes the effects of corticosterone on neuronal activity and on sexual behavior in amphibians [97].

With respect to the “wanting” or motivational aspect of reward, it is thought that dopaminergic neurons, originating the ventral tegmental area (VTA) of the mid brain, and projecting to forebrain areas such as the orbitofrontal cortex and the nucleus accumbens or ventral striatum play a crucial role [83]. In rats, peripheral administration of corticosterone increases dopamine outflow in the nucleus accumbens [98]. Hence, both in rats [99] and in humans [100] glucocorticoids are suggested to contribute to the stress-induced increase of dopamine release in this brain area. The relationship between (striatal) dopamine and food intake seems, however, rather complex. Dopamine acts through several dopamine receptors (D1–D5), which seem to mediate distinct effects on food intake and food preference: selective D1 receptor activation resulted in increased caloric intake and preference for highly palatable foods, whereas combined D2/D3 activation showed an opposite effect [101]. Human studies showed that a single bolus administration the dopamine transporter protein (DAT)-inhibitor, methylphenidate, results in a reduction of food intake, suggesting that high synaptic dopamine levels reduce the reinforcing value of food [102]. In contrast to acute effects, chronic elevation of synaptic dopamine may result in an increased wanting for rewarding foods, as indicated by the increased efforts and motivation of DAT-knockdown mice to obtain a sweet reward [103]. Possibly, shifts in the sensitivity and/or distribution of the different dopamine receptors may underlie this apparent discrepancy. In this case, it is noteworthy that obese subjects exhibit lower striatal D2 receptor availability [104], hence, it cannot be excluded that in obesity the orexigenic effect of D1 activation may become considerably more predominant in the effects of dopamine on food intake. Whether this mechanism is also involved in the effects of glucocorticoids or stress on food intake in obesity, however, needs to be established.

It should be noted, however, that above homeostatic and non-homeostatic pathways regulating feeding behavior are not completely separate neural systems: significant interaction at different levels exists. In this respect, the adipocyte-derived hormone, leptin, has gained a particular interest. Leptin receptors have been found in the VTA, leptin has been shown to reduce firing rate of VTA dopaminergic neurons in brain slices, and direct administration of leptin into the VTA of rats decreased food intake [105]. Notably, a decreased performance in behavioral paradigms that assess the rewarding properties of food has also been observed when leptin was administered intracerebroventricular [106] and even intrahypothalamic [107]. Thus, leptin may reduce food intake by lowering the rewarding value of food. It is tempting to speculate that the leptin resistance following glucocorticoid suppletion [55] is also represented by a diminished influence of leptin on the neuronal pathways involved in food reward [43,56].

In conclusion we described several mechanisms like hormonal pathways, food reward and dietary restraint, through which HPA axis functioning influences energy intake, but also energy expenditure is influenced.

### 3.4. HPA axis functioning and energy expenditure

With respect to the effect of HPA axis functioning on energy expenditure, the literature is not as extensive as on the effect on energy intake. Like with the regulation of food intake, CRH and cortisol may exert distinct effects on energy expenditure. CRH infusion in humans resulted in a 14% increase in resting energy expenditure [108]. CRH may act through activation of the central sympathetic system, both in the hypothalamus as well as in the locus ceruleus of the brain stem [1]. However, as the increase in energy expenditure following CRH infusion was not associated with increases in plasma catecholamines, other mechanisms may also be involved.

With respect to the effects of glucocorticoids on energy expenditure, the literature shows a dichotomous response. When hydrocortisone was infused for 60 h, it led to an increase in resting energy expenditure [109]. Also, when hydrocortisone was infused for 16 h at two different concentrations, it lead to an increase in resting energy expenditure of 9–15% [110]. On the contrary, two other studies showed that infusion of glucocorticoids for 168 h did not alter energy expenditure [111]. In addition, chronic dexamethasone treatment in infants did not affect energy expenditure [112]. Also, no difference in resting energy expenditure (corrected for the amount of lean body mass) was found between normal and patients with Cushing’s syndrome [113,114]. It may be hypothesized that glucocorticoids exert dual effects on energy expenditure, and that the stimulatory actions of glucocorticoids on energy expenditure [109,110] are overruled by other, inhibitory actions during prolonged or chronic exposure [115].

Several mechanisms may underlie the inhibition of energy expenditure by glucocorticoids. Firstly, suppression of CRH
release by glucocorticoids as part of the negative feedback regulation of HPA axis functioning [1]. Secondly, it has been shown that chronic increased levels of cortisol in Cushing’s disease leads to inhibition and promotes breakdown of muscle, resulting in muscle wastage. Since the amount of muscle mass is positively correlated to (resting) energy expenditure, chronic hypercortisolism, as in patients with Cushing’s disease, may ultimately result in lower energy expenditure [61]. Thirdly, glucocorticoids have shown to affect the hypothalamus–pituitary–thyroid axis. Glucocorticoids inhibit the production of thyrotropin-releasing hormone as well as thyroid-stimulating hormone, and the conversion of thyroxine (T4) to triiodothyronine (T3), ultimately resulting in decreased plasma T3 levels [1,116], which may subsequently result in a reduced basal metabolic rate [115].

In summary we described that glucocorticoids exert dual effects on energy expenditure, and that the stimulatory actions of glucocorticoids on energy expenditure are overruled by other, inhibitory actions during prolonged or chronic exposure.

4. Summary and conclusions

The hypothalamus–pituitary–adrenal axis affects energy balance on different levels, at different ways, and with different underlying mechanisms. All in all, prolonged exposure to elevated glucocorticoid levels may result in a positive energy balance, by increasing energy intake, without affecting resting energy expenditure. The stimulatory effects of glucocorticoids on energy intake may involve both homeostatic and non-homeostatic pathways involved in the regulation of eating behavior. The homeostatic pathways may include a suppression of CRH release, induction of leptin resistance and the stimulation of NPY release. Non-homeostatic pathways may include the individuals’ attitude towards eating, as well as neural systems involved in both the “wanting” (dopaminergic) and “liking” (opioidergic) aspects of food reward. The latter systems may, just like insulin [37], also be involved in a shift in food choice towards high energetic sweet and high fat foods. The effects of glucocorticoids on energy expenditure may depend on the duration of exposure, with mechanisms such as a decrease in CRH release, increased loss of lean body mass and decreased circulating T3 levels ultimately counteracting an initial stimulation of resting metabolic rate.

The resulting positive energy balance is likely to result in increased lipogenesis and fat storage, under influence of glucocorticoids and elevated concentrations of insulin. In addition, glucocorticoids may even increase adipogenesis due to an up-regulation of the NPY Y2 receptor in abdominal adipose tissue.
tissue [51]. Notably, visceral adipocytes have a fourfold higher number of glucocorticoid receptors than adipocytes in other fat depots [8]. Accordingly, the stimulatory effects of dexamethasone on lipoprotein lipase activity were more pronounced in visceral adipocytes than in subcutaneous adipocytes [67]. Thus, the increased fat storage due to prolonged hypercortisolism may show some site-specificity, with a preference for the visceral regions.

The increased adiposity may lead to an increase in weight dissatisfaction [75], which will lead to dieting in an attempt to achieve and maintain of desired body weight. Dieting is done through cognitively controlling eating behavior and, hence, is accompanied with an increase in dietary restraint [117]. However, dietary restraint can act as a chronic physiological stressor, and like all other chronic stress will lead to alterations in HPA axis functioning. We found that the level of dietary restraint was positively correlated to 5-hour plasma cortisol patterns, and negatively correlated to the ability of the GR-agonist, dexamethasone, to suppress cortisol release under a strenuous exercise protocol [Rutters, in press].

Therefore, we propose that chronic hyperactivity of the HPA axis initiates a vicious circle (Fig. 1), which puts chronic stress as a major risk factor for excessive weight gain and (visceral) obesity. Whether this mechanism is the primary cause for the obese state in the visceral obese remains to be elucidated, but it should be noted that HPA axis hyperactivity is typical in visceral obese subjects [9–11] and that HPA axis functioning in obese women was not significantly affected by weight loss [118]. Therefore, the HPA axis may therefore be an important causal factor in to the obesity epidemics of the Western society, where high levels of ambient stress and availability of high fat, sweet foods are abundantly present.

References


