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Effects of energy restriction on activity of the hypothalamo-pituitary-adrenal axis in obese humans and rodents: implications for diet-induced changes in body composition

Abstract

Background: Obesity treatments aim to maximize fat loss, particularly abdominal or visceral fat, without compromising lean or bone mass. However, the literature contains numerous examples of obesity treatments that – in addition to fat loss – result in loss of lean mass and/or bone mass.

Materials and methods: Because of the known effects of energy restriction to increase activity of the hypothalamo-pitutiary adrenal (HPA) axis in lean humans and animals, and because increases in circulating glucocorticoid levels could potentially contribute to adverse body compositional changes with obesity treatments, we conducted a systematic PubMed search to determine whether HPA axis activation also occurs in response to energy restriction in obese humans and animals.

Results and conclusions: In most studies in obese humans, short-term severe energy restriction increased circulating cortisol levels, and this response was also seen in two longer-term human studies involving severe or moderate energy restriction. These findings parallel studies on short- or long-term energy restriction in obese rodents, with most studies showing increases in circulating corticosterone concentrations, and no change or actual increases in hypothalamic expression of corticotropin-releasing hormone, urocortin 3 or their receptors. However, a significant proportion of studies involving longer-term severe or moderate energy restriction in obese humans showed no change or decreases in HPA axis function. There was variability among human studies in the duration of energy restriction and timing of the HPA axis investigations (i.e., during energy restriction, or after a period of post-restriction weight maintenance). In order to unambiguously determine changes in HPA axis function with energy restriction in obese humans, it will be important to assess HPA axis function at multiple time points *during* energy restriction, given that obese individuals may spend many weeks or months in severe or moderate energy restriction in order to reduce excess weight, and given that increases in glucocorticoid function can have significant effects on body composition within weeks to months.

Keywords: animals; caloric restriction; HPA axis; humans; obesity.

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Introduction

Obesity is a condition defined as abnormal or excessive fat accumulation and has been identified as a risk factor for a number of disorders, including type 2 diabetes [1] and cardiovascular diseases [2]. The worldwide prevalence of obesity continues to increase and has more than doubled since 1980.

An important aspect of curbing the impact of the obesity epidemic is providing effective long-term treatments. The aim of obesity treatments is to maximize the loss of fat mass, particularly abdominal or visceral fat mass, without compromising lean body mass or bone mass. However, the literature contains numerous examples of obesity treatments that – in addition to inducing fat loss – result in loss of lean mass and/or bone mass, particularly when supervised strength training is

not incorporated into the treatment regime [3–7], when dietary protein intake falls below certain critical levels [8], and possibly also when weight loss is rapid, as in severely energy-restricted diets [9], or as a result of some forms of bariatric surgery [10]. Understanding the mechanisms underpinning changes in body composition in response to obesity treatments could lead to improved clinical outcomes from such treatments.

We hypothesise that increased activity of the hypothalamo-pituitary-adrenal (HPA) axis in response to energy restriction in obese people may contribute to less than optimal body compositional outcomes. The rationale for this hypothesis is that energy restriction in lean humans or animals is known to up-regulate activity of the HPA axis, with resultant increases in circulating glucocorticoid levels [11]. Moreover, because glucocorticoids per se can cause accretion of white adipose tissue – particularly visceral adipose tissue – as well as loss of lean tissue and bone mass in humans and animals, such increases in circulating glucocorticoid levels probably contribute to the loss of lean tissue and bone in severely energy-restricted people (e.g., patients with anorexia nervosa or elite gymnasts), as well as the preferential accretion of central fat with re-feeding in anorexia nervosa [11]. One might argue that an obese individual undergoing energy restriction to lose excess weight is under a less extreme form of nutritional stress than an already lean or underweight individual in severe energy restriction caused by anorexia nervosa or competitive sports requirements. However, because obesity per se is already associated with heightened activity of the HPA axis, as will be briefly discussed below, any effects of energy restriction on HPA axis activity in obesity may not be negligible.

In light of these considerations, we conducted a systematic search of the literature in the PubMed database from 1975 to June 2013 in order to ascertain the effects of energy restriction on activity of the HPA axis in obese animals and humans. Our search strategy included the following Medical Subject Heading (MeSH) terms: [diet, reducing OR diet, weight loss OR caloric restriction OR obesity/diet therapy OR food deprivation OR body weight (only in animal search)] AND [corticotropin-releasing hormone OR receptors, corticotropin-releasing hormone OR corticotroph OR receptors, corticotropin OR glucocorticoid OR receptors, glucocorticoid OR adrenocorticotropic hormone OR hydrocortisone OR corticosterone OR corticoreleasing factor (only in animal search)] AND (obesity). We limited our search to articles in English and studies in humans and animals. The search yielded 105 human and 741 animal articles. We retrieved the full text and reviewed in depth only those articles that included investigation of the effect of energy restriction on the HPA axis in obese humans or animals (mice and rats), as stated in the article title or abstract. Sixteen human and 10 animal articles met these criteria and were thus included in our review. These articles are cited in the sections below entitled "Effects of energy restriction on activity of the HPA axis in obese humans", and "Effects of energy restriction on activity of the HPA axis in obese rodents".

Before outlining the results of our systematic literature search, we will first provide an overview of the HPA axis, as well as the effects of obesity per se and eating on activity of this axis, as this provides important background to our literature review.

Overview of the HPA axis

The HPA axis is a major neuroendocrine system that helps to protect against stressors by regulating the secretion of glucocorticoids [12]. Stress induces the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus. CRH is released into the hypophyseal portal system and is transported to the pars distalis in the anterior lobe of the pituitary gland, where it stimulates the secretion of adrenocorticotropin (ACTH) from the anterior pituitary. ACTH, in turn, stimulates glucocorticoid production from the adrenal cortex, and glucocorticoids are transported in the circulation bound to corticosteroid-binding globulin (CBG). The availability of glucocorticoids in target tissues is dependent on activity of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD). The 11β-HSD1 isoform converts the inactive glucocorticoids (cortisone in humans and 11-dehydrocorticosterone in rodents) into their active form (cortisol in humans and corticosterone in rodents), and the 11β-HSD2 isoform inactivates cortisol and corticosterone [13]. Glucocorticoids exert actions in target tissues by binding to and activating the glucocorticoid receptor. Glucocorticoids participate in the control of whole body homeostasis and the response to stress, and play a key role in regulating basal activity of the HPA axis. The glucocorticoid receptor initiates or represses gene transcription, and induces negative feedback of the HPA axis, for termination of the stress response, by acting on the hypothalamus and the pituitary gland [14]. The inhibitory glucocorticoid feedback on the HPA axis limits duration of the total tissue exposure to glucocorticoids, thus minimizing catabolic, anti-reproductive and immunosuppressive effects of these hormones.

Obesity is associated with dysregulation of the HPA axis

Previous studies have shown that obesity is associated with HPA axis dysregulation that may originate from increased forward drive, decreased sensitivity to negative feedback regulation, or altered sensitivity of peripheral tissues such as fat and skeletal muscle tissue to glucocorticoids [15, 16]. Obese humans show a hypersensitive response to stimulation of the HPA axis, the magnitude of this exaggerated response being dependent on fat distribution [17, 18]. After physical or psychological stressors, or after exogenous administration of CRH, obese individuals showed exaggerated circulating ACTH and glucocorticoid levels [17, 19]. This exaggerated response was significantly greater in those obese people who have a more visceral distribution of body fat than those with a more subcutaneous distribution [17]. Greater visceral adiposity is also associated with a higher HPA axis response in lean people [19]. Sex also plays an important role in determining HPA axis response, where cortisol exposure is inversely related to fat mass index (calculated as fat mass/height^2 in kg/m^2) in men and waist to hip ratio in women [18, 20–23].

While the exact direction(s) of causality in this association between visceral adiposity and HPA response is unclear, the relationship may be caused by the physiology of visceral fat, which contains a higher density of glucocorticoid receptors than subcutaneous fat without an increase in binding affinity [24]. This could in turn influence glucocorticoid production and subsequent negative feedback to the brain. Indeed, it has been shown that people with a greater visceral fat distribution may have increased pituitary sensitivity to CRH [18]. Another factor that may contribute to the observation of increased HPA activity in people with more adiposity is that obesity is characterized by a state of chronic mild inflammation [25, 26], with enhanced circulating levels of inflammatory markers, including cytokines [27]. Cytokines – like stress – have been shown to stimulate the HPA axis at the level of the hypothalamus, anterior pituitary gland, and the adrenal cortex [14, 28].

In summary, obesity in humans – particularly visceral obesity – is associated with increased activity of the HPA axis, and this may be due in part to specific qualities of visceral adipose tissue.

The HPA axis and food intake

Before examining the effects of long-term energy restriction, as in 'dieting' in obese humans and animals, this section provides an overview of the effects of daily rhythms in food intake on activity of the HPA axis. This knowledge is important, because the recent nutritional status of research subjects at the time of investigation can profoundly influence results.

Food intake has been shown to be a synchronizer of diurnal rhythm of the HPA axis, a rhythm that is characterized in humans by maximum glucocorticoid levels in the early morning and minimum levels at night [29–31]. Under normal circumstances, surging levels of cortisol enter the bloodstream after a midday or evening meal, contributing to the undulating nature of daily HPA axis activity [30, 32].

Fasting is a state of stress [29] that alters the normal HPA axis rhythm. If overnight fasting is extended throughout the day, circulating cortisol levels peak later in the afternoon and follow an overall higher, flattened profile [32–34]. This change likely contributes to energy homeostasis in cases of insufficient exogenous energy intake, because hypercortisolemia promotes an appetite for calorie-dense, highly palatable food and processes such as gluconeogenesis to convert stored forms of energy into useable glucose [29, 33, 35–38].

The exact mechanism by which the HPA axis responds to acute changes in food intake remains elusive. It seems that the type of macronutrient ingested plays an important role in HPA axis stimulation. High protein meals stimulate a significantly higher cortisol secretion than do high carbohydrate or high fat meals [39–41]. Although scientists are still unclear of how a signal reaches the HPA axis once food has been ingested, one study has shown that nasogastric compared to intravenous administration of nutrients induces a much more significant cortisol response, suggesting that the signalling emanates from the stomach or duodenum before the metabolites enter the blood stream [40].

While activity of the HPA axis is influenced by the presence of food, human and animal studies (as discussed below) have shown that energy restriction, be it severe or moderate, also affects the HPA axis on several levels.

Effects of energy restriction on activity of the HPA axis in obese humans

A number of studies have looked at the effect of short-term periods of severe energy restriction on circulating or urinary cortisol levels in obese humans, with conflicting evidence. Two studies have shown a decrease in

circulating cortisol levels, after 48 h [42], or urinary cortisol levels after 3 days [43] of short-term severe energy restriction, while three other studies using short-term total fasting reported an increase in circulating cortisol [44–46]. These latter studies involved an 84-h total fast [44] or 6–11 days of starvation in obese men [45, 46], and were found to increase circulating cortisol levels [44–46] – both total and unbound [46] – with no change [45] or only a slight increase [46] in total or free urinary cortisol. On balance, the majority of the studies (three out of five) that have investigated the effects of severe short-term energy restriction on circulating cortisol levels in obese humans have shown significant increases in this parameter.

There have been somewhat mixed results with longer-term severe energy restriction on HPA axis function in obese humans. The majority of studies report no change in function. Four weeks of severe energy restriction of ~380 kcal/day in obese female identical twins had no effect on circulating levels of cortisol [47]. In addition, a severely energy-restricted diet to achieve a weight loss of >10% of initial body weight, followed by a 1-week refeeding regime, resulted in no change in circulating cortisol levels in obese individuals [48]. Similarly, 3 weeks on a severely energy-restricted diet of ~600 kcal/day, followed by 1 week of weight maintenance and then 2 weeks of ad libitum feeding, did not alter circulating cortisol levels in obese men [45]. Further, following 12-weeks on a severely energy-restricted diet of 800 kcal/day in obese women, circulating ACTH levels and ACTH response to ovine CRH stimulation were unaltered relative to pre-diet levels and did not differ between the obese participants and lean controls [49]. However, in that study cortisol concentrations decreased after weight loss, and there was a reduced cortisol response to ovine CRH stimulation [49]. Another study also showed a decrease in circulating cortisol levels in obese males and females following a 4-week severely energy-restricted diet of ~380 kcal/day [50]. While the majority of studies involving long-term severe energy restriction in obese humans have shown either no change (three studies) or a decrease (two studies) in circulating cortisol levels or cortisol response, this is not a unanimous finding. When obese participants were treated with a severely energy-restricted diet of 450 kcal/day for 16 weeks, followed by a hypocaloric diet for 32 weeks, circulating cortisol levels increased in women, with no significant change in men, when measured at 8 and 18 weeks after commencing the severely energy-restricted diet [51].

Similar to the findings with longer-term severe energy restriction, it is also unclear if longer-term moderate energy restriction, commonly used in the management of overweight and obesity, influences circulating cortisol levels or function of the HPA axis, with published studies reporting no change, inhibitory or stimulatory effects. Moderate (30%) energy restriction in overweight and obese individuals over a period of 12 weeks resulted in no significant differences in 24-h urinary free cortisol/cortisone, circulating CBG or free cortisol levels during a low dose ACTH simulation test [52]. Similarly, 6 months of moderate energy restriction (a 250–350 kcal/day deficit) in obese women had no effect on circulating levels of cortisol [53]. These findings support a shorter-term study that showed no differences in salivary cortisol levels following 18 days on a moderately energy-restricted diet of 1000 kcal/day [54]. Also, 3 months on a moderately energy-restricted diet of 1000 kcal/day, followed by a period where participants were transitioned back to solid-foods over 2 weeks and then spent 3 months on a weight maintenance diet, had no effect on cortisol production rate, either absolute values or normalized to fat free mass [55]. However, in that study cortisol production rate normalized to fat mass or intra-abdominal fat mass increased by 40% and 100%, respectively, after weight loss [55]. While these three studies involving moderate energy restriction showed no clear changes in HPA axis function, another study of a 90-day diet of 800–1500 kcal/day in obese women showed decreased ACTH and cortisol levels measured during an oral glucose tolerance test [56]. In contrast, moderate energy restriction (a 500 kcal/day deficit) over 10 weeks in obese men increased circulating cortisol levels and decreased that of ACTH [57].

Taken together, the available literature shows that energy restriction in obese adults results in disturbances in HPA axis function, albeit the direction of change is not clear. In most [44–46] but not all [42, 43] studies in obese humans, short-term severe energy restriction produced an increase in circulating cortisol levels, and this response was also seen in women but not men in one longer-term study involving severe energy restriction [51]. However, most studies involving longer-term severe energy restriction in obese humans showed no change in HPA axis function [45, 47 ,48], and two studies suggested a decrease in activity of this axis [49, 50]. Similarly, longer-term moderate energy restriction in obese humans has been reported to result in increases [57], no change [52–55] or decreases [56, 57] in HPA axis function.

A possible explanation for these widely discrepant findings in humans could be the time relative to the commencement of energy restriction when HPA axis function was measured. Many of the studies reviewed in this section involved a period of post-diet re-feeding or weight maintenance prior to investigation of HPA axis function. This experimental paradigm enables the effects of weight

loss per se to be examined, independent of any effects of energy restriction. Indeed, certain adaptations to energy deficit, notably reduced metabolic rate and impaired thyroid function, are seen when measured during energy restriction but not after a period of 10 days to 3 months in energy balance in weight-reduced individuals [58, 59]. As such, it is reasonable to propose that HPA axis function may be different depending upon whether it is measured during energy restriction or following a period of weight maintenance at the reduced body weight. Given that obese individuals may spend several months in severe or moderate energy restriction in order to reduce excess weight, and given that increases in glucocorticoid function can have significant effects on fat, lean and bone mass within 2–3 months [60, 61], it is important to assess HPA axis function *during* energy restriction. Another factor that could contribute to the discrepant findings reported in this section is negative feedback regulation of the HPA axis; initial increases in circulating cortisol levels can feed back on the pituitary gland and hypothalamus and lead to eventual normalization or even inhibition of the axis. Support for this concept comes from a study involving continuous central administration of neuropeptide Y to rats [62], an experimental paradigm that mimics many aspects of energy restriction [63]. This paradigm initially increased circulating corticosterone and ACTH concentrations, but subsequently led to normalization of these parameters, as well as down-regulation of hypothalamic CRH mRNA expression [62]. In light of these considerations, we propose that a more complete understanding of HPA axis function with energy restriction in obese humans would be obtained if investigations were made at several time points during energy restriction.

Effects of energy restriction on activity of the HPA axis in obese rodents

Studies in obese rodents have revealed a profound, predominantly stimulatory, impact of energy restriction on activity of the HPA axis, either when compared to non-restricted obese controls, or when compared with effects of energy restriction in lean rodents.

A number of studies have looked into the effect of overnight, short-term and longer-term food deprivation on corticosterone concentrations in obese mice and rats [64–67]. These studies showed that following 12 [65], 24 [66, 67] and 48 [67] h of fasting, or following 3 weeks [64] of 33% energy restriction, there was an increase in circulating corticosterone concentrations in obese rodents. A similar effect was also seen with longer-term food deprivation. Following a 30% energy-restricted diet for 12-weeks, Otsuka Long Evans Tokushima Fatty rats had greater circulating corticosterone concentrations when compared with an unrestricted control group [68]. Interestingly, in that study no increase in corticosteronemia was seen when similar reductions in body weight, adiposity and leptinemia were achieved by 12 weeks of wheel running [68]. It must be noted that one study in obese mice showed a decrease (rather than an increase) in circulating corticosterone concentrations following 6-weeks of food deprivation when compared with ad libitum-fed obese mice [69].

It can be seen from the above that short- or long-term energy restriction in obese rodents generally increases circulating corticosterone levels. This effect is likely mediated by the hypothalamus, because energy restriction influences hypothalamic expression of CRH or CRH receptors in obese rodents. One study looked at the effects of 48-h food deprivation on hypothalamic mRNA levels of urocortin 3 (Ucn3) and type 2 corticotropin-releasing hormone receptor (CRH_2-R) in lean and obese Zucker rats [70]. Ucn3 is part of the CRH family and binds specifically to CRH_2-R to decrease food intake, therefore playing an important role in responding to food-related stress. An interesting outcome of this experiment was that although lean rats showed decreases in hypothalamic Ucn3 and CRH_2-R mRNA levels in response to energy restriction, obese Zucker rats showed no change [70]. Similar findings were reported in another study, where CRH concentrations were measured in three regions of the hypothalamus of lean and obese mice: the arcuate nucleus (ARC), paraventricular nucleus (PVN), and ventromedial hypothalamus (VMH). Obese mice had half the CRH concentrations in the ARC as lean mice in the un fasted state, but – unlike their lean counterparts – they showed no change (i.e., no decrease) in ARC CRH concentrations following 24 h of food deprivation [71]. While these studies showed no effect of food deprivation on central CRH expression in obese rodents, unlike food-deprived lean animals, another study has shown actual increases in brain CRH mRNA levels or activation of CRH-expressing hypothalamic cells with energy restriction in obese Zucker rats [72]. After 3, 6, 12 and 24 h of food deprivation, obese Zucker rats, compared to lean rats, showed a relative increase in CRH mRNA expression or cellular activation of CRH-expressing neurons (as indicated by induction of c-fos expression) in several brain regions, the changes being most pronounced in the PVN. Obese rats also exhibited a marked increase in

type 1 corticotropin-releasing hormone receptor (CRH_1-R) mRNA levels in the PVN starting at 6 h after fasting, compared to lean rats, with no significant changes in CRH_2-R [72]. In light of the observation that energy deprivation in obese rodents generally increases circulating corticosterone levels [64–67], these findings of no change – or an actual increase – in the hypothalamic expression of CRH, Ucn3 or their receptors suggest that during energy restriction in obesity, the HPA axis may exhibit impaired negative feedback regulation at the level of the hypothalamus.

While obese rodents generally show energy restriction-induced increases in circulating corticosterone levels and no decrease or an actual increase in central expression of CRH or CRH receptors, obese mice have been shown to have a decreased pituitary content of ACTH following a significant period of energy restriction. A group of genetically obese *ob/ob* mice were put on an energy-restricted diet at 5 weeks of age, when their weights were slightly over normal weight (overweight) [73]. Under normal circumstances, adult obese mice were found to have roughly 14 times higher levels of ACTH in the pituitary gland than lean mice. However, after 7 weeks of caloric restriction, the obese mice showed pituitary ACTH levels nine times less than their obese, non-restricted counterparts, as well as a significant decrease in ACTH secretion from the isolated perifused pituitary gland. These differences in pituitary ACTH levels between lean and obese mice were not reflected by differences in plasma ACTH and corticosterone levels [73]. This study did not report on the effect of energy restriction on circulating ACTH levels in obese mice.

In summary, the HPA axis of obese rodents shows marked changes in response to short- or longer-term energy restriction, with most but not all studies showing increases in circulating corticosterone concentrations compared to non-restricted levels, and no change or actual increases in hypothalamic expression of CRH, Ucn3 or their receptors. Additionally, one study from 1975 showed a decrease in pituitary ACTH levels or secretion with longer-term energy restriction in obese mice.

Effects of changes in activity of the HPA axis on body composition

It is often assumed that activation of the HPA axis in response to energy restriction would only be observed under cases of extreme stress, such as in lean humans with anorexia nervosa or cachexia, or in lean animals. However, our review of the literature in obese humans and rodents shows that – as is the case for the known effects of energy restriction on activity of the HPA axis in lean humans and animals – obese humans and rodents sometimes also display enhanced HPA axis activity in response to energy restriction. While further work is required to confirm this possibility, such an effect could potentially contribute to less than optimal changes in body composition during energy restriction for the treatment of obesity.

Not only does the binding of glucocorticoids to glucocorticoid receptors produce effector responses that have implications for metabolism and appetite, it also is involved in the regulation of adipocyte and myocyte synthesis, as well as regulating osteoblasts and osteoclasts. Glucocorticoids, through their interaction with insulin, promote the differentiation of pre-adipocytes into mature fat cells as well as stimulating lipoprotein lipase activity, which facilitates fat accumulation, particularly in the abdomen [33, 74, 75]. High levels of glucocorticoids inhibit myocyte synthesis and promote breakdown through stimulating protein catabolism pathways [33, 76]. This process is further accelerated in the absence of insulin [77]. This would most likely be seen in the fasting scenario, where insulin levels are reduced and the body needs to convert stored energy to useable energy [76]. Additionally, the reduced circulating insulin concentrations typically observed during weight loss interventions in obese individuals might therefore be expected to enhance the catabolic effects of glucocorticoids on myocytes. Further to effects on adipocytes and myocytes, glucocorticoids promote apoptosis in osteobalasts and osteocytes, which would be expected to decrease bone formation, as well as prolonging the lifespan of osteocalsts, which would be expected to increase bone resorption [78].

In keeping with the effects of glucocorticoids on fat, muscle and bone cells observed in vitro, lean men and women taking a high dose of oral glucocorticoid treatment (≥40 mg/day of a prednisolone equivalent) for 2 months showed a 10% increase in fat mass, a 10% decrease in lean body mass, and significant decreases in bone mineral density and bone mineral content in the absence of effects on body weight [60]. Longer-term use (more than 60 days) of oral glucocorticoids is associated with self-reported weight gain in over 60% of patients, including those on lower doses (e.g., 10 mg/day prednisone for 6 months), and weight gain is the most commonly reported adverse event in patients taking glucocorticoids [61]. Additionally, people with Cushing's syndrome, associated with primary hypercortisolism, exhibit hyperphagia, weight gain, visceral obesity and muscle wasting [19, 76, 79], further demonstrating a primary role of increased glucocorticoid action in the propensity to store fat (particularly central fat) at the expense of lean tissues.

It remains to be determined whether any changes in circulating glucocorticoid concentrations with energy restriction in obese individuals contributes to adverse effects on body composition.

The gap in knowledge and significance

Our review of the literature has not ruled out the possibility that energy restriction in obese individuals is perceived as a nutritional stress, resulting in indications of enhanced HPA axis function in most rodent studies and in some – but certainly not all – human studies. Studies in obese humans on effects of energy restriction on HPA axis function showed a great deal of variability, with reports of increased, unchanged or decreased circulating cortisol levels. As recent nutritional status influences function of the HPA axis, and because changes in HPA axis activity can be masked by feedback regulation of the axis by glucocorticoids, we propose that a more complete understanding of HPA axis function with energy restriction in obese humans would be obtained if investigations were made at several time points *during* energy restriction, as opposed to after a period of post-restriction re-feeding, as was the case in several human studies hereby reviewed. Additionally, correlating changes in HPA axis function with changes in parameters of body composition, such as fat mass and distribution, lean body mass, muscle strength and bone mineral content, could shed light on the role of altered HPA axis function, if any, in mediating favourable or unfavourable changes in body composition in response to obesity treatments. Such knowledge could aid in the quest for obesity treatments that maximize the loss of fat mass, particularly abdominal or visceral fat mass, without compromising lean body mass or bone mass.

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