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Review

Brief review: Glucocorticoid excretion in obesity☆,☆☆

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ABSTRACT

Cortisol secretion and glucocorticoid excretion rates are regularly increased in obesity and associate with indices of body size and visceral adiposity. Different mechanisms may underlie the elevated urinary excretion rates of cortisol metabolites in obesity. In the present brief overview, potential mechanisms are discussed, paying special attention to cortisol metabolism. Besides, potential confounding factors in the evaluation of urinary glucocorticoid excretion are highlighted.

Contents

1. Introduction

Obesity is one of the leading causes of preventable death. Following the rapid increase in its incidence worldwide in the past decades, obesity reached epidemic proportions with major health consequences at an individual as well as a public health level [1]. In light of the limited health care resources, understanding of the underlying pathophysiological mechanisms is of key interest, with the aim to improve the treatment of obese patients and to prevent the development of obesity. Obesity is a multifactorial disorder which results from variable interactions between genetic, lifestyle and environmental factors [2]. Given that visceral adiposity is a prominent finding in hypercortisolism (Cushing's syndrome), the

Abbreviations: ACTH, adrenocorticotropin; BMI, body mass index; CRF, corticotrophin-releasing factor; HPA, hypothalamic–pituitary–adrenal; 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; THF, tetrahydrocortisol; UFE, urinary free cortisone; UFF, urinary free cortisol; WHR, waist-to-hip circumference ratio.

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role of glucocorticoids in the development of general obesity has been of particular interest in the past years.

2. Glucocorticoid secretion in obesity

It is well known that cortisol secretion or production is regularly increased in obesity [3,4]. Urinary free cortisol (UFF) and glucocorticoid metabolite excretion rates are frequently elevated in obese subjects [5–7]. In particular, subjects with visceral adiposity depict increased cortisol secretion rates. Mårin et al. [5] found positive associations of urinary cortisol output with waist-to-hip circumference ratio (WHR) and abdominal sagittal diameter, both of which indices of visceral fat accumulation, in obese women. Pasquali et al. [7] confirmed that daily UFF excretion rates were 1.6-fold higher in women with abdominal body fat distribution than in women with peripheral body fat distribution and in normal-weight controls. As shown in a further study, in female patients with abdominal body fat distribution, nocturnal cortisol secretion appeared to be mildly higher than in females with peripheral body fat distribution [8].

The reasons for the elevated urinary excretion of cortisol metabolites in obesity are only partially understood and several potential explanations are discussed. One is that the rise in cortisol secretion is appropriate to the increase in lean body mass in obesity [9]. A second explanation postulates an overactivity of the hypothalamic–pituitary–adrenal (HPA) axis [10,11]. Thirdly, increased cortisol secretion may result from enhanced cortisol metabolic rate with compensatory changes in the HPA axis [12].

3. Influence of lean body mass on glucocorticoid excretion

In light of the close association of adrenal gland size with body surface area [13] and body mass index [14], it appears to be appropriate to normalize urinary glucocorticoid metabolite excretion rates for measures of body size. Correction for differences in lean body mass by calculating the ratio of daily glucocorticoid excretion rates to urine creatinine, an established surrogate parameter of muscle mass, resulted in similar cortisol production rates in obese and non-obese adult subjects [9,15]. In agreement with these data, we have recently shown that the differences in absolute daily glucocorticoid secretion and the potentially bioactive-free-glucocorticoids between severely obese subjects and lean controls were no longer detectable after correction for body surface area [16]. This relationship applies particularly to adults. In children the situation is complicated by the fact that body composition, body mass index (BMI), and especially muscularity and consequently 24-h urinary creatinine excretion vary considerably with age and height. These particularities have been discussed in detail elsewhere [17].

4. Activity of the hypothalamic–pituitary–adrenal axis in obesity

The results of a previous study, showing a more pronounced increase of adrenocorticotropin (ACTH) and cortisol after corticotrophin-releasing factor (CRF) administration in women suffering from visceral adiposity in comparison to lean controls, suggested a hyperactivity of the HPA axis in women with abdominal body fat distribution [7]. However, in the majority of studies, plasma cortisol and ACTH response to CRF did not differ between obese and lean subjects [18] or were even blunted [19,20]. A normal suppression of the HPA axis in response to dexamethasone administration in obesity is supported by numerous studies [5,18,21–24], with only few exceptions [25]. Previous findings which also argue against an overactivity of the HPA axis in obesity are the subnormal 24-h mean cortisol plasma concentrations in obese children [26,27] and in obese adults [12,25].

Diminished circulating cortisol levels rather indicate an increased cortisol metabolic rate especially if the corticosteroid binding globulin is decreased [12,28]. Several studies provided direct evidence of an increased metabolic clearance rate of cortisol in obesity [6,12,18,29]. The increased metabolic clearance rate in turn can increase adrenocortical activity (i.e., adrenal cortisol secretion) to compensate for the higher cortisol degradation and to maintain free cortisol blood levels [4]. Accordingly, a reduced metabolic cortisol clearance due to weight loss can decrease the compensatory HPA axis activation frequently seen in obese people [30].

However, this mechanism of parallel changes in metabolic clearance and adrenocortical activity has not been observed in all obese subjects [31]. In principle, metabolic cortisol clearance in liver and fat involves varying 11β-oxidation, leading to reduced or increased conversion rates of cortisol to cortisone, and depends on A-ring reduction, resulting in formation of the irreversible 5α- and 5β-tetrahydrocortisol (THF) metabolites [32].

5. Glucocorticoid metabolism in obesity

Previous studies have shown that 5α- and 5β-reductase enzymes which catalyze A-ring reduction are dysregulated in obesity. In a murine model of obesity, hepatic 5α-reductase activity was found to be increased [33]. In line with these findings, in humans, 5α- and 5β-reductase enzyme activities, as assessed by urinary excretion of 5α- and 5β-reduced cortisol metabolites, were associated with anthropometric indices of obesity, such as BMI, waist circumference, and WHR [34,35]. A recent study suggests that it is not body composition per se which enhances 5α-reductase activity in obese subjects, but rather their fat mass-related insulin resistance [30].

Activities of the isoenzymes 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts cortisol to inactive cortisone, and 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which reactivates cortisone to active cortisol, also appear to be tissue-specifically altered in obesity. Mice overexpressing 11β-HSD1 selectively in adipose tissue developed visceral obesity and common features of the metabolic syndrome, comprising marked insulin resistance, glucose intolerance, and hyperlipidaemia, pointing to an important role of 11β-HSD1 in the molecular pathophysiology of visceral adiposity and metabolic syndrome [36]. In contrast, mice which selectively overexpressed 11β-HSD1 in the liver, developed mild insulin resistance and dyslipidaemia, but not obesity, indicating tissue-specific actions of 11β-HSD1 [37]. In line with these findings, obese Zucker rats depicted increased 11β-HSD1 activity in omental adipose tissue and diminished mRNA expression and activity in the liver [33]. The metabolically disadvantageous effects of increased 11β-HSD1 activity were also supported by previous animal knockout experiments. When fed a high-fat diet, mice with selective disruption of the 11β-HSD1 gene were resistant to weight gain and glucose intolerance, demonstrated improved lipid profile, and deposited fat in peripheral, but not in visceral sites [38–40]. In agreement with the animal data, numerous studies showed an increase in mRNA levels and activity of 11β-HSD1 in subcutaneous [18,41,42] and omental [43–46] adipose tissue in human obesity, whereas the enzyme activity was decreased in human liver [6,18,29]. 11β-HSD1 activity in adipose tissue was associated with measures of obesity, including BMI, percentage body fat, and waist circumference [6,42] and features of the metabolic syndrome, such as insulin resistance [42].

While the dysregulation of 11β-HSD1 in obesity has been extensively elucidated in animal obesity models as well as in human

adiposity, so far, only a limited number of studies investigated the role of 11β-HSD2 in obesity. In rodent models of obesity, the expression and activity of 11β-HSD2 were enhanced in kidney [33] and subcutaneous adipose tissue [47]. Associations were found between 11β-HSD2 mRNA levels in adipose tissue and indices of obesity, including body weight and body fat content, and obesity-related parameters, such as insulin resistance [47]. In line with these data, we have recently found a markedly elevated rise in renal 11β-HSD2 enzyme activity in severely obese subjects compared to normal-weight controls [16], though an increase of 11β-HSD2 activity in obesity has not been reported in a previous study [29]. The reasons for the observed discrepancies are currently unknown, but might be due to differences in the size of the study populations and kidney function.

In light of the low binding of cortisone to corticosteroid binding globulin and albumin and the correspondingly relatively high free plasma concentrations [48], cortisone serves as an additional, relatively rapidly available glucocorticoid pool that is activated to cortisol directly in the corresponding target tissues, e.g., in adipocytes. Thus, a rise in renal 11β-HSD2 activity may result in an intensified supply of the direct substrate cortisone for extra-renal 11β-HSD1 which may fuel visceral adiposity and insulin resistance. In accordance with this assumption and with a recent study showing strong associations between elevated 11β-HSD2 mRNA levels and indices of obesity and insulin resistance in a murine obesity model [47], 11β-HSD2 activity was negatively associated with insulin sensitivity in severely obese subjects [16].

6. Chronic stress and visceral obesity

A growing body of evidence from animal [49,50] as well as from human [51,52] studies points to the association between chronic exposure to environmental stress and increased rates of both obesity and metabolic syndrome. The neuroendocrine response to chronic stress involves activation of the HPA axis and the sympathetic nervous system [53]. Prolonged hyperactivation of the HPA axis and, consequently, chronic hypercortisolaemia in the setting of unlimited food supply favours the development of visceral obesity and related features of the metabolic syndrome [54]. In light of the high number of glucocorticoid receptors [55], visceral adipose tissue is particularly responsive to the actions of glucocorticoids, comprising adipocyte differentiation and lipid deposition [56]. Furthermore, enhanced HPA reactivity appears to link emotional stress to increased food intake [57]. However, the deleterious effects of chronic stress on body composition via hyperactivation of the HPA axis can be overcome by stress-reduction interventions. Application of an established stress-reduction tool acutely diminished salivary cortisol levels in overweight Latino adolescents [58].

7. Urine volume: a confounder of glucocorticoid excretion

Much of the data on adrenal function in human obesity is based on urinary glucocorticoid assessment. However, potential confounding factors have to be taken into account. Urine volume is an established confounding factor in the adrenocortical evaluation based on renal glucocorticoid excretion. Several studies in normal-weight adults and children showed that a high fluid intake and a corresponding high urine volume increased renal excretion rates of UFF and urinary free cortisone (UFE) [59–62] (Table 1). Mericq and Cutler [60] found that a high fluid intake caused a 1.6-fold increase in UFF excretion in normal-weight adults. In line with this finding, the frequency of UFF exceeding the upper normal limit was almost four times higher during elevated fluid intake. In contrast, fluid intake did not influence urinary excretion of 17-hydroxycorticosteroids, indicating that the increase in UFF was not consequence of activation of the hypothalamic–pituitary–adrenal axis. Fenske [61] confirmed these findings showing a two-fold increase of UFF and even a four-fold increase of UFE excretion following fluid intake. In agreement with these findings, the association between urine volume and UFE was stronger than the

Table 1
Associations between urine volume and excretion of urinary free cortisol and cortisone.

Reference	Study population	Age (years)	Body mass index (mean ± S.D.) [kg/m^2]	Analyte	Methods	Results
Bertrand et al. [59]	103 healthy school children (33 girls, 70 boys)	7–18.5 (range)	–	UFF	Competitive protein-binding assay	UFF amount increased with urine volume
Mericq and Cutler [60]	6 normal volunteers (3 females, 3 males)	22–45 (range)	23.2 ± 3.6	UFF	RIA	High fluid intake increases UFF
Fenske [63]	15 volunteers (6 women, 9 men)	23–52 (range)	23.9 ± 1.9	UFF	RIA and combined thin-layer chromatography/RIA, respectively	No influence of short-term water diuresis on UFF
Putignano et al. [64]	88 healthy women	24.7 ± 0.7 (mean ± S.D.)	27.2 ± 1.7	UFF	Dichloromethane extraction RIA	No relation between UFF and daily urine output
Fenske [61]	8 healthy men	30 ± 5 (mean ± S.D.)	25 ± 3	UFF and UFE	Thin-layer chromatography–competitive protein-binding assay	UFF/UFE excretion is correlated with urine volume
Shi et al. [62]	100 pre-pubertal (50 males, 50 females) and 100 pubertal healthy children (50 males, 50 females)	Pre-pubertal children: 8.5 ± 0.5; pubertal children: 13.0 ± 0.7 (mean ± S.D.)	–	UFF and UFE	RIA	Excretion rates of UFF and UFE are affected by daily urine volume
Müssig et al. [65]	59 obese subjects (16 males, 43 females) and 20 lean subjects (8 males, 12 females)	Obese subjects: 40 ± 13; lean subjects: 31 ± 5 (mean ± S.D.)	Obese subjects: 45.3 ± 8.9; lean subjects: 22.1 ± 1.8	UFF and UFE	RIA	Associations between urine volume and UFE in lean and obese subjects; association between urine volume and UFF only in lean subjects

RIA: radioimmuno assay; S.D.: standard deviation; UFE: urinary free cortisone; UFF: urinary free cortisol.

association between urine volume and UFF, indicating that the influence of water diuresis on UFE excretion is more pronounced than on UFF excretion. In deed, water load-induced stimulation of UFF and UFE excretion appears to be regulated by distinct mechanisms. Elevated UFF excretion results mainly from escape of cortisol from reabsorption in the proximale tubule, whereas, enhanced UFE excretion is a consequence of the increased conversion of cortisol to cortisone by 11β-HSD2 in the distal tubule. Also in normal-weight children the association between urine volume and UFE was found to be stronger than the association between urine volume and UFF [60,62]. Besides, the indicator of glucocorticoid secretion, the sum of the three major urinary glucocorticoid metabolites THE, THF, and 5α-THF, was not related to urine volume, confirming the previous data by Mericq and Cutler [60] showing that the rise in UFF excretion is independent of adrenocortical activation. However, an association between urine volume and excretion of UFF and UFE has not been found in all studies [63,64]. For instance, in lean subjects, UFF was not associated by short-term water diuresis [63]. The reasons for these discrepancies are currently unknown. Potential explanations comprise varying fluid intake and methodological differences, such as time and duration of urine sampling and analytical methods.

The impact of urine volume on UFF and UFE excretion in obesity has been investigated, so far, only by one study [65]. In severe obese subjects, urine volume was associated with UFE and 11β-HSD2 activity, but not with UFF. These discrepant findings may result from an enhanced cortisol to cortisone conversion in the distal tubule, due to the increased renal 11β-HSD2 activity which has been described in animal obesity models [33] as well as in human obesity [16]. Thus, UFE, but not UFF, which is frequently used as screening test in the work-up for endogenous hypercortisolism, appears not to be affected by water load in severe obesity.

8. Conclusions

The majority of studies do not support the existence of systemic hypercortisolism in animal models of obesity or human obesity despite frequently increased glucocorticoid secretion and excretion rates. However, a growing body of evidence supports a tissue-specific intracellular cortisol excess in obesity, with a rise in 11β-HSD1 enzyme activity as the underlying pathophysiological cause.

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