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Cortisol dysregulation in obesity-related metabolic disorders

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Abstract

Purpose of review—The understanding of how adrenal function is challenged by the interplay of our genetic and environmental milieu has highlighted the importance of inappropriate cortisol regulation in cardiometabolic disorders. Increased adipose tissue in obesity is associated with hypothalamic-pituitary-adrenal axis over-activation, increased cortisol production at the local tissue level, and probably higher mineralocorticoid receptor activation in certain tissues.

Recent findings—Due to the clinical resemblance of obesity-related metabolic disorders with the Cushing syndrome, new studies have investigated the intracellular regulation and metabolism of cortisol, new measurements in scalp hair as a tool for long-term exposure and the cortisol-mineralocorticoid receptor pathway. Thus, current and future pharmacological interventions in obesity may include specific inhibition of steroidogenic and regulatory enzymes as well as antagonists of the mineralocorticoid and glucocorticoid receptors.

Summary—This review highlights recent investigations focusing on the role of dysregulated cortisol physiology in obesity as a potential modifiable mechanism in the pathogenesis of obesity related cardiometabolic disorders.

Keywords

obesity; cortisol; mineralocorticoid receptor; metabolic syndrome; hypertension

Introduction

Cortisol plays an essential role in maintaining physiologic homeostasis; it is involved in many metabolic and immune processes, the diurnal sleep-wake cycle, the human stress response, and blood pressure regulation. Evolutionary pressures have resulted in complex

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cortisol regulatory mechanisms and modes of action that include: input from the brain and hypothalamic-pituitary apparatus, a highly specific circadian secretagogue pattern (e.g ACTH), intricate adrenal steroidogenic pathways, tissue specific conversion enzymes (e.g. 11β-hydroxysteroid dehydrogenases), and the capacity to activate more than one steroid receptor (e.g. mineralocorticoid receptor=MR and glucocorticoid receptor=GR).

However, it is becoming increasingly clear that contemporary environmental factors and some prevalent non-communicable diseases (such as obesity) can disturb these established cortisol regulatory and effector pathways, resulting in, or exacerbating, human disease states. Population-based studies have suggested that dysregulated cortisol physiology associates with mortality by demonstrating links between inappropriately high cortisol levels, even within normal reference ranges, and death [1] [2*]. The classical concept of circulating cortisol concentrations reflecting the main source of bioavailable cortisol has been reshaped by recent evidence suggesting that the local tissue milieu of cortisol activation and inactivation plays an even more important role in influencing the cellular exposure to cortisol and modulating tissue specific selectivity for steroid receptors [3, 4]. For instance, obesity is a widespread condition where cortisol has an important pathogenic role related to both increased cortisol production and altered local regulation; however, the clinical assessment of “cortisol status” has been challenging due to the limitation in our available methods to evaluate relative hypercortisolism.

Herein, we review studies available from the prior 18 months that address the regulation and dysregulation of cortisol physiology and its relation to obesity-related cardiometabolic diseases. We review the cortisol regulatory pathway from an evolutionary perspective, the current status in our contemporary environment and lifestyle, and current methods to assess and potentially treat dysregulated cortisol physiology.

Obesity and adrenal dysregulation from an evolutionary perspective

The evolutionary process reflects both changes in our genomic and environmental milieus. Our changing environmental surroundings and cultural lifestyle represent new factors influencing the gene-environment interactions that pressure endocrine physiology [5]. For instance, low sodium intake, high physical activity, and a diurnal behavior including longer sleep hours likely served as major selective forces in the evolution of our current genetic make-up with respect to cortisol regulatory physiology; however, our current “Western” lifestyle and diet are rapidly transforming into a nearly contradictory composition [6]. Thus, it is not surprising that the interplay between our newly adopted post-industrial revolution diet and lifestyle, with our genomic and physiologic regulation, may result in a higher incidence of several preventable diseases [5] [7]. Obesity may be the best example of a disease state that is a consequence of our modern lifestyle; increased availability and consumption of high caloric foods, in combination with decreased physical activity and sleep, has resulted in a state of excess adiposity that contributes to a number of related cardiometabolic disorders, including hypertension, heart disease, stroke, and diabetes [8].

Our understanding of adipose tissue has evolved from simply existing as an energy store and thermal insulating device to an active endocrine organ that actively participates in

metabolism, coagulation and reproduction [9]. From an evolutionary perspective, it has been postulated that among primate species, humans developed a higher capacity for survival due to greater adipose tissue reservoirs serving as energy depots in times of scarce food availability [10]. Although the presence of larger adipose tissue depots may have been vital for human evolution (including cognitive expansion, reproduction and prolonged fasting), in an environment with excess caloric availability, this evolutionary advantage has now become a disadvantage and risk factor of modern public health disorders [10, 11]. An excellent model to test how modern life leads to obesity and hormonal imbalance are studies that describe the adverse effects of urbanization in developing countries [12] [13]. In a recent study, unfavorable habits of urbanization in a rural population of Namibia were dramatically associated with higher rates of obesity, metabolic syndrome, diabetes and hypertension. Interestingly, this abnormal phenotype was associated with cortisol circadian rhythm dysregulation, suggesting that adoption of this “modern” urbanized lifestyle can result in altered endocrine modulation[12].

Phylogenetic analyses have shown that steroidogenic enzymes needed to secrete adrenocortical hormones and steroid receptors co-evolved during the different stages of vertebrate evolution, improving tissue and receptor selectivity and playing a key role in diversification and adaption to new environments [4] [14]. Further, these phylogenetic studies have demonstrated that genes encoding the machinery for cortisol secretion likely preceded those for aldosterone secretion, that hydroxysteroid dehydrogenases evolved as gatekeepers of inappropriate MR activation, and that the close homology between the MR and GR is explained by a shared common ancestor [4] [14]. These studies shed further insight on many mysteries of cortisol physiology. For instance, the high affinity of cortisol for the the GR and MR, and the newly discovered roles of the MR in adipose, cardiovascular, and brain tissue, beyond its classic role in renal sodium and potassium regulation [15, 16] [17, 18] [19].

Cortisol dysregulation in obesity: the adrenal gland and adipose tissue

Obesity, resulting in ectopic fat deposition mainly in the central trunk, as well as in tissues such as the liver and skeletal muscle, is highly prevalent and has been linked to adverse cardiometabolic profiles such as metabolic syndrome, diabetes, dyslipidemia and hypertension. Given the rising global prevalence of obesity [7] and the associated excess mortality with both general and central obesity [20], a better understanding of dysregulated physiologic pathways that contribute to disease in obesity is crucial.

A growing body of evidence suggests that metabolic and cardiovascular morbidities in obesity may be partially explained by dysregualted cortisol physiology [21] [22] [23] [24, 25*]. Glucocorticoid secretion not only depends on the hypothalamic-pituitary-adrenal (HPA) circadian rhythm, but also on the pre-receptor intracellular regulation of cortisol by 11β-hydroxysteroid dehydrogenases (11β-HSD) [26] [27]. The enzyme 11β HSD1, catalyzes the conversion of the inactive metabolite cortisone to active cortisol, thus amplifying glucocorticoid action locally, mainly in the liver, but also in muscle and adipose tissue [28] [29]. This local regulation is relevant because it represents a key tissue-level source of cortisol, and a potential ligand of both the GR and MR, that may not be reflected in

circulating cortisol levels alone. Further, since 11β–HSD1 is expressed in adipose tissue whose mass can dramatically increase in obese individuals, the activity of 11β–HSD1 may be an important component of excess GR and/or MR activation in obesity [26] [29] [30]. In contrast, 11β–HSD2 inactivates cortisol into the inactive metabolite cortisone, thereby reducing the activation of the GR, and improving the selectivity of the MR for aldosterone, which circulates in several magnitudes of order lower concentrations than cortisol. This balance of local cortisol activation and inactivation may play a essential role in metabolic disorders that are related to obesity, particularly when the balance is tilted towards increased local-tissue cortisol production. Therefore, the eventual influence of cortisol in obesity relies on interplay between adrenocortical cortisol secretion in response to the HPA axis, and local cortisol activation or inactivation in adipose and other tissues.

Although increased cortisol production has been described in the MetS and when comparing classic obesity to metabollicaly healthy obese subjects [31] [22], it has been challenging to decipher the individual contributions of local 11β–HSD1 overexpression versus overactivation of the HPA axis resulting in excess adrenal cortisol secretion [25*][32]. The pathogenic role of cortisol in central obesity and related disorders has been demonstrated in transgenic murine models and several human studies, mainly implicating increased 11β–HSD1 activity [24] [25*]. A decade ago, Masuzaki et al developed a rodent model with selective 11β–HSD1 overexpression in adipose tissue leading to visceral obesity, diabetes and dyslipidemia [33]. The opposite effects were seen in 11β-HSD1 adipose-tissue knock-out mice – when challenged with hypercaloric diets- these knock out animals had reduced visceral fat mass and did not develop diabetes [34].

Human studies have suggested an increased production of local cortisol in morbid obesity, hypertension, dyslipidemia, diabetes, metabolic syndrome and non-alcoholic fatty liver [28, 30, 35] [29, 36]. The classic concept proposed by Bujalska two decades ago suggesting that central obesity might be a “Cushing’s disease of the omentum” has been difficult to assess mainly due to limitations in measuring real-time local 11β HSD1 activity [37]. Although there are murine studies showing splanchnic hypercortisolism in obesity [36], radiolabeled cortisone studies in humans have not supported this concept [38]; and this has been the focus of on-going studies evaluating the differeing activity of 11β HSD1, particularly in pathophysiologic states such as obesity and diabetes [25*][23] [39]. Interestingly, Morgan and colleagues recently described that mice with complete knock-out of 11β-HSD1 did not develop metabolic abnormalities with exogenous glucocorticoids. Of note, adipose-specific 11β-HSD1 KO but not liver-specific KO mice, do not develop Cushing syndrome suggesting that adipose-tissue 11β-HSD1 is key in metabolic disorders associated with hypercortisolemia [40*]. Also, new human studies shown that obese patients with MetS compared with obese patients without MetS had higher visceral adipose tissue expression of 11β-HSD1, higher adipose-tissue expresión of the GR, and increased HPA axis activity [41]. Consistently, the study by Methlie et al showed that weight loss achieved by bariatric surgery resulted in decreased circulating cortisol levels and adipose-tissue 11β-HSD1 expression when compared to non-obese controls [42]. Woods and colleagues described that obesity is associated with higher subcutaneous adipose tissue expression of 11β-HSD1 and increased HPA axis driven cortisol secretion that is restored after bariatric surgery [43*]. To further complicate our understanding of the dynamic in the interaction between circulating

and local cortisol and the GR, cortisol-binding globulin concentrations are often significantly reduced in obesity, resulting in higher free levels of cortisol that may not be appreciated by “total cortisol” measurements [24].

It is important to note, that cortisol is a glucocorticoid but also a mineralocorticoid. The MR can be activated by both cortisol and aldosterone. In addition, excess adiposity and obesity are known to be associated with the development of elevated blood and urinary aldosterone levels and increased RAAS activity [44, 45] as well as a lack of normal suppressibility and stimulation of adrenal aldosterone secretion [46]. The explanation for this excess aldosterone is probably a combination of inappropriate adrenal aldosterone secretion, local adipose-tissue aldosterone production [47], and the result of adipose-derived adrenal aldosterone secretagogues [48] [45]. Animal studies have shown that MR expression is increased in obese states, further supporting the concept of a combination of higher ligand (both cortisol and aldosterone) and receptor activation (both GR and MR) in obesity [47].

Novel assessments of cortisol production and receptor activation

The resemblance of the metabolic syndrome phenotype with that of Cushing syndrome has generated an interest in understanding the role of cortisol in cardiometabolic disorders. Due to the aforementioned challenges in assessing “cortisol status” in obesity, new approaches have focused on developing novel methods and assays to assess cellular cortisol exposure and integrated cortisol status over time.

Glucocorticoid metabolites represent a surrogate marker of daily cortisol production [22]. Cortisol is inactivated mainly by liver reductases to tetrahydrometabolites that can be used to estimate 11β-HSD1 and reductase activity. We, and others, have reported that subtle increases in cortisol production can be detected by these cortisol metabolites due to the fact that increase glucocorticoid clearance by reductases may be a protective mechanism to reduce tissue exposure to glucocorticoids [40, 49] [50]. Consistently, 5α-reductase deficiency in mice induces insulin resistance and hepatic steatosis, suggesting intrahepatic accumulation of glucocorticoids [51]. Similarly, in humans, Crowley et al also recently showed that increased glucocorticoid production and higher reductase activity were associated with abnormal glucose tolerance and higher BMI after five years of follow up [52*]. This first of its kind longitudinal study relating cortisol secretion with future abnormal metabolic phenotypes supports the concept of cortisol dysregulation in obesity-related disorders that could be related to increased 11β-HSD1 and/or reduced 5α-reductase activity.

The commonly used cortisol measurements in body fluids such as plasma, saliva and urine reflect short-term integrated cortisol activity and have several pitfalls due to the variations in circadian rhythm, changes in cortisol binding globulin, and the pre-receptor metabolism of 11β-HSD1. New studies have validated the use of cortisol measurements from scalp hair to assess an integrated measure over time [53*]. This available tool evaluates the effects of long-term exposure to free cortisol since scalp hair grows roughly at a rate of 1cm/month. Higher hair cortisol measurements have been associated with increased cardiovascular risk and diabetes in the elderly [54], the MetS [55], and childhood obesity [56]. Thus,

measurement of glucocorticoids in hair may provide an easy way to assess chronic cortisol dysregulation. However, the effect of hair products, the role of hair cortisone and the pending widespread use of mass spectrometry are potential limitations of this technique.

Finally, the dynamic between cortisol and the GR and the MR in local tissues is an area of active research [53]. Recently Iqbal et al. demonstrated that cardiac 11β-HSD2 activity is very scarce, resulting in excessive cardiac MR activation by cortisol that could be inhibited with an MR antagonist [17]. Adipocyte inflammatory phenotype is induced by cortisol in cultured adipocytes is reversed by an MR antagonist but not by a GR antagonist, highlighting the potentially important role of cortisol-MR interactions in adipocyte dysfunction, differentiation and inflammation [57, 58]. Consistently, the expression of MR and 11β-HSD1 in human adipose-tissue were higher with increased BMI, especially in visceral fat, with no relation between GR levels, BMI or fat distribution[59]. Because of the scarce activity of 11β–HSD2 in heart, vasculature and adipose tissue, it is likely that some of the described effects of cortisol are due to activation of the MR rather than the GR, thus future studies exploring the glucocorticoid-MR pathway are warranted.

Potential interventions to interrupt cortisol dysregulation in human health

New knowledge regarding adrenal function and cortisol dysregulation can help design future treatments to target steroidogenic and regulatory enzymes (e.g.11β-HSD1) or receptors (MR or GR).

Tissue-specific inhibitors

To date several selective 11β-HSD1 inhibitors have been tested in human phase II trials, mainly in obese diabetic subjects, demonstrating moderate reductions in weight (roughly 1 kg), HbA1c, HOMA-IR and blood pressure (≈ 4 mm Hg), but these findings have not been consistently observed across studies [60] [61] [62]. Due to the availability of other more potent anti-diabetic agents on the market, and the inconsistent findings across studies, further phase III trials have been postponed. There are several explanations for these inconsistent results, including the complex physiology and tissue-specificity of 11β-HSD1, the dual activity of the enzyme (it can also inactivate cortisol similarly to 11β-HSD2), a potential compensatory increase in ACTH when tissue cortisol levels decline, and the efficacy of the inhibitor in various tissue [25*][23]. With the new studies presented above supporting 11β-HSD1 as a target for obesity and MetS, future trials may need to evaluate new inhibitors with higher specificity for the enzyme and a preference for adipose-tissue. To date, trials of 11β-HSD1 inhibition in Cushing syndrome have not been attempted.

Adrenal synthesis inhibitors

Inhibiting the adrenal synthesis of cortisol to treat Cushing syndrome is well-established using non-specific steroidogenic inhibition such as ketoconazole, metyrapone or mitotane [63]. Due to the potential side effects of these agents, new compounds that are more potent and specific for 11β-hydroxylase are being developed and could be tested in the future in obesity-related metabolic disorders [64]. Further, inhibition of aldosterone synthase has the potential to reduce circulating aldosterone levels and serve as an anti-hypertensive [65] [66].

Interestingly, due to the high homology between the enzymes of aldosterone and cortisol synthesis, next-generation aldosterone synthase inhibitors could potentially inhibit both aldosterone and cortisol synthesis thus having a potentially synergistic effect on cardiometabolic disorders [66]. For example, LCI699, an aldosterone synthase blocker is also a potent 11β-hydroxylase inhibitor, and was recently shown to normalize urinary cortisol and blood pressure in patients with Cushing's síndrome [67].

Receptor antagonists

Since MR blockers are widely available, are well tolerated, and decrease mortality in heart failure (e.g RALES and EPHESUS trials) [68], their use is now being tested in obesity and MetS. The use of an MR blocker has the potential benefit of blocking both aldosterone and cortisol effects in some tissues, and has been shown to improve resistant hypertension and myocardial abnormalities in MetS subjects [69] [70] but with inconsistent results in obesity and endothelial dysfunction [18] [71]. Future trials are needed to understand how to adequately select subjects for a study in order to enrich for a population that would optimally benefit from an MR antagonist intervention (e.g. circulating levels of cortisol/aldosterone, specific comorbidities or sodium intake, and others). Finally some studies have shown potential metabolic benefits, such as improved glycemia and insulin levels, by blocking the GR with mifepristone in subjects with diabetes [72]; also, a currently on-going trial is recruiting participants with metabolic syndrome for treatment with mifepristone.

Conclusion

Cortisol can activate the GR and the MR. This function likely played a crucial role in our survival and evolution as a species; however, as our environment, diet, and lifestyle rapidly changes in the post-industrial revolution era, the interaction of increasing adiposity with cortisol physiology has been demonstrated to result in a number of adverse effects. Emerging data continues to suggest that excess adiposity and obesity result in increased adrenal cortisol secretion, circulating bioavailability, and local tissue activation particularly in adipose tissue. All of these resulting effects suggest a heightened availability of local tissue cortisol to activate the GR and/or the MR, which are likely to be notable contributors to disease. Although antagonists to the GR and MR exist, a more refined understanding of the dynamic that results in excess local cortisol availability, and methods to mitigate its adverse effects, are important future goals with high public health value.

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Key Points

- Local tissue level cortisol regulation is strongly influenced by obesity and modern environmental inputs that play a major role in the risk of developing obesity-related metabolic disorders.
- Increased adipose tissue observed in obesity is associated with hypothalamic-pituitary-adrenal axis over-activation and increased cortisol production at a local level that can serve as a ligand for the glucocorticoid and/or mineralocorticoid receptors.
- New methods of assessing cortisol exposure and local activity have focused on scalp hair measurements of cortisol and the cortisol-mineralocorticoid receptor pathway.
- Future treatments for obesity related metabolic disorders may include highly specific inhibitors of adrenal biosynthesis,11β-HSD1 or the GR or MR pathways.