Adipose Tissue Expression of 11β-Hydroxysteroid Dehydrogenase Type 1 in Cushing's Syndrome and in Obesity

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ABSTRACT

Glucocorticoids have a major role in determining adipose tissue metabolism and distribution. 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) is a NADPH-dependent enzyme highly expressed in the liver and adipose tissue. In most intact cells and tissues it functions as a reductase (to convert inactive cortisone to active cortisol). It has been hypothesized that tissue-specific deregulation of cortisol metabolism may be involved in the complex pathophysiology of the metabolic syndrome (MS) and obesity. Transgenic mice overexpressing 11βHSD1 in adipose tissue develop obesity with all features of the MS, whereas 11βHSD1-knockout mice are protected from both. The bulk of evidences points to an overexpression and increased activity of 11βHSD1 also in human adipose tissue. However, 11βHSD1 seems to adjust local cortisol concentrations independently of its plasma levels. In Cushing's syndrome, 11βHSD1 is downregulated and may not be responsible for the abdominal fat depots; it also undergoes downregulation in response to weight loss in human obesity. The nonselective 11βHSD1 inhibitor carbenoxolone improves insulin sensitivity in humans, and selective inhibitors enhance insulin action in diabetic mice liver, thereby lowering blood glucose. Thus, 11βHSD1 is now emerging as a modulator of energy partitioning and a promising pharmacological target to treat the MS and diabetes. **(Arq Bras Endocrinol Metab 2007;51/8:1397-1403)**

Keywords: 11β-hydroxysteroid dehydrogenase type 1; Adipose tissue; Cortisol; Cortisone; Metabolic syndrome; Obesity; Cushing's syndrome

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RESUMO

Expressão da 11β-Hidroxisteróide Desidrogenase Tipo 1 no Tecido Adiposo na Síndrome de Cushing e na Obesidade.

Os glicocorticóides (GC) têm papel importante na determinação do metabolismo e da distribuição do tecido adiposo. A 11β-hidroxisteróide desidrogenase tipo 1 (11βHSD1) é uma enzima dependente de NADPH, altamente expressa nos tecidos hepático e adiposo. Em muitas células e tecidos intactos, ela funciona como redutase (convertendo cortisona em cortisol). Postula-se que uma desregulação tecido-específica do cortisol estaria envolvida na complexa fisiopatologia da síndrome metabólica (SM) e obesidade. Ratos que superexpressam 11βHSD1 no tecido adiposo desenvolvem obesidade e todas as características da SM, enquanto ratos *knockout* para 11βHSD1 são protegidos. Evidências apontam para uma super-expressão e aumento da atividade 11βHSD1 também no tecido adiposo humano. Entretanto, a 11βHSD1 parece ajustar a concentração local de cortisol independente da sua concentração sérica. Na síndrome de Cushing, a expressão da 11βHSD1 é regulada para baixo, não devendo ser a causa dos depósitos de gordura visceral; em obesos, há também regulação para baixo em resposta à perda de peso. A carbenoxolona, um inibidor não seletivo da 11βHSD1, melhora a sensibilidade insulínica em humanos e inibidores seletivos aumentam a sensibilidade insulínica hepática e melhoram o controle glicêmico em ratos diabéticos. Assim, a 11βHSD1 está emergindo como um modulador da compartimentalização de energia e um alvo farmacológico promissor para o tratamento da SM e do diabetes. **(Arq Bras Endocrinol Metab 2007;51/8:1397-1403)**

Descritores: 11β-hidroxisteróide desidrogenase tipo 1; Tecido adiposo; Cortisol; Cortisona; Síndrome metabólica; Obesidade; Síndrome de Cushing

THE INTRIGUING HISTORY OF 11β-HYDROXYSTEROID DEHYDROGENASE

THIRTY YEARS AGO (1977), Stanley Ulick described a syndrome characterized by hypertension, hypokalemia and reduced plasma renin activity (1), typical manifestations of mineralocorticoid excess. Interestingly, blood and urine levels of all known mineralocorticoids were normal. Accordingly, this condition was termed "syndrome of *apparent* mineralocorticoid excess" (AME). The defect did not appear to be in the renin–angiotensin–aldosterone system, but instead in the peripheral metabolism of cortisol (F), as shown later (2).

In the late 1980s, 11β-hydroxysteroid dehydrogenase (11βHSD) was described as an enzyme responsible for inactivation of physiologically active F to inert cortisone (E). This process occurs mainly at the kidney level, conferring protection to the unselective mineralocorticoid receptor (MCR). Congenital deficiency of 11βHSD is responsible for the AME syndrome that could be reproduced by exaggerated licorice ingestion (glycirrhyzinic acid, the active principle of licorice, inhibits 11βHSD). In both conditions, F acts as a potent mineralocorticoid in the kidney tubule, activating the MCR similarly to aldosterone, but at a higher concentration.

At that time, however, 11βHSD had an unexplained two-way function: to convert F into E and, conversely, E into F. Early on, two isoforms of 11βHSD were cloned and characterized: 11βHSD type 1 (11βHSD1) and 11βHSD type 2 (11βHSD2) (3,4). The former is a low-affinity NADP(H)-dependent dehydrogenase/oxoreductase (cortisol to cortisone and vice-versa, respectively), which was originally identified in the liver, but that is also highly expressed in adipose, gonadal, and central nervous system tissues. By contrast, 11βHSD2 is a high-affinity NAD-dependent dehydrogenase, whose sole action is to protect the non-selective MCR in the kidney, colon, and salivary glands from cortisol occupancy. 11βHSD1 was first regarded by Lakshmi and Monder (3) as a weaker version of 11βHSD2, because it showed dehydrogenase activity in tissues homogenates and microsomes, however evidence has now accumulated to show that in most intact cells and organs 11βHSD1 catalyses the reverse reaction (figure 1) (5).

It has been hypothesized that tissue-specific dysregulation of cortisol metabolism may be involved in the complex pathophysiology of the metabolic syndrome (MS) and simple obesity. 11βHSD1 is expressed in both adipocyte and preadipocyte (6); based
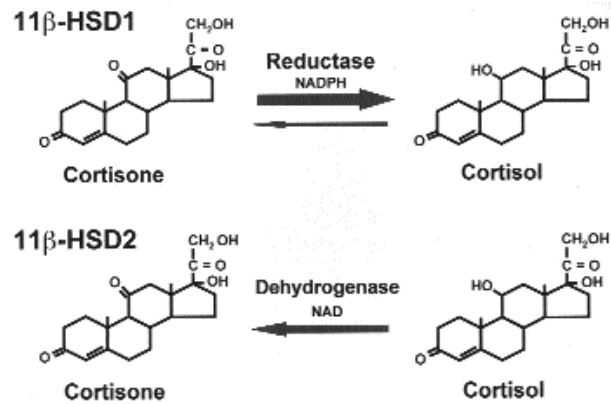

Figure 1. The 11βHSD isoenzymes: **(1)** 11βHSD1 is a NADPH-dependent reductase (that converts inactive cortisone to active cortisol) and a dehydrogenase (that converts cortisol to cortisone), expressed in the liver, adipose, gonadal and central nervous system tissues. 11βHSD1 functions mostly as a reductase in intact cells and organs. **(2)** 11βHSD2 is a NAD-dependent dehydrogenase enzyme that is highly expressed in the kidney and colon.

on the evidence that glucocorticoids induce adipocyte differentiation *in vitro* (7), adipose autocrine generation of F from E may be implicated in the pathogenesis of central obesity and its associated metabolic complications. In support to this hypothesis, transgenic mice overexpressing 11βHSD1 in adipose tissue develop obesity with all the features of the MS (8); conversely, 11βHSD1-knockout mice are protected from obesity and MS (9). Aside some controversies, the bulk of evidences show that 11βHSD1 mRNA and activity are upregulated in human obesity.

CUSHING'S SYNDROME AND METABOLIC SYNDROME: HIGH CIRCULATING LEVELS *VERSUS* HIGH TISSUE CONCENTRATIONS OF GLUCOCORTICOIDS

Cushing's syndrome: Effects of chronic exposure to high concentrations of circulating cortisol

In 1932, Harvey Cushing reported on eight patients with adrenal hyperplasia associated with pituitary basophilic adenomas (10), defining a new clinical entity that now bears his name: "Cushing's disease". His meticulous description gives information about the deleterious effects of cortisol excess. Cushing's syndrome (CS) causes hypertension in more than 90% of the cases, central obesity in more than 80%, osteoporosis in 50% (11), in addition to other typical signs and symptoms (12).

Glucocorticoids have a major role in determining adipose tissue metabolism and distribution. Sub-

jects with endogenous or exogenous Cushing's syndrome develop a central obesity pattern that is reversible upon treatment or glucocorticoid withdrawal. Cortisol augments directly or indirectly the total mass of adipose tissue and redistributes it from peripheral to central depots (13). Glucocorticoids also regulate multiple processes in the adipose tissue. They influence fat cell size, so that enlarged abdominal fat cells are seen in CS (14); promote differentiation of human preadipocytes into mature adipocytes, increasing fat cell number (7); and activate lipolyses, releasing free fatty acids into circulation. Chronically, however, as seen in CS, lipoprotein lipase activity is elevated 2–3 fold with a low lipolytic capacity (14).

Moreover, part of the glucocorticoid actions is regulated at a pre-receptor level by 11β-HSD1. This enzyme is co-localized with the glucocorticoid receptor in several cells, including adipose tissue and liver, where it is ideally positioned to amplify glucocorticoid action. Bujalska et al. (6) cultured omental adipose stromal cells with cortisol and showed an increased activity of 11β-HSD1. This observation led to the speculation that 11β-HSD1 is upregulated in the visceral adipose tissue of subjects with Cushing's syndrome. However, recent data evidence the opposite, as will be discussed below. 11β-HSD1 seems not to be the cause of the metabolic syndrome, but instead a modulator of energy partitioning (15).

Obesity and metabolic syndrome: Increased adipose tissue concentrations of cortisol

Since the original description of "Syndrome X" by Gerald Reaven in 1988 (16), obesity has been associated, to some extent, to abnormalities in the hypothalamus–pituitary–adrenal (HPA) axis. Similarities between Cushing's syndrome and the clinical features of the metabolic syndrome (visceral obesity, hyperglycemia, hypertension, and dyslipidemia) led to the hypothesis that obesity may be associated with glucocorticoid excess in the latter.

Correlations between abdominal fat and hyperactivity of the HPA axis have been found, although there is considerable controversy in the literature. The proposed alterations include resistance to the negative feedback (impaired suppression) exerted by low oral dexamethasone or intravenous doses of glucocorticoids (17-19); elevated diurnal ACTH levels and altered pulsatile secretory ACTH dynamics (20), hyperesponsiveness to different peptides (CRH, AVP) (21), and increased cortisol production rate, as measured by stable isotope ratio (22).
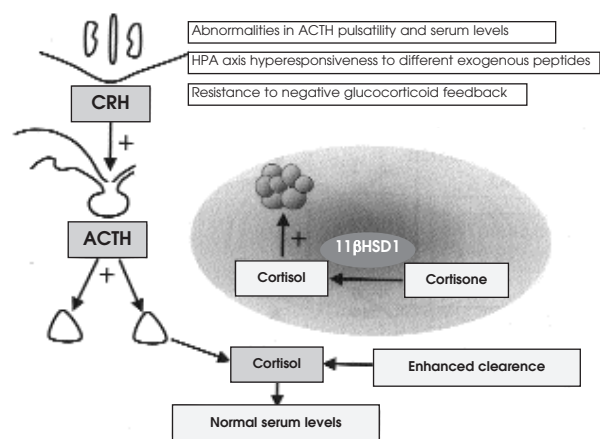

Figure 2. Abnormalities in the central regulatory control and in the peripheral metabolism of cortisol in obesity. Increased hypothalamus–pituitary–adrenal axis (HPA) drive appears to result from elevated peripheral cortisol clearance, the balance of which yields normal plasma levels. Peripherally, mRNA expression and enzymatic activity of 11βHSD1 is increased in the adipose tissue (inset).

The increased HPA axis drive and production of cortisol observed in obese subjects is counterbalanced by enhanced urinary excretion rate of free cortisol and its metabolites and also by its enhanced peripheral clearance (21-23), resulting in normal (or even low) blood levels (figure 2). This has been recently explained by observations that there is a tissue-specific deregulation of cortisol metabolism in human obesity in which 11βHSD1 activity is upregulated in adipose tissue and underegulated in the liver, resulting in lower plasma cortisol levels with a compensatory rise in ACTH and cortisol production (see below).

11β-HSD1 IN OBESITY AND METABOLIC SYNDROME

In vitro studies and animal models

Omental adipose stromal cells treated with cortisol and insulin show increased 11βHSD1 reductase activity (generation of active cortisol from inactive cortisone), suggesting that obesity may reflect a "Cushing's disease of the omentum" (6). These cells in early stage of differentiation show a switch from dehydrogenase (inactivation of cortisol into cortisone) to reductase activity, ensuring autocrine generation of cortisol, which will induce adipocyte differentiation (7). Thus, 11βHSD1 seems to play a key role in adipocyte differentiation and in regulating adipose tissue depots.

Series of studies in animal models of obesity have shown increased 11βHSD1 mRNA expression

and activity in adipose tissue. Transgenic mice overexpressing 11βHSD1 in adipose tissue develop obesity and other features of the metabolic syndrome, presenting with elevated intra-adipose glucocorticoid concentrations and higher glucocorticoid receptor alpha (GRα) expression (24). In contrast, 11βHSD1-knockout mice are protected from obesity and its metabolic complications (9). Overexpression of 11βHSD1 in the liver does not induce obesity or hyperglycemia, although there are changes in serum lipids, insulin sensitivity and blood pressure (25). Besides, 11βHSD1 appears to be involved in the homeostatic adaptation to macronutrient intake; it undergoes downregulation in adipose tissue of high-fat feeding mice (26).

In rodents, pharmacologic inhibition of 11βHSD1 is effective in enhancing hepatic insulin sensitivity and lowering blood glucose in diabetic mice (27) and inducing weight loss in obese mice (28).

Human studies

The bulk of evidences points both to an overexpression and an increased activity of 11βHSD1 in subcutaneous (SAT) and visceral adipose tissue (VAT) of obese subjects, although biopsies of the omentum were conducted in but a few studies. Several groups have shown higher 11βHSD1 mRNA expression in obese compared to non-obese subjects (29-32), although not all studies agree (33). Direct *in vivo* measurements using microdialysis in SAT also suggest an increase in the conversion rate of cortisone to cortisol (34). Moreover, 11βHSD1 mRNA expression positively correlates with obesity (body mass index and abdominal circumference), body composition, insulin resistance (30-32), resistins and other cytokines, as TNFα, IL-6, and leptin (35).

The whole body 11βHSD1 activity reflects mainly hepatic expression. Initial studies that relied on measurements of cortisol-to-cortisone metabolites in urine (23,36) should be taken with caution as indicative of 11βHSD1 activity, because several other cortisol and cortisone metabolizing enzymes are deregulated in obesity (36). Of greater importance is the finding of reduced hepatic 11βHSD1 activity measured by the conversion of orally administered cortisone to cortisol (23,37). Thus, 11βHSD1 upregulation in obesity seems not to be a generalized process. In both the whole body and the splanchnic circulation there are no differences between obese and lean subjects regarding cortisol regeneration rates (as measured by [^{2}H4]-cortisol tracer), presumably because an upregulation in adipose tissue is counterbalanced by a downregulation in the liver (15).

Polymorphisms in the *11βHSD1* gene were identified in an attempt to clarify the basis for the increased activity of adipose tissue 11βHSD1 in obesity. In two populations, polymorphisms were associated with an increased risk of diabetes and hypertension, but not obesity (38,39). A polymorphism was also found that predicts lower 11βHSD1 expression and protection against diabetes (40).

11β-HSD1 IN CUSHING'S SYNDROME

In view of this background, it has been speculated that visceral fat depot in Cushing's syndrome (CS) was due to increased 11βHSD1 activity. However, there is only one published study to date on CS that shows the opposite. Mariniello et al. (41) found no differences in 11βHSD1 mRNA expression between CS patients and normal weight controls, although 11βHSD1 mRNA was 13-fold higher in obese subjects. Recent observations performed by our group (42) are in agreement with Mariniello group's data (41). Our data in patients with CS also establish the absence of correlation between 11βHSD1 mRNA expression in VAT and salivary free cortisol (42). In CS, 11βHSD1 expression may be downregulated by chronic exposure to cortisol levels with a compensatory upregulation of GRα (42).

11βHSD1 is emerging as a key component in homeostatic adaptation, rather than the cause of fatty-acid accumulation in adipose tissue. Recent studies suggest that the enzyme is influenced by the nutritional status (15); accordingly, its lack of increase in CS may suggest a protective mechanism against the metabolic complications. Indeed, when the opposite occurs, e.g., weight loss in simple obesity, 11βHSD1 undergoes upregulation (43), although this is not a universal finding (32). Thus, there are some evidences that 11βHSD1 adjusts local cortisol concentrations independently of its circulating levels.

REGULATION OF 11β-HSD1 EXPRESSION

A number of factors are known to regulate mRNA 11βHSD1 levels and activity. In cultured adipose cells, glucocorticoids, PPARγ agonists, pro-inflammatory citokynes (TNFα, IL1), and leptin, all increase 11βHSD1 expression, whereas GH and thiazolidinediones inhibit it [for review see Tomlinson et al. (44)] (figure 3). However, it should be appreciated that findings in isolated cell cultures and in rodents are not always reproducible in humans. For example, Wake et al. (45) found that rosigli-
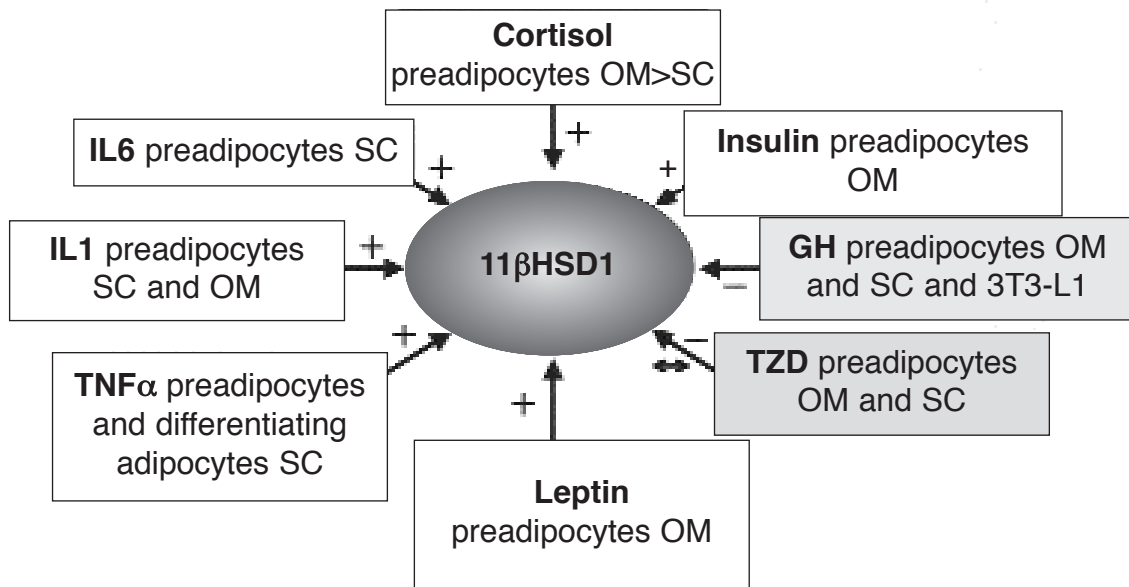
Figure 3. Some of the factors involved in the complex adipose tissue regulation of 11βHSD1 enzyme. [+], [-], [↔]: increase, inhibit, or do not change expression, respectively.
OM: omental adipose tissue, SC: subcutaneous adipose tissue, IL-6: interleukyne 6, IL-1: interleukyne 1, TNFα: tumor necrosis factor-α, TZD: thiazolidinediones, GH: growth hormone.

tazone, a PPARγ agonist, did not change 11βHSD1 mRNA expression and activity in human SAT, at least acutely.

In addition, recent research has begun to address the question of 11βHSD1 regulation in healthy subjects, and suggest that the enzyme is influenced by the nutritional status (15). A single mixed meal induces a rise in whole body rates of regeneration of cortisol by 11βHSD1 (46), an effect that seems mediated by hyperinsulinemia (47).

11β-HSD1 AS A THERAPEUTIC TARGET FOR THE METABOLIC SYNDROME AND DIABETES

Inhibition of 11βHSD1 shows a considerable promise as a therapeutic target to the metabolic syndrome and type 2 diabetes. It offers a key advantage over other strategies for manipulating glucocorticoid action, in that circulating cortisol levels and the response to stress are not impaired. Ideally, it would reduce glucocorticoid action selectively within the metabolically active tissues such as adipose and liver, without blunting the negative feedback regulation at the HPA axis. 11βHSD1 is important for glucocorticoid action also in the brain, in addition to HPA axis regulation (48). To avoid hypothalamic interference by specific

11βHSD1 inhibitors, such drugs must not cross the blood-brain barrier (49).

Pharmacologic inhibition of 11βHSD1 with the anti-ulcer drug carbenoxolone improves insulin sensitivity in healthy human subjects (50) and in patients with type 2 diabetes (51). However, carbenoxolone is neither selective nor very potent and does not appear to inhibit 11βHSD1 in adipose tissue. Aryl-sulphonamidothiazoles were the first 11βHSD1 selective inhibitors to be synthesized; in diabetic mice, they enhance insulin action in the liver, thereby lowering blood glucose concentrations (27).

To date approximately eighteen pharmaceutical companies and other organizations have filled patents for 11βHSD1 inhibitors (15). Results of clinical studies with novel potent inhibitors are therefore eagerly awaited.

CONCLUSION

Several controversies on 11βHSD1 expression and activity in human adipose tissue remain unsolved. However, there are accumulating evidences that intra-adipocyte generation of cortisol contributes for the development of features of the MS and type 2 diabetes. Several groups have shown upregulation of 11βHSD1 in obesity and its correlation with abdominal circumference, BMI, and

insulin resistance. In Cushing's syndrome, 11βHSD1 is downregulated, suggesting that it may adjust local cortisol concentrations independently of its plasma levels. 11βHSD1 seems also to play a role in the complex pathophysiology of the MS and in energy partitioning. Future clinical studies are envisioned to prove the efficacy of selective 11βHSD1 inhibition.

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