Endocrinol Nutr. 2011;**58(4):**153–156

ENDOCRINOLOGÍA Y NUTRICIÓN

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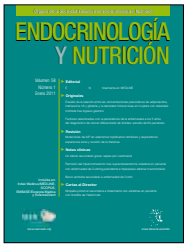

EDITORIAL

The metabolic syndrome as intrahepatocytic Cushing's syndrome

El síndrome metabólico como síndrome de Cushing intrahepatocitario

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The similarity of metabolic syndrome of common (idiopathic) obesity to Cushing's syndrome has led to the hypothesis that there could be some degree of hypercortisolism underlying the concurrence of metabolic changes and arterial hypertension in metabolic syndrome[1]. Indeed, a number of parameters of cortisol metabolism positively correlate to components of metabolic syndrome. Thus, basal plasma cortisol levels correlate to waist circumference, blood pressure, blood glucose, insulin resistance, and triglyceride levels. Free urinary cortisol levels also correlate to waist circumference and triglyceride levels, and inversely to HDL-C levels. In addition, visceral obesity correlates to resistance to suppression with low dexamethasone doses, circadian rhythm changes, and cortisol response to intake. However, the general function of the adrenocortical axis is essentially normal in metabolic syndrome[2]. What then could be the role of this supposed hypercortisolism of metabolic syndrome? Sophisticated studies in dogs[3] and obese humans[4] using a cortisol infusion tetralabeled with deuterium (F-4D) showed that more the 50% of daily cortisol production comes from cortisone being activated by the action of extra-adrenal, basically hepatic, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). 11β-HSDs are two intracellular enzymes that modulate glucocorticoid action at prereceptor-level[5]. 11β-HSD1 reduces cortisone (E) (inactive) to cortisol (F), acting as an intracellular amplifier of glucocorticoid action. By contrast, 11β-HSD2 oxidizes F to E, inactivating it (Fig. 1). Both enzymes are coded by different cloned and well characterized genes. 11β-HSD1 expression is highly ubiquitous[6,7], in keeping with the widespread occurrence of F target cells. Maximum expression occurs in the liver[8], followed by visceral adipose tissue (where expression is approximately ten times lower). A marked expression is also seen in subcutaneous adipose tissue, muscle, and pancreatic beta cells, all of them tissues which are highly related to energy metabolism[9]. 11β-HSD1 reducing activity is fully dependent on the NADPH[10] co-factor, resulting from the action of hexose-6-phosphate dehydrogenase, the enzyme starting the pentose pathway, and co-located with 11β-HSD1 in the inner aspect of the endoplasmic reticulum[11]. 11β-HSD2 expression is maximal in the distal nephron, where it inactivates F to E, protecting the mineralocorticoid receptor from illicit occupation by cortisol[12].

Many experimental[13] and human[2,9] studies have related 11β-HSD1 to metabolic syndrome. 11β-HSD1 knockout mice exhibit a non-obese phenotype resistant to the development of metabolic syndrome. In addition, specific 11β-HSD1 inhibitors improve metabolic syndrome and prevent atherosclerosis. By contrast, selective 11β-HSD1 overexpression in adipose tissue by transgenization results in animals with obesity and metabolic syndrome. On the other hand, selective 11β-HSD1 overexpression in the liver results in a non-obese animal phenotype, but with metabolic syndrome. In addition, trials in humans with specific 11β-HSD1 inhibitors have shown improved glycemic and lipid control in patients with type 2 diabetes mellitus (DM2)[14].

Many studies have been published in the past decade suggesting that 11β-HSD1 expression/activity is dysregulated in obesity and DM2 in different human tissues, such as the

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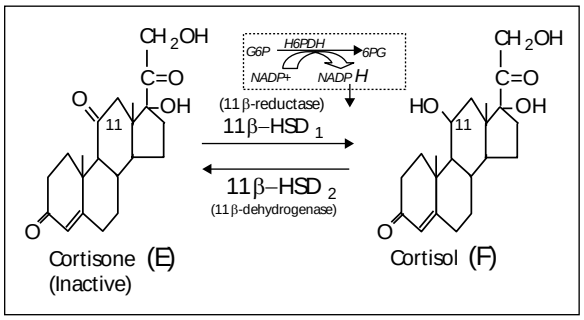

Figure 1 11β-hydroxysteroid dehydrogenases (11b-HSD) as intracellular modulators of glucocorticoid action at pre-receptor level. G6P: glucose-6- phosphate; H6PDH: hexose-6-phosphate dehydrogenase.

liver, visceral and subcutaneous fat, and skeletal muscle. However,the direction of such dysregulation is unclear or inconsistent, and the role of 11β-HSD1 changes in each tissue is ill-defined. There is general agreement that overall 11β-HSD1 activity, mainly reflecting hepatic activity, is reduced in obese as compared to thin people[15-18]. This is also supported by the fact that weight loss increases the activity of this enzyme[19]. However, one study found no change in 11β-HSD1 activity in obese as compared to thin subjects[20]. In obese diabetic patients, overall 11β-HSD1 activity is not reduced, but remains similar to that seen in thin subjects[18]. Little data is available regarding gene expression and the direct activity of 11β-HSD1 in liver tissue in obese as compared to thin subjects and in obese patients with and without metabolic changes. Studies on 11β-HSD1 regulation in fatty, visceral, and subcutaneous tissue show conflicting results. Both increased expression[21,22] and enzyme activity[23] in visceral fat and no differences in gene expression and enzyme activity[24] have been reported in obese subjects. Other studies have reported an *in vitro* increase in 11β-HSD1 mRNA in visceral adipocytes from diabetic patients[25], but no differences in the amount of mRNA in visceral fatty tissue between morbid obese subjects with and without metabolic syndrome[26]. Conflicting data have also been reported for subcutaneous fatty tissue in obese subjects, including increased[27-30] and unchanged[20,24] mRNA, and increased[20,30,31] and unchanged[24] enzyme activity. Other studies reported that weight loss in obese subjects increased 11β-HSD1 mRNA expression in adipocytes isolated from subcutaneous fat[19]. In obese DM2 patients, increased mRNA in subcutaneous fat was reported as compared to their non-diabetic counterparts. Increased mRNA[32,33] and enzyme activity[32] levels were also found in subcutaneous fat in obese patients with carbohydrate intolerance and insulin resistance. In addition, a greater *in vitro* 11β-HSD1 expression was found in myotubes from type 2 diabetics as compared to controls with mild obesity[34]. These differences in the results of the various studies, particularly as regards expression in adipose tissue, may be due to the heterogeneity of the populations and models studied: sex, age, types of tissue, tissue or global enzyme activity and *in vitro* or *in vivo* gene expression.

A recent study reported as a poster found that morbid obese subjects with metabolic syndrome had a greater liver expression of 11β-HSD1 and the glucocorticoid receptor than those with no metabolic syndrome[35]. Moreover, such overexpression positively correlated to the number of components of metabolic syndrome found and was absent from fatty tissue. Hepatocytes contain the full repertoire of gene expression, related not only to cortisol regeneration, but also to the glucocorticoid receptor and the target genes of its action, such as the key neoglucogenesis genes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6Pase) (Fig. 2). The results of studies in dogs showing that oral administration of a specific 11β-HSD1 inhibitor represses hepatic expression of PEPCK and G-6Pase[36] support the causative link between 11β-HSD1 and hepatic neoglucogenesis. Moreover, very recent work by Rosenstock et al has shown that the addition of a specific 11β-HSD1 inhibitor to DM2 patients with poor glycemic control on metformin monotherapy has a summatory hypoglycemic effect[14], which suggests that 11β-HSD1 could be involved in the pathogenesis of hyperglycemia in DM2. Overall, this evidence supports the hypothesis of Iwasaki et al[37] that metabolic syndrome could be an "intracellular Cushing state"[37]. This concept is based on regulation studies in a human hepatoma cell line stably transfected with the 11β-HSD1 promoter. Preliminary data showing a greater hepatic expression in obese patients with metabolic syndrome speak in favor of the concept of metabolic syndrome as intrahepatic hypercortisolism.

Increased cortisol production in the liver by obese patients with metabolic syndrome is not associated with systemic hypercortisolism because both sources (adrenal and hepatic) of circulating cortisol are in a dynamic equilibrium, and increased liver production is compensated for by an increased cortisol catabolism in the liver and a decreased activity of the adrenocortical axis, as shown by the dose-dependent increase in ACTH in response to treatment with specific 11β-HSD inhibitors[14].

To sum up, downregulation of 11β-HSD1, mainly in the liver, in obesity could act as a mechanism protecting against the occurrence of 11β-HSD1-associated metabolic changes. The absence of this compensatory mechanism could create a relative local hypercortisolism state –intracellular Cushing- that could promote the occurrence of metabolic changes

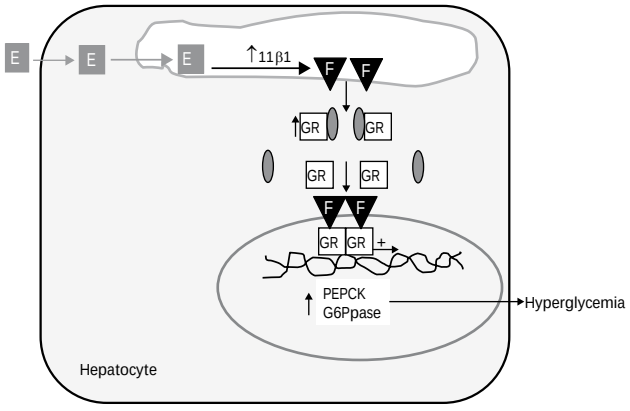

Figure 2 Intrahepatocytic Cushing scenario in metabolic syndrome. E: cortisone; F: cortisol; 11β-HSD1: 11β-hydroxy-steroid dehydrogenase 1; GR: glucocorticoid receptor; PEPCK: phosphoenolpyruvate carboxykinase; G-6Pase: glucose-6-phosphatase.

associated with obesity. In addition, 11β-HSD1 is a potential target for drug treatment of metabolic syndrome.

Acknowledgement

Authors thank Fundación Mutua Madrileña and Sociedad Madrileña de Endocrinología, Nutrición y Diabetes for their financial support.

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