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11β-Hydroxysteroid Dehydrogenase Type 1 and the Metabolic Syndrome

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1. Introduction

In the past few years, efforts are being made to unravel the mechanisms endowed with the metabolic disturbances associated with obesity that predispose to the metabolic syndrome (MetSyn). The special pathogenic role of liver and visceral adipose tissue (VAT) functions has been particularly intriguing, and many hypotheses have been advanced to explain this association. Tissue-specific actions of glucocorticoids (GCs) go far beyond the circulating levels of the hormones and can be controlled by local intracellular enzymes. In the past few years, evidence is being gathered not only on the relevance of such enzymes to GC physiological actions but also on their involvement in the pathophysiology of certain chronic disease states, in which circulating GC levels are not necessarily altered. These enzymes are 11β-hydroxysteroid dehydrogenases (11β-HSDs, EC 1.1.1.146) which interconvert inactive GCs, such as cortisone and dehydrocorticosterone, and the active hormones, cortisol and corticosterone.

2. Brief overview of the hypothalamus-pituitary-adrenal (HPA) axis

The regulation of tissue GC levels is critical for the maintenance of homeostasis, playing a central role in essential physiological processes, such as stress responses, energy metabolism, electrolyte levels, blood pressure, immunity, cell proliferation and differentiation and cognitive functions (Atanasov & Odermatt, 2007). Cortisol release by the adrenal gland is under the control of the HPA axis. Briefly, corticotrophin releasing hormone (CRH) is produced by parvicellular hypothalamic neurons and acts on anterior pituitary cells increasing the production and release of adenocorticotrophic hormone (ACTH) into the blood stream in a pulsatile fashion and with circadian rhythm: peak in the morning and valley later in the afternoon (Gathercole & Stewart, 2010; White B., 2008b). Cortisol is synthesized in the cells of the zona fasciculata of the adrenal cortex. Under the influence of ACTH, cholesterol esters, stored in the foamy cytoplasm of these cells, are unsterified by cholesterol ester hydrolase and converted to cortisol (Tomlinson et al., 2004; White B., 2008a). GCs are able to bind and activate GC receptors (GR) and mineralocorticoid receptors (MR), which are ligand-regulated nuclear receptors and members of the steroid hormone receptor family (Gathercole & Stewart, 2010). Cortisol and the principal GC in rodents, corticosterone, are active steroids whereas cortisone and 11-dehydrocorticosterone, the latter in rodents, are inactive (Tomlinson et al., 2004). Cortisol is metabolized in the liver

through conjugation with glucuronide and sulfate for posterior renal excretion (Tomlinson et al., 2004; White B., 2008a). Moreover, in the liver, 5α- and 5β-reductases inactivate cortisol and cortisone, in conjunction with 3α-HSD, to tetrahydrometabolites: 5α-tetrahydrocortisol (5α-THF), 5β-tetrahydrocortisol (5β-THF) and tetrahydrocortisone (THE) (Campino et al., 2010).

3. 11β-HSDs – enzymology, tissue expression and physiological role

3.1 11β-HSD type 2 (11β-HSD2)

Because cortisol and aldosterone have the same *in vitro* affinity for the MR (Gathercole & Stewart, 2010), 11β-HSD2, that catalyzes the inactivation of cortisol to inert cortisone, in humans, or of corticosterone to 11-dehydrocorticosterone, in rodents, avoids MR actions of GCs. 11β-HSD2 was the first isoform to be identified and is a NAD^+ dependent dehydrogenase. 11β-HSD2 is present in high amounts in the distal convoluted tubule of the kidney, colon, salivary and sweat glands as well as in other locations such as the human placenta and vascular wall to avoid deleterious actions of active GC overstimulation (Anagnostis et al., 2009; Andrews et al., 2003; Edwards et al., 1988; Ferrari, 2010; Funder et al., 1988; Gathercole & Stewart, 2010; Palermo et al., 2004). The importance of 11β-HSD2 activity is illustrated in the case of congenital deficiency of 11β-HSD2 in humans (Gathercole & Stewart, 2010; Stewart et al. 1996), transgenic deletion in mice (Kotelevtsev et al., 1999) or by its pharmacological inhibition which produces the apparent mineralocorticoid excess (AME) syndrome in which the lack of cortisol inactivation in the kidney allows its mineralocorticoid action, producing sodium retention, hypertension and hypokalemia, despite normal circulating levels of cortisol and an intact HPA axis (Anagnostis et al., 2009; Andrews et al., 2003; Edwards et al., 1988; Gathercole & Stewart, 2010; Monder et al., 1986; Mune et al., 1995; Palermo et al., 2004; Quinkler & Stewart, 2003; Stewart et al., 1996; Walker & Andrew, 2006). Thus AME has been considered 'Cushing's disease of the kidney' where there are normal circulating levels of cortisol but a tissue-specific excess at the site of MR action (Stewart, 2005).

3.2 11β-HSD type 1 (11β-HSD1)

Pre-receptor metabolism of GCs by 11β-HSD1 amplifies intracellular levels of GCs, through the reduction of inactive cortisone in humans (11-dehydrocorticosterone in rodents) back into active cortisol (corticosterone in rodents) (Anagnostis et al., 2009; Espindola-Antunes & Kater, 2007). 11β-HSD1 is mostly expressed in the liver, adipose tissue (AT), bone, lung and central nervous system. However, its expression can be present in other tissues including pancreas, kidney cortex, adrenal cortex, cardiac myocytes, bone, placenta, uterus, testis, oocytes and luteinized glanulosa cells of the ovary, eye, pituitary, fibroblasts and immune, skeletal and smooth muscle cells (Anagnostis et al., 2009; Bujalska et al., 1997; Cooper & Stewart, 2009; Espindola-Antunes & Kater, 2007; Stewart & Krozowski, 1999; Tomlinson et al., 2004; Whorwood et al. 2001). This enzyme is located in the endoplasmic reticulum, facing the lumen (Gathercole & Stewart, 2010), where there is a high concentration of NADPH owing to the activity of hexose-6-phosphate dehydrogenase (H6PDH), that regenerates NADPH from $NADP^+$ (Atanasov et al., 2008; Bujalska et al., 2005; Draper et al., 2003).

11β-HSD1 is bidirectional, able to act as both a reductase (activating GCs) and a dehydrogenase (inactivating GCs) (Cooper & Stewart, 2009; Tomlinson et al., 2004). However, its main function is as a reductase on intact cells such as hepatocytes (Jamieson et

al., 1995), myocytes (Whorwood et al., 2001) and adipocytes (Bujalska et al., 2002a; Bujalska et al., 2002b), supported by a higher affinity for cortisone than cortisol (Stewart et al., 1994). *In vitro*, when deprived of NADPH regeneration (Seckl & Walker, 2001; Walker & Andrew, 2006) or in certain physiological or developmental states, it may work as a dehydrogenase. For example, in human omental adipose stromal cells, 11β-HSD1 switches from a dehydrogenase to a reductase upon differentiation (Bujalska et al., 2002a; Bujalska et al., 2002b). In the H6PDH null mouse, hepatic or AT, 11β-HSD1 acts mainly as a dehydrogenase (Bujalska et al., 2008b; Lavery et al., 2006). Most studies on the regulation of 11β-HSD1 have been performed on rodent tissues showing that GCs, CCAAT/enhancer binding proteins, peroxisome proliferator-activated receptor (PPAR) agonists and some pro-inflammatory cytokines [tumor necrosis factor-α (TNF-α) and interleukin-1β] increase 11β-HSD1 expression. On the other hand, growth hormone (via insulin-like growth factor-1) and liver X receptor (LXR) agonists inhibit its expression. Some other factors that may influence 11β-HSD1 expression include sex steroids, insulin and thyroid hormone, but effects vary in different tissues and between species (Tomlinson et al., 2004).

Human 11β-HSD1 congenital deficiency has been described as the apparent cortisone reductase deficiency syndrome (Phillipov et al., 1996). The phenotype is related to the lack of regeneration of cortisol in peripheral tissues with compensatory activation of the HPA axis. This results in increased secretion of androgens by the adrenals, and affected females present hirsutism and oligomenorrhea. 11β-HSD1 congenital deficiency does not appear to protect against obesity. The syndrome does not seem to arise only from mutations of HSD11B1, but rather from the co-inheritance of deleterious mutations in both HSD11B1 and H6PDH (Draper et al., 2003), decreasing NADPH supply and switching 11β-HSD1 to the dehydrogenase activity (Lavery et al., 2006).

4. Chronic GC deficiency or excess

The involvement of GCs in human obesity, particularly visceral obesity, and its related metabolic complications, is becoming increasingly evident. As we will discuss further, this is evident not only in subjects with disturbances in the HPA axis, but also in conditions where tissue GCs are locally modified. To illustrate the first case, two conditions reflect the involvement of circulating cortisol on body weight regulation in opposite extremes: Addison's disease (hypocortisolism) and Cushing's syndrome (hypercortisolism) (Rutters et al., 2010). As to the second case, the clinical entity that aggregates visceral obesity along with several metabolic abnormalities in glucose and lipid metabolism as well as in blood pressure, and known as the MetSyn (Reaven, 2011), may constitute the best example. Chronically elevated GC levels cause obesity, type 2 diabetes mellitus (T2DM), heart disease, mood disorders and memory impairments (Wamil & Seckl, 2007). This is demonstrated in Cushing's syndrome, in which elevated GC levels are a result of increased pathological secretion from the adrenal cortex (endogenous) or from prolonged anti-inflammatory GC treatment (iatrogenic) (Newell-Price et al., 2006). A particular case of Cushing's syndrome is Cushing´s disease that consists of hypercortisolism driven by increased ACTH secretion from pituitary adenoma (Cushing, 1932; Stewart, 2005). Patients with Cushing's syndrome are hypertensive, have visceral obesity, insulin resistance (IR; 50% develop T2DM or impaired glucose tolerance) and may present hepatic steatosis (Stewart, 2005), muscle weakness, dyslipidemia, mood disturbances and infertility as well as features more specific to Cushing's syndrome (e.g. easy bruising, facial plethora and violaceous striae) (Carroll & Findling, 2010; Newell-Price et al., 2006).

The increase of AT in states of GC excess, such as Cushing's syndrome, may not seem straightforward. Indeed, one might predict from cortisol metabolic actions that it would increase the availability of energetic substrates, as is seen with its lipolysis-stimulating effects. However, in these settings, particularly if there is positive energy balance, the chronic increase in GCs is concomitant with the increase in insulin (Dallman et al., 2004). This favors fatty acid re-esterification over lipolysis, which, along with pro-adipogenic effects of insulin and GCs (Rosen & MacDougald, 2006), increases AT depots. This is seen particularly on VAT depots, rather than other AT locations, probably for two reasons: higher expression of GR (Bronnegard et al., 1990) and increased reactivation of circulating cortisone due to high 11β-HSD1 expression and/or activity (Alberti et al., 2007; Simonyte et al., 2009).
Diagnostic features of GC excess in Cushing's syndrome overlap many of the MetSyn components suggesting that GCs may contribute to the pathogenesis of both states (Anagnostis et al., 2009; M. Wang, 2011). It has been demonstrated that circulating cortisol concentrations are higher in patients with MetSyn compared with healthy subjects, both in basal conditions and during dynamic stimulation (Duclos et al., 2005; Misra et al., 2008; Phillips et al., 1998; Sen et al., 2008; Weigensberg et al., 2008). Furthermore, increased 11β-HSD1 activity in VAT may generate increased cortisol levels within AT and liver and thereby promote features of the MetSyn (Walker & Andrew, 2006). This effect has been termed 'Cushing's disease of the omentum' (Bujalska et al., 1997; Stewart, 2005).

5. MetSyn definition

In the past few decades, there has been a worldwide increase in the prevalence of obesity and associated metabolic disorders including glucose intolerance, IR, dyslipidemia and hypertension. In the clinical practice, the presence of these conditions defines the MetSyn, which comprises an increased risk of atherosclerotic cardiovascular events and T2DM (or is associated with T2DM) and, additionally, is characterized by a pro-inflammatory and a pro-thrombotic state and occurrence of non-alcoholic fatty liver disease (NAFLD) (Feldeisen & Tucker, 2007; Gathercole & Stewart, 2010; Johnson & Weinstock, 2006; Reaven, 2011).
Distinct organizations have established their own definitions of the MetSyn: the World Health Organization (WHO), in 1998, the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), in 2001 (updated in 2005), and the International Diabetes Federation (IDF), in 2005 (Johnson & Weinstock, 2006; Reaven, 2011). In the attempt to harmonize MetSyn definitions, ATP III and IDF, joined by several other prestigious organizations, reviewed the criteria. Meeting any three of the following criteria is sufficient for the diagnosis: elevated waist circumference (abdominal obesity), triglycerides, blood pressure and fasting glucose (glucose intolerance) and low HDL-cholesterol levels. The cut points for an elevated waist circumference are not the same for all population groups (with population-specific reference values) and drug treatment is sufficient to meet the criteria for the other four components. The latest WHO report states that the 'MetSyn should not be a clinical diagnosis', but rather viewed as 'a pre-morbid condition, and should thus exclude individuals with established T2DM or cardiovascular disease' (Reaven, 2011).

6. 11β-HSD1 and MetSyn components: evidence from human and animal studies

Evidence has been accumulated that strongly argues for an etiological role of 11β-HSD1 in obesity, T2DM and MetSyn (Cooper & Stewart, 2009; Gathercole & Stewart, 2010; London &

Castonguay, 2009; Masuzaki & Flier, 2003; Morton, 2010; Staab & Maser, 2010; Tomlinson & Stewart, 2007; van Raalte et al., 2009; Wamil & Seckl, 2007).

Initial studies in obese humans, that measured the ratio of cortisol to cortisone metabolites in urine as an indirect index of total body 11β-HSD activity, produced inconsistent results (such ratios, however, are inadequate as they may be influenced by other enzymes involved in cortisol metabolism). Recently, more trustworthy results from various more tissue-specific measures were obtained (Andrews et al., 2002; Andrews et al., 2003; Desbriere et al., 2006; Gathercole & Stewart, 2010; Karlsson et al., 2010; Morton, 2010; Paulmyer-Lacroix et al., 2002; Rask et al., 2001; Rask et al., 2002; Sandeep et al., 2005; Stewart & Tomlinson, 2009; R. Stimson et al., 2011; Tomlinson et al., 2008; Valsamakis et al., 2004; Wamil & Seckl, 2007). After studies in men and women, representing a wide range of body compositions and insulin sensitivities (but without T2DM), 11β-HSD1 activity is found selectively increased in the abdominal subcutaneous AT (SAT) in obese humans (Rask et al., 2001; Rask et al., 2002; Sandeep et al., 2005), to a similar degree as the increase in transgenic overexpressing mice (Andrews et al., 2003), but impaired in the liver (Rask et al., 2001; Rask et al., 2002; Stewart et al., 1999). This decrease in hepatic tissue may represent a compensatory mechanism to preserve insulin sensitivity and to decrease hepatic glucose output (Gathercole & Stewart, 2010; Morton, 2010; Valsamakis et al., 2004; Wamil & Seckl, 2007). Increased adipose 11β-HSD1 activity results from increased 11β-HSD1 mRNA expression (Desbriere et al., 2006; Paulmyer-Lacroix et al., 2002) in the abdominal SAT in adipocytes, and also in the VAT in both adipocytes and stroma (Paulmyer-Lacroix et al., 2002). Valsamakis et al. report a lack of inhibition of 11β-HSD1 activity with increasing body mass index (BMI) in diabetic patients *versus* non-diabetic BMI- and age-matched controls (where the inhibition is closely associated with VAT mass), and suggest that a reduction in 11β-HSD1 activity might act as an autocrine protective mechanism to prevent increasing adiposity and increased hepatic glucose output with advancing obesity. This adaptive mechanism of reduced cortisol regeneration does not occur in obesity-associated T2DM and might contribute to the underlying pathogenesis of the disease (Gathercole & Stewart, 2010; Morton, 2010; Valsamakis et al., 2004; Wamil & Seckl, 2007). In contrast, in lean patients with T2DM (controlled by diet alone) a relatively small decrease in hepatic 11β-HSD1 activity, and no change in gluteal SAT enzyme activity, has been reported, but only by one group (Andrews et al., 2002; Andrews et al., 2003). Abdominal SAT 11β-HSD1 expression is higher in obese women with impaired glucose tolerance than in obese women with normal glucose tolerance, despite AT (total and regional) being similar between the two groups, and positively correlated with glucose area under curve levels across an oral glucose tolerance testing (Tomlinson et al., 2008). Whole-body 11β-HSD1 activity is increased in obese men with T2DM, compared to healthy normal-weight control subjects, whereas liver 11β-HSD1 activity is sustained, unlike in euglycemic obesity (R. Stimson et al., 2011). The evidences presented raise the hypothesis that hepatic 11β-HSD1 inhibition in obese people who develop impaired glucose tolerance may protect from progression to T2DM (Gathercole & Stewart, 2010; Morton, 2010; Wamil & Seckl, 2007). Additionally, in line with this, myotubes established from obese T2DM subjects show an increased expression of 11β-HSD1 mRNA compared to healthy obese subjects (Abdallah et al., 2005). SAT 11β-HSD1 mRNA levels decrease during very low calorie diet (16 weeks) and anthropometric measurements and metabolic parameters are associated with 11β-HSD1 mRNA levels in obese subjects without the MetSyn (following the WHO definition). However, in obese subjects with the MetSyn these associations were lost or in the opposite direction. In another cohort, this difference is also observed in skeletal muscle (vastus lateralis) between subjects with T2DM or with normal glucose tolerance (Karlsson et al., 2010).

6.1. Findings of 11β-HSD1 biology from rodent models

6.1.1 The aP2-HSD11B1 transgenic rodent model

Transgenic mice with 2–3-fold overexpression of 11β-HSD1, comparable to that seen in obese humans, in white AT have been generated, exploiting the murine adipocyte fatty acid binding protein (aP2) promoter. These aP2-HSD11B1 transgenic mice have elevated corticosterone levels in the AT, but unaltered systemic plasma concentrations, and many features of the MetSyn: glucose intolerance and IR [exacerbated further by high-fat (HF) feeding], dyslipidemia, apparent leptin resistance, truncal obesity and hypertension associated with activation of the circulating renin-angiotensin system. 11β-HSD1 expression correlates strongly and positively with adipocyte size (London & Castonguay, 2009; Masuzaki & Flier, 2003; Masuzaki et al., 2001; Masuzaki et al., 2003; Morton, 2010; Staab & Maser, 2010; van Raalte et al., 2009; Wamil & Seckl, 2007). TNF-α and leptin are elevated whereas resistin and insulin-sensitizing adiponectin are reduced. aP2-HSD11B1 transgenic mice are hyperphagic and obese, predominantly in the VAT. Expression of the GR-α is higher in VAT compared to SAT, while the expression of the transgene HSD11B1 is similar in all AT depots. The greater effects in VAT may reflect the higher GR and/or higher lipoprotein lipase in mesenteric AT. aP2-HSD11B1 transgenic mice have elevated corticosterone and free fatty acids (FFA) levels in the hepatic portal vein that drains blood from VAT to the liver (Masuzaki et al., 2001; Masuzaki et al., 2003; Morton, 2010; Wamil & Seckl, 2007). The aP2-HSD11B1 model shows that altered AT metabolism of GCs (similar to human MetSyn levels) could be the primary driver of many features of this disease (Masuzaki & Flier, 2003; Masuzaki et al., 2001; Masuzaki et al., 2003; Morton, 2010).

6.1.2 The apolipoprotein E (apoE)-HSD11B1 transgenic rodent model

To examine the impact of elevated liver GCs, mice overexpressing 11β-HSD1 selectively in that tissue under the control of the human apoE promoter have been generated. Transgenic lines with 2- and 5-fold-elevated 11β-HSD1 activity exhibit unaltered systemic corticosterone, modest IR (but lacking glucose intolerance), unaltered AT mass (lacking obesity or central adiposity), hepatic fat accumulation (mainly as triglycerides) and dyslipidemia (elevated circulating FFA and HF diet-induced dyslipidemic cholesterol lipoprotein profile), with increased hepatic lipid synthesis/flux associated with elevated hepatic LXR-α and PPAR-α expression as well as impaired hepatic lipid clearance. Increased expression of GC-inducible cholesterol 7α-hydroxylase present in apoE-HSD11B1 transgenic livers may drive increased bile acid synthesis, contributing to stimulation of LXR-α-regulated pathways (and further potentiation of cholesterol 7α-hydroxylase expression) as well as PPAR-α. ApoE-HSD11B1 transgenic mice also have a marked, transgene-dose-associated hypertension, paralleled by incrementally increased liver angiotensinogen expression. Elevated 11β-HSD1 hepatic expression may relate to the pathogenesis of specific fatty liver, insulin-resistant and hypertensive syndromes without obesity in humans as may occur in, possibly, the metabolically obese normal-weight individual (Paterson et al., 2004).

6.1.3 The HSD11B1 knockout (KO) rodent model

HSD11B1 KO mice have been generated, which are viable and healthy but unable to convert inert 11-dehydrocorticosterone to corticosterone. Despite compensatory adrenal hyperplasia and increased adrenal secretion of corticosterone, on fasting, HSD11B1 KO mice have attenuated activation of the hepatic gluconeogenic enzymes, presumably, because of relative

intra-hepatic GC deficiency. The HSD11B1 KO mice resist hyperglycemia provoked by obesity or stress (Kotelevtsev et al., 1997). HSD11B1 KO mice, fed *ad lib*, have markedly lower plasma triglyceride levels, driven by increased hepatic expression of enzymes of fat catabolism and PPAR-α. HSD11B1 KO mice also have increased plasma HDL-cholesterol, with elevated liver mRNA and serum levels of apoAI. Conversely, hepatic Aα-fibrinogen expression is decreased. Upon fasting, the normal elevation of hepatic PPAR-α mRNA is lost in HSD11B1 KO mice, consistent with attenuated GC induction. Despite this, crucial oxidative responses to fasting are maintained. Refeeding (4 h and/or 24 h) shows more rapid and/or marked induction of genes encoding lipogenic enzymes/transcription factors and a more rapid and/or marked suppression of genes for fat catabolism in HSD11B1 KO mice, implying increased liver insulin sensitivity. PPAR-α is suppressed by 4 h of refeeding (similarly in wild type and HSD11B1 KO mice), but PPAR-α levels are higher after 24 h of refeeding in HSD11B1 KO mice when compared to wild type mice, reestablishing the *ad lib*-fed pattern. Concordant with this, 24 h refed HSD11B1 KO mice have higher plasma triglycerides than 24 h refed wild type mice and *ad lib*-fed HSD11B1 KO mice. 24 h Refed HSD11B1 KO mice have lower plasma glucose levels than 24 h refed wild type mice and *ad lib*-fed HSD11B1 KO mice. HSD11B1 KO mice also have improved glucose tolerance. 11β-HSD1 deficiency may produce an improved lipid profile, hepatic insulin sensitization and a potentially atheroprotective phenotype (Morton et al., 2001). HSD11B1 KO mice on the control diet express, compared to wild-type mice, lower leptin, resistin and TNF-α but higher PPAR-γ, adiponectin and uncoupling protein-2 (UCP-2) mRNA levels in epididymal AT, indicating insulin sensitization. On the control diet, in mesenteric VAT, PPAR-γ mRNA is elevated in HSD11B1 KO mice, though leptin, resistin, TNF-α, adiponectin and UCP-2 mRNA levels are unaltered, compared to wild-type mice. With HF feeding, the elevated PPAR-γ mRNA level in control-fed HSD11B1 KO mice is further increased selectively in VAT, what does not happen in the epididymal AT depot of HSD11B1 KO or wild-type mice. HSD11B1 KO mice also show a HF–mediated induction of UCP-2 selectively in VAT, which is greater than that observed in wild-type mice. Isolated adipocytes from HSD11B1 KO mice exhibit higher basal and insulin-stimulated glucose uptake. HSD11B1 KO mice also display reduced VAT accumulation upon HF feeding. HF-fed HSD11B1 KO mice rederived onto the C57BL/6J strain (obesity/T2DM/metabolic disease-susceptible) resist T2DM and weight gain despite consuming more calories. These data provided the first *in vivo* evidence that AT 11β-HSD1 deficiency beneficially alters AT distribution and function (Morton et al., 2004), complementing the just above-described effects of hepatic 11β-HSD1 deficiency or data presented further bellow regarding 11β-HSD1 pharmacological inhibition. Since PPAR-γ ligands cause insulin sensitization and AT redistribution to the periphery, a mechanism for the beneficial AT redistribution is suggested, on the assumption that increased circulating FFA during HF feeding act as endogenous ligands for PPAR-γ receptors. Further, UCP-2 levels are higher in HSD11B1 KO mice AT, consistent with GC and PPAR-γ regulation. This higher PPAR-γ-responsive UCP-2 expression in HSD11B1 KO mice AT may drive increased energy dissipation within the adipocytes (Morton, 2010). Interestingly, when mice are fed a HF diet they preferentially gain weight in peripheral AT rather than in VAT what can be explained by an increased expression of PPAR-γ and UCP-2 in VAT (Morton, 2010; van Raalte et al., 2009; Wamil & Seckl, 2007).

Mice overexpressing the cortisol inactivating enzyme specifically on the AT (aP2-HSD11B2 mice) are phenotypically similar to HSD11B1 KO mice, exception only for food intake, what

emphasizes the importance of AT as a target for enzyme inhibition (Wamil & Seckl, 2007). 11β-HSD1 gene deficiency is associated with a number of improvements of adipose and hepatic functions, what highlights the importance of adipose and hepatic 11β-HSD1 in the development of metabolic disease.

6.2 11β-HSD1 and T2DM/IR

A role for 11β-HSD1 in exacerbating IR and T2DM has been proposed. Animals with targeted deletion of HSD11B1 manifest increased hepatic and adipose insulin sensitivity (Kotelevtsev et al., 1997; Morton et al., 2001; Morton et al., 2004), and when backcrossed onto the C57BL/6J strain appear to resist the development of IR in response to HF feeding (Morton et al., 2004). Additionally, specific 11β-HSD1 inhibitors improve insulin sensitivity (glycemic control and/or glucose and/or insulin levels) in animal models (associated or not with HF feeding) of hyperglycemia, obesity (by damage of feeding center or diet-induced), T2DM (also ob/ob) and combined T2DM, dyslipidemia and atherosclerosis (Alberts et al., 2002; Alberts et al., 2003; Barf et al., 2002; Gathercole & Stewart, 2010; Hermanowski-Vosatka et al., 2005; Morgan et al., 2009; Park et al., 2011; X. Zhang et al., 2009b).

It is well known that excess GCs increase IR and can, in susceptible individuals, precipitate T2DM. In line with this, it has been suggested that the increased production of cortisol from VAT seen in obesity could drain through the portal circulation to the liver and pancreas contributing to IR (Cooper & Stewart, 2009; Masuzaki et al., 2001; Morton, 2010; R. Stimson et al., 2009; Walker & Andrew, 2006; Wamil & Seckl, 2007). This hypothesis was investigated *in vivo* in humans by Stimson et al. by quantifying, for the first time, selectively, the contributions of SAT, visceral tissues and liver to whole-body cortisol production by 11β-HSD1. Stimson et al. confirmed that splanchnic cortisol production is substantial, originating entirely from the 11β-HSD1 activity in the liver. However, although release of cortisol by 11β-HSD1 into the portal vein, which drains a number of visceral organs, is not detected, a significant cortisol release into veins draining exclusively SAT has been found. So, cortisol release from SAT into the systemic circulation is unlikely to have effects in other organs because the feedback control by the HPA axis will adjust adrenal cortisol secretion to maintain circulating cortisol concentrations. Therefore, the most likely impact of this source of cortisol will be intracrine or paracrine in the local AT environment (R. Stimson et al., 2009).

Skeletal muscle represents a key target tissue for insulin-stimulated glucose uptake, metabolism and utilization (Abdul-Ghani & DeFronzo, 2010; Benito, 2011; Van Cromphaut, 2009). There are just a few studies regarding 11β-HSD1 in skeletal muscle from T2DM, although with non-consensual results (Cooper & Stewart, 2009). Whorwood et al. found, with kinetic analysis, that 11β-HSD1, in intact cultured human skeletal myoblasts (from both lean-moderately overweight and obese adult men, few with T2DM but without therapy), acts exclusively as a reductase and is down-regulated by insulin, which may maintain insulin sensitivity in skeletal muscle tissue by diminishing GC antagonism of insulin action (Whorwood et al., 2001). Cortisone reduces glucose uptake in myotubes established from obese T2DM men (treated either by diet alone or in combination with sulfonylurea or metformin, withdrawn one week before performing the biopsy), what could be mediated by an increased mRNA 11β-HSD1 expression (previously mentioned) emphasizing that the local conversion of inactive to active GCs may be important in IR pathogenesis (Abdallah et al., 2005). Accordingly, Zhang et al., in an animal model of T2DM (Wistar rats with HF feeding, combined with multiple low dose streptozotocin injection), report increased 11β-

HSD1 mRNA and protein levels in skeletal muscle extracts of the diabetic animals *versus* the non-diabetic animals, what may be related to disturbances in insulin signaling pathway observed in the skeletal muscle (M. Zhang et al., 2009a). Jang et al. demonstrated that the activities of skeletal muscle 11β-HSD1 and 11β-HSD2 (in vastus lateralis biopsies) are altered in T2DM patients (treated by diet alone or oral hypoglycemic agents) *versus* healthy age- and sex-matched controls (altogether overweight and obese subjects): 11β-HSD1 activity is reduced and 11β-HSD2 activity is higher in T2DM subjects (negative correlation between both enzyme activities; with similar mRNA levels in T2DM and control subjects for both enzymes), and, more importantly, 11β-HSD1 reductase activity is significantly lower in T2DM subjects whereas 11β-HSD1 dehydrogenase activity is significantly higher in the T2DM group (with very low levels of 11β-HSD1 dehydrogenase activity in both groups). Together these results may indicate a reduced intracellular cortisol generation, potentially conferring metabolic protection (Jang et al., 2007). In what regards the AT, Balachandran et al. demonstrated that insulin stimulates adipocyte 11β-HSD1 activity and expression both *in vitro* (in 3T3-L1 adipocytes) and *in vivo* (Wistar rat white AT) (Balachandran et al., 2008).
Morgan et al. established a strong connection between a key player in insulin signaling, the insulin receptor substrate 1 (IRS1), and 11β-HSD1 in skeletal muscle: in KK/Ta Jcl mice (an hyperglycemic model) treated with A2, inducing selective 11β-HSD1 inhibition, skeletal muscle pSer^{307}IRS1 decreases, pThr^{308}Akt/PKB increases and lipogenic and lipolytic gene expression decreases (Morgan et al., 2009). 11β-HSD1 has also been proposed to have effects on insulin secretion itself. Davani et al. report 11β-HSD1 mRNA expression in human and ob/ob mice (non-insulin-dependent diabetes model) pancreatic β-cells, and also characterize the 11β-HSD1 activity in intact pancreatic rodent islets (where the reductive reaction prevails). In ob/ob mice islets, in the absence of carbenoxolone, 11-dehydrocorticosterone markedly inhibits insulin release, whereas a reversal of this effect is noted in the presence of carbenoxolone, indicating an important role of 11β-HSD1 in the regulation of insulin release (Davani et al., 2000). A more recent report describes a similar effect of dehydrocorticosterone on insulin release in human and murine pancreatic cells, but it appears that enzyme expression is absent in β-cells, with this effect being mediated indirectly through expression within α-cells. This α-cell expression additionally inhibits insulin-stimulated glucagon secretion (Cooper & Stewart, 2009; Swali et al., 2008).

6.3 11β-HSD1 and hypertension

GC hormones act on the cardiovascular system (Nussinovitch et al., 2010; Raff & Findling, 2003; Walker et al., 2000; Wallerath et al., 1999). Cortisol and 11β-HSDs have been implicated in hypertension (Anagnostis et al., 2009; Andrews et al., 2003; Campino et al., 2010; Cicala & Mantero, 2010; Edwards et al., 1988; Ferrari, 2010; Franks et al., 2004; Funder et al., 1988; Gathercole & Stewart, 2010; Y. Liu et al., 2008; Malavasi et al., 2010; Masuzaki et al., 2003; Millis, 2011; Monder et al., 1989; Morales et al., 2008; Mune et al., 1995; Palermo et al., 2004; Paterson et al., 2004; Quinkler & Stewart, 2003; Raff & Findling, 2003; S. Shah et al., 2011; Stewart et al., 1996; Walker & Andrew, 2006; Walker et al., 1993; Wallerath et al., 1999; White et al., 1997).
The fact that 11β-HSD2 is important in protecting MR in the distal nephron from stimulation by GCs revealed its role in the regulation of arterial blood pressure. Pharmacological inhibition or genetic deficiency of 11β-HSD2 leads to the development of hypertension (Anagnostis et al., 2009; Andrews et al., 2003; Edwards et al., 1988; Ferrari, 2010; Funder et al., 1988; Gathercole & Stewart, 2010; Palermo et al., 2004; Walker et al., 1993; White et al.,

1997). HSD11B2 can be epigenetically regulated, what is also involved in hypertension development (Millis, 2011). In the same line, defects and polymorphisms in HSD11B2 have also been shown to play a role in human hypertension and cardiovascular disease [e.g. essential hypertension (Soro et al., 1995; Walker et al., 1993) and 'salt-sensitive' hypertension (Lovati et al., 1999)] (Bailey et al., 2008; Cooper & Stewart, 2009; Henschkowski et al., 2008).
Campino et al. reported a high percentage of alterations in the cortisol metabolism at the pre-receptor level in hypertensive patients, previously misclassified as having essential hypertension, where 18% of the patients present reduced 11β-HSD2 activity or imbalance of 11β-HSD1 activity in comparison to 11β-HSD2 (Campino et al., 2010). As referred above, hypertension is induced in mice genetically modified to overexpress 11β-HSD1 either in the liver or AT (Masuzaki et al., 2003; Paterson et al., 2004). HSD11B1 polymorphisms have been described, affecting enzyme expression and activity *in vitro* and/or *in vivo*, and/or being associated with hypertension (Franks et al., 2004; Malavasi et al., 2010; Morales et al., 2008). Variants of HSD11B1 were associated with the risk of hypertension in Pima Indians (Franks et al., 2004). Liu et al. showed that suppression of 11β-HSD1 expression in the renal medulla attenuates salt-induced hypertension in Dahl salt-sensitive rats (Y. Liu et al., 2008). Taking into consideration that diet is one important factor on MetSyn development, it is interesting to mention that in Dahl salt-sensitive hypertensive rats, fed a high-salt diet for 4 weeks, peri-renal AT corticosterone concentration and 11β-HSD1 activity as well as GR, 11β-HSD1 and TNF-α expression increase when compared with Dahl salt-resistant rats fed the same diet (Usukura et al., 2009).

6.4 11β-HSD1 and NAFLD

NAFLD is being increasingly recognized as a common liver disorder that represents the hepatic manifestation of the MetSyn. NAFLD is more frequent among people with T2DM and obesity, and it is almost universal amongst T2DM patients who are morbidly obese (Bellentani et al., 2000; Fabbrini et al., 2010; Gupte et al., 2004; Konopelska et al., 2009; Ratziu et al., 2010; Wree et al., 2010). Non-alcoholic steatohepatitis (NASH) is the progressive form of liver injury that carries a risk of progressive fibrosis, cirrhosis and end-stage liver disease. There is strong evidence that IR and increased FFA are a major cause of NASH (Brunt, 2004; Konopelska et al., 2009; Ratziu et al., 2010; Scheen & Luyckx, 2002). Inflammation plays an important additional role with increased production of reactive oxygen species and pro-inflammatory cytokines. In addition, several studies support a link between VAT and NASH (Kern et al., 2003; Konopelska et al., 2009; McCullough & Falck-Ytter, 1999). Konopelska et al., for the first time in patients with elevated liver enzymes (that after liver biopsies had histological diagnosis of normality, steatosis, NASH and other forms of hepatitis or cirrhosis), found no association between increased liver fat accumulation or different stages of liver inflammation and hepatic 11β-HSD1 expression, suggesting that, probably, there is no major role of this enzyme in the inflammatory process from fatty liver to NASH in humans (Konopelska et al., 2009). In contrast, as mentioned before, transgenic mice with hepatic overexpression of 11β-HSD1 develop fatty liver and dyslipidemia (Paterson et al., 2004). 11β-HSD1 expression correlated positively with H6PDH expression in the liver and negatively with waist-to-hip ratio in women (this being in accordance to obesity results we have mentioned previously). No evaluation of 11β-HSD1 and H6PDH protein or activity levels was done (Konopelska et al., 2009).
Given all the above evidences, 11β-HSD1 has thus emerged as a major potential drug target for the treatment of obesity and its associated metabolic abnormalities.

7. 11β-HSD1 inhibition studies

Several and distinct selective 11β-HSD1 inhibitors are being produced, developed and tested *in vitro*, *ex vivo* and *in vivo*, in normal animals, rodent models of metabolic alterations or disease (hyperglycemia, dyslipidemia, atherosclerosis, IR, T2DM, obesity, diet-induced obesity and/or MetSyn) and some of them already in humans, healthy or not (Alberts et al., 2002; Alberts et al., 2003; Barf et al., 2002; Bhat et al., 2008; Bujalska et al., 2008a; Cho et al., 2009; Cooper & Stewart, 2009; Coppola et al., 2005; Courtney et al., 2008; Feig et al., 2011; Gathercole & Stewart, 2010; Ge et al., 2010; Hale et al., 2008; Hale & Wang, 2008; Hermanowski-Vosatka et al., 2005; Hollis & Huber, 2011; Hughes et al., 2008; Hult et al., 2006; Johansson et al., 2008; Julian et al., 2008; J. Liu et al., 2011; Morgan et al., 2009; Morgan & Tomlinson, 2010; Morton, 2010; Park et al., 2011; Rosenstock et al., 2010; S. Shah et al., 2011; U. Shah et al., 2010; Siu et al., 2009; Stewart & Tomlinson, 2009; Tiwari, 2010; Tu et al., 2008; van Raalte et al., 2009; Véniant et al., 2010; S. J. Wang et al., 2006; Webster et al., 2010; Yuan et al., 2007; X. Zhang et al., 2009b). Besides inhibition of 11β-HSD1 reductase activity, increase of 11β-HSD1 dehydrogenase (oxidase) activity, without inhibition of 11β-HSD2, may provide a better therapeutic strategy for T2DM, obesity and MetSyn (Ge et al., 2010). 11β-HSD1 is also inhibited by natural compounds, such as an active ingredient of various Chinese herbs (emodin), derivatives or analogues of the licorice root, coffee extract, flavanone (and the monohydroxylated flavonoid 2′-hydroxyflavanone), endogenous steroids and their metabolites and bile acids (Andrews et al., 2003; Atanasov et al., 2006; Chalbot & Morfin, 2006; Classen-Houben et al., 2009; Diederich et al., 2000; Feng et al., 2010; Gathercole & Stewart, 2010; Hollis & Huber, 2011; Latif et al., 2005; Livingstone & Walker, 2003; Maeda et al., 2010; Monder et al., 1989; Morris et al., 2004; Odermatt & Nashev, 2010; Sandeep et al., 2005; Schweizer et al., 2003; Su et al., 2007; Taylor et al., 2008; Tomlinson et al., 2007; van Raalte et al., 2009; Walker et al., 1995a; Wamil & Seckl, 2007). Glycyrrhetinic acid, the active pharmacological ingredient of the licorice root and some of its derivatives, as well as its steroidal synthetic analogue carbenoxolone (hemisuccinate derivative of glycyrrhetinic acid) are inhibitors of both 11β-HSD1 and 11β-HSD2 (the magnitude of the effect being dependent on *in vitro versus in vivo* environment, dose, administration mode, tissue and specie as well as compound structure) (Abdallah et al., 2005; Andrews et al., 2003; Classen-Houben et al., 2009; Gathercole & Stewart, 2010; Hollis & Huber, 2011; Jellinck et al., 1993; Livingstone & Walker, 2003; Monder et al., 1989; Sandeep et al., 2005; Su et al., 2007; Taylor et al., 2008; Tomlinson et al., 2007; van Raalte et al., 2009; Walker et al., 1995a; Wamil & Seckl, 2007). Both 7-oxygenated steroids and 7-ketocholesterol modulate 11-HSD1 activity (Balázs et al., 2009; Odermatt & Nashev, 2010; Wamil et al., 2008; Wamil & Seckl, 2007). From all the bile salts tested *in vitro* and found to inhibit 11β-HSD1, Diederich et al. reported that chenodesoxycholic acid does not affect *in vivo* the activity of 11β-HSD1 when given in therapeutic doses to healthy men (Diederich et al., 2011).

7.1 Human 11β-HSD1 inhibition studies

In a study with carbenoxolone it is observed, in healthy non-diabetic men, a small (although significant) increase in whole body insulin sensitivity (Hollis & Huber, 2011; Walker et al., 1995a). Walker et al. infered that carbenoxolone, by inhibiting hepatic 11β-HSD1 and reducing intra-hepatic cortisol concentration, increases hepatic insulin sensitivity and decreases hepatic glucose production (Walker et al., 1995b). Further developing their research on carbenoxolone 11β-HSD1 inhibition, Walker et al. report decreased glucagon-stimulated glucose production

and glycogenolysis in T2DM men (non-obese normotensive, treated with diet alone), but not in healthy subjects, and decreased total cholesterol in healthy subjects, but not in T2DM patients. Carbenoxolone has no effect on gluconeogenesis, peripheral glucose uptake or insulin-mediated reduction of plasma FFA (Andrews et al., 2003). So, as just described, carbenoxolone enhances hepatic insulin sensitivity in healthy men and in non-obese normotensive T2DM. However, Sandeep et al. describe later, in non-diabetic obese men, a highly effective inhibition of whole-body 11β-HSD turnover by carbenoxolone, but without inhibiting the conversion of cortisone to cortisol in SAT or modifying insulin sensitivity (Sandeep et al., 2005). Nevertheless, 11β-HSD1 inhibition in AT by carbenoxolone has been reported. After both a single dose and posterior 72 h of continuous treatment with carbenoxolone, in healthy male volunteers, Tomlinson et al. observe a decrease not only on serum cortisol generation, after oral administration of cortisone acetate (although only significantly for continuous treatment), but also on cortisol concentrations, after oral cortisone acetate, and glycerol concentrations, after oral prednisone, both within SAT interstitial fluid (in the latter location being indicative of inhibition of GC-mediated lipolysis) (Tomlinson et al., 2007). It is important to mention that 11β-HSD2 inhibition, with licorice or carbenoxolone, can lead to cortisol-dependent mineralocorticoid excess, with hypertension, sodium retention, hypokalemia and fluid retention (Andrews et al., 2003; Edwards et al., 1988; Ferrari, 2010; Gathercole & Stewart, 2010; Palermo et al., 2004; Stewart et al., 1990; Stewart et al., 1987). 11β-HSD2 is expressed principally in the distal nephron, where it inactivates cortisol to cortisone and thereby protects MR from cortisol (Andrews et al., 2003; Edwards et al., 1988; Ferrari, 2010; Funder et al., 1988; Palermo et al., 2004). PF-915275 is a potent and selective 11β-HSD1 inhibitor, without adverse side effects in a wide range of orally tested doses, that is selective for the human and primate enzymes (Bhat et al., 2008; Courtney et al., 2008). A modest pharmacodynamic effect of PF-915275 on 11β-HSD1 activity in the healthy human liver is reported, but experiments to assess its inhibitory effect in the AT have not been performed (Courtney et al., 2008; Hollis & Huber, 2011). So far, to our knowledge, there are no reports of PF-915275 activity in patients with T2DM or MetSyn (or any of the associated components). Bhat et al. showed, in normal cynomolgus monkeys, that PF-915275 dose-dependently inhibits 11β-HSD1-mediated conversion of prednisone to prednisolone and reduces insulin levels (Bhat et al., 2008). Hollis et al. reviewed the clinical results obtained with the selective 11β-HSD1 inhibitor INCB13739. In patients with T2DM inadequately controlled with metformin, INCB13739 treatment achieves significant reductions in hemoglobin A1c, fasting plasma glucose and HOMA-IR (homeostasis model assessment-IR), and improves hyperlipidemia and hypertriglyceridemia (when present). Adverse events (occurring in ≥ 3%: nasopharyngitis, headache, diarrhea, cough, nausea, arthralgia and upper respiratory tract infection) were similar across all treatment groups. Interestingly, those positive effects are observed primarily in subjects categorized as obese (BMI > 30 kg/m²) and not in subjects categorized as overweight (BMI ≤ 30 kg/m²), underscoring the likely importance of AT 11β-HSD1 activity to the cardiometabolic sequelae of obesity (Hollis & Huber, 2011; Rosenstock et al., 2010). Feig et al. showed that 11β-HSD1 selective inhibition with MK-0916 is generally well tolerated in patients with T2DM and MetSyn (NCEP ATP III-defined) (Feig et al., 2011; S. Shah et al., 2011). Although no significant improvement in fasting plasma glucose is observed with MK-0916 compared to placebo, modest improvements in hemoglobin A1c, body weight and blood pressure are observed (Feig et al., 2011). These patients were only mildly hypertensive, with 55% receiving ongoing anti-hypertensive therapy, and yet treatment with MK-0916 led to

reductions from baseline of 7.9 and 5.4 mmHg in systolic and diastolic blood pressure, respectively, relative to placebo (Feig et al., 2011; S. Shah et al., 2011). Further developing the research on 11β-HSD1 selective inhibition, Shah et al. reported that, in overweight-to-obese hypertensive patients, reduction in trough sitting diastolic blood pressure with MK-0736 is not statistically significant. Nonetheless, MK-0736 is well tolerated and appears to modestly improve other blood pressure endpoints as well as LDL-cholesterol and body weight. The 24 h ambulatory blood pressure measurements data (from the subset of patients who participated in ambulatory blood pressure measurements) suggest that MK-0736 has blood pressure-lowering efficacy over a 24 h period not adequately represented by measuring sitting diastolic blood pressure and sitting systolic blood pressure, notably a greater blood pressure-lowering effect during daytime than during night-time (S. Shah et al., 2011). 11β-HSD1 inhibitors may improve a number of metabolic disturbances, unlike current available anti-diabetic compounds, that occur in obesity, T2DM and/or MetSyn patients, as seen from genetically engineered animal studies (Kotelevtsev et al., 1997; Morton et al., 2001; Morton et al., 2004) as well as from animal (Alberts et al., 2002; Alberts et al., 2003; Barf et al., 2002; Cooper & Stewart, 2009; Feng et al., 2010; Gathercole & Stewart, 2010; Hermanowski-Vosatka et al., 2005; Johansson et al., 2008; J. Liu et al., 2011; Livingstone & Walker, 2003; Morgan et al., 2009; Park et al., 2011; Taylor et al., 2008; Véniant et al., 2010; S. J. Wang et al., 2006; X. Zhang et al., 2009b) and human 11β-HSD1 inhibition studies (Andrews et al., 2003; Courtney et al., 2008; Feig et al., 2011; Gathercole & Stewart, 2010; Hollis & Huber, 2011; Morton, 2010; Rosenstock et al., 2010; Sandeep et al., 2005; S. Shah et al., 2011; Tomlinson et al., 2007; van Raalte et al., 2009; Walker et al., 1995a; Wamil & Seckl, 2007). Taking this into account, pharmacological inhibition of 11β-HSD1 to lower intracellular cortisol concentrations in the liver and AT, without altering circulating cortisol concentrations or responses to stress, is an exciting potential therapy in those conditions and likely to be most effective in obese T2DM patients (Andrews et al., 2003; Courtney et al., 2008; Feig et al., 2011; Gathercole & Stewart, 2010; Hollis & Huber, 2011; Morton, 2010; Rosenstock et al., 2010; Sandeep et al., 2005; S. Shah et al., 2011; R. Stimson et al., 2011; Tomlinson et al., 2007; van Raalte et al., 2009; Walker et al., 1995a; Wamil & Seckl, 2007).

8. Conclusion

According to the rising prevalence of the MetSyn and the burden of its associated cardiometabolic complications, the study of the mechanisms of disease as well as of possible prophylactic and therapeutic approaches is becoming increasingly necessary. The recognition of the involvement of GCs and 11β-HSD1, as likely etiological factors, adds new avenues for MetSyn management. Lately, research focusing on 11β-HSD1 inhibition has shown promising results. The role of dietary patterns on MetSyn development and of dietary components on 11β-HSD1 modulation for the prevention and/or treatment of metabolic disorders is now starting to be unraveled and may be a worthwhile investigation.

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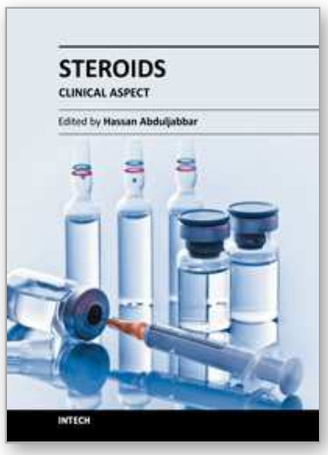

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Steroids: The basic science and clinical aspects covers the modern understanding and clinical use of steroids. The history of steroids is richly immersed and runs long and deep. The modern history of steroids started in the early 20th century, but its use has been traced back to ancient Greece. We start by describing the basic science of steroids. We then describe different clinical situations where steroids play an important role. We hope that this book will contribute further to the literature available about steroids and enables the reader to further understand this interesting and rapidly evolving science.

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