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Inhibition of 11β-Hydroxysteroid Dehydrogenase Type 1 in Obesity

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Excessive glucocorticoid exposure (Cushing's syndrome) results in increased adiposity associated with dysmetabolic features (including insulin resistance, hyperlipidaemia, and hypertension). Circulating cortisol levels are not elevated in idiopathic obesity, although cortisol production and clearance are increased. However, tissue glucocorticoid exposure may be altered independently of circulating levels by 11β-hydroxysteroid dehydrogenase type 1 (11HSD1), an enzyme which generates active glucocorticoid within tissues, including in adipose tissue. Transgenic overexpression of 11HSD1 in mice causes obesity. In human obesity, 11HSD1 is altered in a tissue-specific manner with reduced levels in liver but elevated levels in adipose, which may lead to glucocorticoid receptor activation and contribute to the metabolic phenotype. The reasons for altered 11HSD1 in obesity are not fully understood. Although some polymorphisms have been demonstrated in intronic and upstream regions of the *HSD11B1* gene, the functional significance of these is not clear. In addition, there is mounting evidence that 11HSD1 may be dysregulated secondarily to factors that are altered in obesity, including substrates for metabolism, hormones, and inflammatory mediators. 11HSD1 is a potential therapeutic target for the treatment of the metabolic syndrome. 11HSD1 knockout mice are protected from diet-induced obesity and associated metabolic dysfunction. Although many specific inhibitors of 11HSD1 have now been developed, and published data support their efficacy in the liver to reduce glucose production, their efficacy in enhancing insulin sensitivity in adipose tissue remains uncertain. The therapeutic potential of 11HSD1 in human obesity therefore remains highly promising but as yet unproven.

Key Words: 11-Beta hydroxysteroid dehydrogenase; glucocorticoids; obesity; metabolic syndrome; adipose.

Introduction

Glucocorticoids in Obesity and the Metabolic Syndrome

Cortisol is the principal active glucocorticoid in man, and an important regulator of many physiological pathways, particularly at times of stress or illness. Cortisol mediates its tissue effects by activation of intracellular receptors. In addition to its physiological role, an intriguing role for cortisol is emerging in pathogenesis of obesity and its associated metabolic phenotype. Excessive glucocorticoid exposure (i.e., Cushing's syndrome), either as a result of endogenous overproduction or exogenous administration (in the treatment of inflammatory diseases), results in increased central adiposity, insulin resistance, dyslipidemia, and hypertension. Idiopathic obesity is also associated with these dysmetabolic features, together defined as "the metabolic syndrome." The phenotype of Cushing's syndrome is reversible upon removal of glucocorticoid excess. It has been proposed that subjects with obesity and the metabolic syndrome have increased glucocorticoid receptor activation, and further that they may be susceptible to therapeutic manipulation of tissue glucocorticoid exposure.

In idiopathic obesity, circulating plasma cortisol levels are not elevated, but dysregulation of cortisol metabolism has been observed, together with loss of the diurnal rhythm of plasma cortisol *(1–3)*. Cortisol secretion is increased in obesity indicating activation of the HPA axis *(1,4–6)*, as evidenced by an increased response to stimulation e.g., by acute stress, CRH/AVP, hypoglycemia, or a standard meal test *(7–9)*. It has been proposed that obesity is associated with resistance to glucocorticoid feedback *(5,6)*, an effect that may be mediated via altered sensitivity of glucocorticoid or mineralocorticoid receptors. Some studies suggest that individuals with common glucocorticoid receptor polymorphisms demonstrate HPA axis abnormalities in addition to a peripheral phenotype of increased adiposity, insulin resistance, and hypertension *(6,7,9,10)*. However, it has become apparent that the abnormalities of the HPA axis in obesity might be explained by alterations in peripheral metabolism of cortisol.

Peripheral clearance of cortisol is mediated, in large part, by the hepatic A-ring reductases (namely, 5α- and 5β-reductase). Increased A-ring reductase activity in obesity was first identified by analysis of cortisol metabolites in the urine *(11,*

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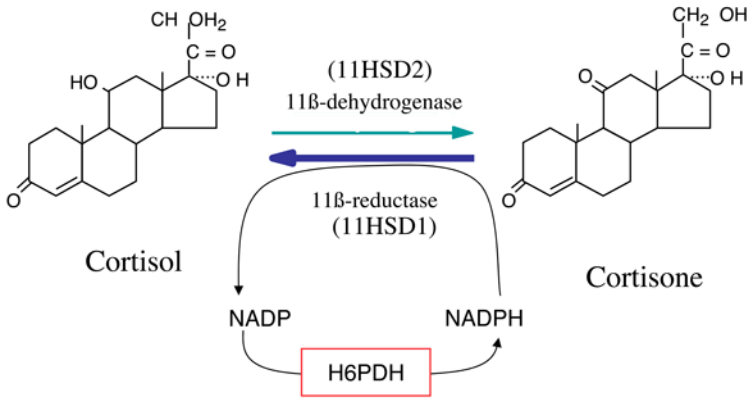

Fig. 1. Reactions catalysed by 11β-hydroxysteroid dehydrogenases in humans Inactive (cortisone) and active (cortisol) glucocorticoids are interconverted by 11keto-reductase and 11β-dehydrogenase activities. In vivo these reactions are predominantly carried out by 11HSD1 and 11HSD2 isozymes, respectively. Reductase activity of 11HSD1 is dependent on cofactor (NADPH) being generated by hexose-6-phosphate dehydrogenase (H6PDH) within the endoplasmic reticulum.

12) and this has been confirmed in both animal *(13)* and human obesity *(14,15)*. The explanation for increases in these enzyme activities is unknown but they may be regulated by nutritional factors such as insulin and lipids, and by substrate availability *(16)*. 5β-Reductase is also a key enzyme involved in cholesterol metabolism and bile acid biosynthesis, which may be disturbed in obesity and thereby alter glucocorticoid metabolism. Increased 5β-reductase has been associated with increased liver fat in healthy volunteers *(17)*.

In addition to changes in peripheral cortisol turnover, cellular glucocorticoid metabolism is altered in obesity, resulting in changes in local glucocorticoid availability. Particular interest has focused on the role of 11β-hydroxysteroid dehydrogenase type 1 (11HSD1), which regulates the balance of active and inactive glucocorticoid at the cellular level. 11HSD1 is altered in obesity and may be a potent target for therapeutic manipulation.

The 11β-Hydroxysteroid Dehydrogenases (11HSDs)

The 11β-hydroxysteroid dehydrogenases (11HSDs) were discovered some 50 yr ago *(18)*, yet their therapeutic potential has only emerged recently. These microsomal enzymes interconvert active and inactive glucocorticoids, thus acting as gate keepers for intracellular receptors *(19,20)*. This system is not unique, and pre-receptor metabolizing enzymes also exist for other hormones, including androgens (5α-reductase type 2), estrogens (aromatase), and thyroxine (5'-monodeiodinase) *(21)*. Indeed, inhibitors of some of these enzymes are useful therapeutically (e.g., inhibition of aromatase in breast cancer and 5α-reductase type 2 in prostate disease). By controlling substrate availability (cortisol in humans, corticosterone in rats and mice), 11HSDs modulate tissue-specific glucocorticoid receptor activation, irrespective of circulating plasma cortisol levels. Glucocorticoids are important regulators of pathophysiological processes in many tissues; therefore, pharmacological manipulation of these novel enzymes may have wide ranging therapeutic effects.

Two 11HSD isozymes have been cloned. 11HSD type 2 is an exclusive NAD-dependent dehydrogenase, converting active cortisol to inactive cortisone. Its main role is in aldosterone-sensitive target tissues (kidney, colon, salivary glands, and placenta). Cortisol circulates in several-fold higher plasma concentrations than aldosterone but both have similar affinity for the non-selective mineralocorticoid receptor. By inactivating cortisol, 11HSD2 prevents flooding of mineralocorticoid receptors leaving free access for aldosterone. This is particularly important in the distal nephron. 11HSD2 was cloned in 1994 *(22)* and since 1995 the rare syndrome of apparent mineralocorticoid excess (SAME) (characterized by hypertension, hypokalemia, and fluid retention due to illicit occupation of mineralocorticoid receptors by cortisol) has been attributed to mutations in the 11HSD2 gene *(23,24)*.

The importance of the 11HSD type 1 isozyme was not realized until much later. It was cloned in 1989 *(25)* but only in the mid-1990s was it confirmed that it acts in vivo predominantly as a NADPH-dependent reductase (performing the opposite role to 11HSD2), i.e., generating cortisol from inactive cortisone *(26–30)* (Fig. 1). 11HSD1 is found in tissues that are abundant in glucocorticoid rather than mineralocorticoid receptors including liver, adipose, gonads, brain, and vasculature. Altered access of ligand to glucocorticoid receptors in these tissues may have implications in many common diseases that share features of Cushing's syndrome, including idiopathic obesity, diabetes mellitus, polycystic ovary disease, and dementia *(20)*.

Transgenic Manipulation of 11HSD1

The potential importance of 11HSD 1 in obesity has emerged from the development of transgenic mice. Striking metabolic consequences are observed by altering 11HSD1 expression. Adipose-specific overexpression of 11HSD1 (under an AP2 promoter) produces a phenotype analogous to the metabolic syndrome (with central obesity, hypertension, insulin resistance, and dyslipidemia) *(31,32)*. This is asso-

ciated with high intra-adipose corticosterone, high levels of plasma leptin, tumor necrosis factor (TNF)-alpha, and adipose lipoprotein lipase (LPL) mRNA. Levels of adipose uncoupling protein-1 (UCP-1) mRNA are low, portal flow of triglycerides is increased, and angiotensinogen production is elevated, which may explain the associated hypertension *(32)*.

Knockout mice, homozygous for a deleted 11HSD1 allele, are conversely protected from the metabolic consequences of obesity *(33,34)*. They have lower intracellular corticosterone levels despite mildly elevated circulating levels *(35,36)*, a favorable lipid profile (lower serum triglycerides and high HDL cholesterol) and resist hyperglycemia induced by stress and during high fat feeding. Changes in glucocorticoid-dependent gene expression are also seen in the liver, with decreased gluconeogenic enzymes (notably PEPCK) and increased enzymes of lipid oxidation. When rederived against an obesity prone genetic background (C57Bl6), 11HSD1 –/– mice are further protected from weight gain on a high fat diet *(37)*.

Overexpression of 11HSD1 in the liver under an ApoE promoter results in fatty liver, dyslipidemia, mild insulin resistance, increased angiotensinogen expression, and hypertension. These animals do not, however, demonstrate increased adiposity or glucose intolerance *(38)*.

The striking phenotype of these transgenic models suggests that 11HSD1 may be a potent pathophysiological force in the development of the metabolic syndrome, and further that there could be wide-ranging therapeutic benefits from 11HSD1 inhibition, including improvements in dyslipidemia, hypertension, insulin resistance, and potentially limitation of weight gain in obesity susceptible individuals. Furthermore, although much of its biology has been elucidated in liver, it appears that the enzyme may have its greatest influence in adipose tissue.

11HSD1 in Obesity

Assessment of 11HSD1 in humans is difficult. Conventional studies examined urine by mass spectrometry to assess the ratios of cortisol:cortisone metabolites—an elevated ratio being taken to indicate increased regeneration of cortisol from cortisone by 11HSD1. However, these measurements have demonstrated conflicting results, showing variably increased *(11,14,39)*, decreased *(40,41)*, or unchanged *(12,42)* cortisol:cortisone metabolite ratio in relation to parameters of obesity. This is probably due to the influence of other enzymes (e.g., 11HSD2 and the A-ring reductases), which can have a confounding influence on the cortisol: cortisone metabolite ratios *(17)*.

Because of these difficulties, urinary measurements should not be used in isolation to assess 11HSD1. It is possible to use stable isotope tracers to quantify the rate of regeneration of cortisol from cortisone. Labeling of cortisol with four deuteriums, one of which is placed in the 11α position and removed on conversion to cortisone, allows measurement of the rate of appearance of cortisol regenerated from cortisone (which no longer carries the 11α-deuterium) *(43, 44)*. This allows dissection of whole-body 11HSD1 activity specifically, but these are laborious techniques. Moreover, it appears that changes in 11HSD1 in obesity are tissue-specific, so measurement in isolated circulation or biopsied tissues may be essential to understand dysregulation of 11HSD1 in human disease.

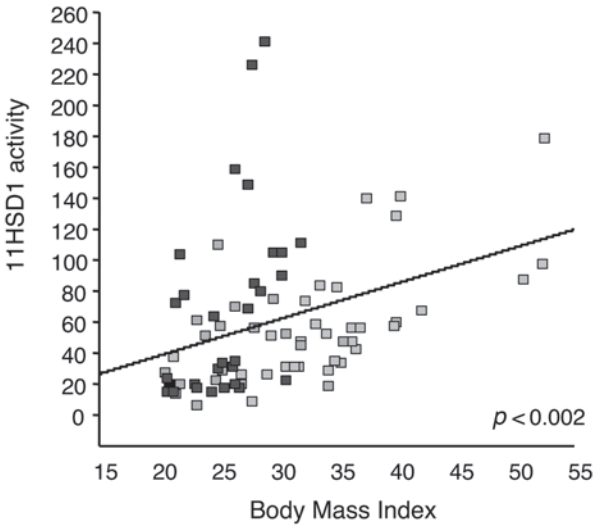

Fig. 2. Subcutaneous adipose 11HSD1 activity is increased in sc adipose in human idiopathic obesity. 11HSD1 activity was measured in subcutaneous adipose biopsies from healthy male and female volunteers. Data presented are a combination from three published cohorts *(14,17,40,48)*. These show positive relationships with body mass index (BMI).

Tissue-Specific Changes in 11HSD1

Obesity-prone, insulin resistant animal models (e.g., obese Zucker rats) were the first to demonstrate tissue-specific dysregulation of 11HSD1 in obesity. 11HSD1 is notably increased in visceral fat and reduced in hepatic tissue *(45)*. Reduced hepatic *(46)* and increased adipose *(31)* 11HSD1 have also been reported in ob/ob mice. Similar tissue-specific dysregulation was subsequently demonstrated in human studies. Hepatic 11HSD1 activity, as determined by impaired conversion of cortisone to cortisol on first pass metabolism through the liver *(41)*, is reduced in obesity. Furthermore, many studies have now demonstrated increased 11HSD1 activity and mRNA in homogenates of subcutaneous and omental adipose tissue *(14,40,47–51)* (Fig. 2). In vivo assessment of adipose 11HSD1 activity using intra-adipose microdialysis also confirmed an increased rate of appearance of cortisol in obese volunteers *(44)*.

The Metabolic Impact of Altered 11HSD1

The altered phenotype in 11HSD1 transgenic rodents suggests a clear role for 11HSD1 as a regulator of glucocorticoid signaling with downstream metabolic consequences.

However, the impact of 11HSD1 in human obesity is less clear. Although adipose 11HSD1 is elevated in obesity and is associated with insulin resistance *(48)*, a causal role has been difficult to determine. 11HSD1 appears to be important in mediating adipogenesis *(52–54)*, but attempts to demonstrate increased intra-adipose cortisol concentrations or demonstrate clear associations with glucocorticoid regulated target genes within the adipose tissue have been inconclusive *(47)*.

In addition to local effects, adipose 11HSD1 may act indirectly on the liver via portal drainage of cortisol resulting in hepatic insulin resistance. Adipose and portal corticosterone levels are elevated in adipose overexpressing transgenic rodents. In humans, studies using hepatic vein sampling suggest that the splanchnic circulation (which includes both visceral adipose tissue and liver) is a major source of cortisol generation, outstripping secretion rates from the adrenal for much of the time *(55,56)*. Moreover, it has been estimated that as much as two thirds of this activity resides in the visceral adipose tissue rather than the liver *(56)*. However, neither total splanchnic cortisol generation nor portal cortisol concentrations have yet been found to be altered in human obesity or diabetes *(57,58)*.

Mechanisms of Altered 11HSD1 in Obesity

HSD11B1 Genetics

Functional mutations in 11HSD type 2 are rare (resulting in SAME) and only a handful of patients with apparent congenital cortisone reductase deficiency (ACRD) have been identified *(59,60)*. These latter individuals have a defect in cortisone to cortisol conversion that has been proposed to be due to combined single allele mutations in 11HSD1 and hexose-6-phosphate dehydrogenase, whereby lack of generation of NADPH by hexose-6-phosphate dehydrogenase within the endoplasmic reticulum further limits the 11β-reductase capacity of 11HSD1 if it is expressed at low levels *(61)*. The same combination of mutations has, however, been found in patients with uncomplicated polycystic ovarian syndrome without low cortisol:cortisone metabolite ratios, casting uncertainty as to their functional significance *(62)*. No widespread common functional mutations in the coding region of *HSD11B1* have been found; however, phenotype–genotype relationships exist with polymorphisms in *HSD11B1* intronic sequences *(63)*, and in the 5' upstream sequence *(64)*. The intronic polymorphisms described by Draper et al. were associated with obesity-related parameters such as waist:hip ratios and hypertension, whereas upstream SNPs in Pima Indians predicted type 2 diabetes, plasma insulin levels, and insulin action independent of obesity, and may occur in areas of transcription factor binding sites *(63,64)*. Many genetic studies are still ongoing and mutations in the promoter region of 11HSD1 are yet to be fully screened. However, given uncertainties over the specificity of urinary cortisol:cortisone metabolite ratios, linking genotype with phenotype of altered enzyme activity in vivo will be difficult.

11HSD1 Regulation

The studies described above indicate that 11HSD1 is altered in a tissue-specific manner in idiopathic obesity. This could be mediated through genetic variations in tissue specific promoters and/or as a result of functional enzyme dysregulation. 11HSD1 is a highly transcriptionally regulated gene with many transcription factor binding sites in its promoter region (including CEBP and HNF, SF1, AP1 and AP2) *(65,66)*. Various regulators have been identified in vitro including glucocorticoids, thyroid hormones, sex steroids, insulin, IGF-1, lipids, leptin, GH, PPAR ligands and cytokines, many of which are altered in obesity *(46,67–70)*. In addition, in vivo 11HSD1 is notably dysregulated in the central adiposity of growth hormone (GH)–deficient patients and in hypothalamic obesity *(71–73)* and the cortisol:cortisone urinary metabolite ratio is lowered with GH therapy *(74,75)*.

New evidence points to an intriguing role for nutritional factors, inflammation, and a potential role for cofactor generation via hexose-6-phosphate dehydrogenase (H6PDH) in the regulation of 11HSD1 in obesity. Understanding these regulatory mechanisms may provide an indirect means of manipulating 11HSD1 activity. It will be a major challenge to dissect the relative importance of these regulatory pathways, and to begin to extend our existing "static" studies of 11HSD1 to understand its dynamic regulation in humans with and without metabolic syndrome.

Nutritional Regulation

Regulation of 11HSD1 mRNA in animal and cell models by high fat feeding *(76)*, insulin *(69,70,77)*, and PPAR/LXR agonists *(67,78)* suggests a potential dynamic role for 11HSD1 in the adaptive response of adipose to altered nutrition. Furthermore, maladaptive dysregulation may underlie increased adipose 11HSD1 in human and rodent obesity.

In rodents, high fat feeding potently downregulates hepatic and adipose 11β-HSD1. Most recently, our group and others *(44,55)* have explored acute downregulation of 11β-HSD1 in humans during hyperinsulinemia. We have shown that both insulin and lipid acutely regulate adipose 11HSD1 (unpublished data), and obese subjects may have an altered response to insulin *(44)*. In addition, dietary manipulation in humans has been shown to alter plasma cortisol/cortisone ratios *(79)* and weight loss results in elevated 11HSD1 mRNA in isolated adipocytes *(19)*, although this finding is not universal *(51)*.

Inflammatory Regulation

Idiopathic obesity is associated with a relative "inflammatory state," and increases in plasma markers of inflammation such as CRP, IL-6, and IL-1β have been shown to predict the risk of progression to type 2 DM, the risk of subsequent diabetic complications *(80)*, and to independently

predict cardiovascular disease risk *(81)*. Activation of inflammatory pathways may mediate increased tissue cortisol generation by 11HSD1 in obesity, and a reduction in 11HSD1 may underlie the insulin sensitizing effects of anti-inflammatory agents. In vitro studies have shown that inflammatory cytokines (e.g ,TNF-α and IL-1) increase tissue 11HSD1 activity in many cell types *(70,77,82,83)*. In vivo, inflammatory conditions such as HIV lipodystrophy and TB are associated with increased adipose and hepatic 11HSD1, respectively *(84,85)*. Furthermore, inflammatory signaling pathways (e.g., NFκ-B) regulate activation of intracellular glucocorticoid receptors *(86)* as seen in inflammatory conditions such as rheumatoid arthritis. In obesity, activation of both 11HSD1 and GR in adipose tissue and liver by inflammatory mediators may be detrimental, leading to increased glucocorticoid signaling resulting in an adverse metabolic (pro-atherogenic) phenotype.

Regulation by Cofactor

11HSD1 may also be regulated post-transcriptionally by factors determining enzyme directionality. 11HSD1 is a predominant reductase in vivo generating active glucocorticoid, but in tissue homogenates and some cultured cells 11HSD1 performs the opposite role, acting as a dehydrogenase *(87)*. The reasons remain unclear, but a recent intriguing hypothesis has been proposed by Stewart and colleagues that the directionality may be determined by cofactor availability. 11HSD1 relies on NADPH to function as a reductase (converting inactive cortisone to their active cortisol). Hexose-6-phosphate dehydrogenase (H6PDH) is closely associated with 11HSD1 on the inner endoplasmic reticulum and controls local NADPH availability. NADPH generated in this manner may maintain the predominant reductase activity seen in intact cells in vivo, which is lost following homogenization or in culture, when H6PDH and 11HSD1 are dissociated. Furthermore, alterations in H6PDH expression may be associated with changes in 11HSD1 activity and enzyme directionality *(88–90)*. Combined mutations in H6PDH and 11HSD1 have been observed in apparent cortisone reductase deficiency as discussed above *(59–61)*. With extreme variations, cofactor availability clearly determines reaction direction of 11HSD1; whether more subtle variations are important physiologically, and what regulates H6PDH, remains uncertain.

11HSD1 Inhibition

Inhibition of tissue cortisol generation, particularly within adipose tissue, may limit the downstream consequences of obesity. Some existing drugs, such as insulin-sensitizing thiazolidinediones (PPARγ agonists) may mediate their action in part indirectly through inhibition of adipose 11HSD1, an effect demonstrated in cultured adipocytes *(67)*. Likewise, the lipid-lowering agent fenofibrate (a PPARα agonist), inhibits 11HSD1 in hepatocytes *(91)*.

Various compounds have been shown to inhibit 11HSDs directly, but none until recently was selective, potent, and drug-like. Liquorice-based compounds such as glycyrrhetinic acid or carbenoxolone (previously used as a treatment for peptic ulcer disease) are potent but select poorly between the 11HSD isoforms (type 1 and type 2) *(92)*. Side effects as a result of 11HSD2 inhibition include hypertension, fluid retention, and hypokalemia. Many other non-specific inhibitors exist including alcohol, bioflavinoids, triterpenoids, polyphenols in cotton seed, grapefruit juice, and tea, and environmental agents such as gossypol *(93,94)*. Chenodeoxycholic acid is a selective inhibitor of the 11HSD type 1, but drug potency is poor.

In view of the potential wide ranging benefits of type 1 enzyme inhibition, the search for more selective inhibitors of 11HSD1 has been hastening. One promising class of both potent and selective inhibitors of 11HSD type 1 are the arylsulfonamidothiazoles *(95)*. A number of these compounds have been employed in in vitro and in vivo studies. The key target tissues examined so far are liver and adipose.

In vitro, 11HSD1 inhibition can limit regeneration or synthesis of glucocorticoids and attenuate the biological activity of cortisone on adipose tissue, e.g., by limiting adipocyte differentiation *(53)* and aromatase expression *(96)*. In vivo, glycyrrhetinic acid, a nonspecific HSD inhibitor causes weight loss and reduced corticosterone levels in lean but not obese rats *(97)*. Treatment of lean and obese Zucker rats with carbenoxolone inhibited 11HSD1 in the liver but not adipose tissue *(98)*, increased HDL cholesterol, but had no effect on weight gain, food intake, or oral glucose tolerance; the lack of effect on obesity and insulin sensitivity was attributed to the lack of adipose inhibition.

Similar results have been obtained in humans *(44)*. In healthy human volunteers carbenoxolone improve insulin sensitivity *(99)* without a measurable increase in forearm glucose uptake (principally skeletal muscle) and so was attributed to enhanced hepatic insulin sensitivity. Reduced hepatic 11HSD1 activity may result in impaired hepatic gluconeogenesis as a result of modulation of key glucocorticoid responsive gluconeogenic enzymes (e.g., PEPCK). A further study in lean-diet-controlled type 2 diabetic patients and healthy volunteers demonstrated reduced glucagon stimulated hepatic glucose production and glycogenolysis in diabetics (Fig. 3) and reduced total cholesterol in healthy volunteers upon carbenoxolone treatment *(100)*, but no increase in glucose uptake. Arylsulfonamidothiazoles show encouraging results in animal studies, with lowering of blood glucose in diabetic mice. These effects seem to be mediated through inhibition of glucocorticoid-dependent expression of PEPCK and glucose-6-phosphate as a result of 11HSD1 inhibition in the liver *(95,101,102)*. Interestingly, a small study of topical application of glycyrrhetinic acid has been shown to reduce subcutaneous thigh fat in women but systemic metabolic changes were not assessed *(103)*. 11HSD1 inhibitors predominantly affect liver rather than adipose

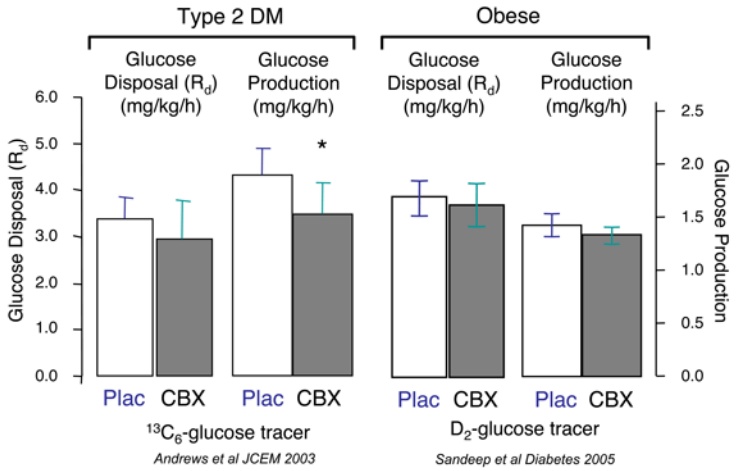

Fig. 3. Effects of the 11β-hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes and obesity. Data are mean ± SEM for glucose disposal and production during a hyperinsulinaemic euglycaemic clamp measured by $^{13}C_6$-glucose tracer infusion in six lean patients with type 2 diabetes mellitus and six obese euglycemic patients treated for 7 d with placebo or carbenoxolone (CBX) in randomized double blind crossover studies. Carbenoxolone did not enhance peripheral glucose disposal in either group but did decrease hepatic glucose production in lean diabetic patients, consistent with enhanced hepatic insulin sensitivity. This effect in the liver is lost in obese subjects, in whom 11HSD1 is known to be downregulated.

tissue. In obesity, the most therapeutic benefit is likely to be gained from adipose inhibition, as liver 11HSD1 levels are already low but adipose 11HSD1 is pathologically elevated. The development of specific drugs that sequester in adipocytes may therefore be particularly useful.

Potential Caveats for 11HSD1 Inhibitors

Potential side effects of global inhibition of 11HSD1 could be wide ranging as 11HSD1 is found in many other tissues (e.g., gonads, lung, immune cells, vascular tissues, and bone) *(20)*. Reassuringly, 11HSD1–/– mice are healthy, live a full lifespan, and reproduce normally *(34)* and maintain their advantageous metabolic phenotype throughout life.

It is likely that 11HSD1 inhibition may result in increased adrenal androgen production, as is seen in individuals with apparent cortisone reductase deficiency. This occurs as a result of reduced peripheral cortisol production, leading to secondary activation of the HPA axis and subsequent activation of adrenal androgen pathways *(104)*. There has also been concern that inhibition of 11HSD1 in pituitary, hypothalamus, and hippocampus may interfere with HPA feedback regulation and elevate plasma glucocorticoids *(35)* but this is a subtle effect, and in 11HSD1–/– mice it is insufficient to overcome the lack of glucocorticoid regeneration in peripheral tissues.

11HSD1 inhibition may potentially affect the response to inflammation and infection. Glucocorticoids have a potent anti-inflammatory action, and circulating cytokines (e.g., TNF-α and IL-1) can increased tissue glucocorticoids (via HSD1) *(105)*, thus limiting the inflammatory response. Furthermore, 11HSD1 may be required for the differentiation of monocytes to macrophages *(106)*. 11HSD1 inhibition may therefore alter the response to inflammation and infection.

Recent data suggest that absence of 11HSD1 attenuates glucocorticoid-dependent inhibition of angiogenesis in response to ischemia and wounding *(107)*. While this may be beneficial, for example, in improving myocardial function following infarction, it may also promote new vessel formation in tumours or in diabetic retinopathy. This possibility requires urgent exploration.

Reducing glucocorticoid action in tissues which are not influential in obesity may have beneficial effects, however. In CNS, loss of 11HSD1 prevents glucocorticoiddependent neurotoxicity and protects cognitive function with ageing in 11HSD1 –/– mice *(36)*. In humans, short-term administration of carbenoxolone to healthy elderly men or patients with type 2 diabetes also improves memory *(108)*.

Conclusions

Glucocorticoid metabolism is altered in obesity with increased cortisol production, peripheral clearance, and notably altered tissue glucocorticoid availability via 11HSD1. The role of 11HSD1 as a therapeutic target in obesity is attractive, particularly within adipose tissue where enzymes levels are elevated. Transgenic rodent models suggest an important role for 11HSD1 in the pathogenesis of the metabolic syndrome and ongoing adipogenesis. The impact of 11HSD1 in human obesity has, however, been more difficult to assess and trials of specific 11HSD1 inhibitors that function in adipose tissue will ultimately be required.

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