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ROLE OF 11 β-HYDROXYSTEROID DEHYDROGENASE INHIBITORS IN METABOLIC SYNDROME AND ITS EXPANSION IN OTHER THERAPEUTIC OPTIONS

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Abstract: The metabolic syndrome is a constellation of interrelated metabolic risk factors that appear to promote the development of diabetes and cardiovascular disease. These risk factors include abdominal obesity, insulin resistance, hypertension and dyslipidemia. This article was aimed to review the pathophysiological and pharmaco therapeutic aspects of 11beta-Hydroxysteroid dehydrogenase (11beta-HSD). It catalyzes the interconversion of glucocorticoids through the activity of two isozymes: type 1 (11beta-HSD1) and type 2 (11beta-HSD2). 11beta-HSD1 converts inactive glucocorticoid to the active form, whereas 11beta-HSD2 converts active glucocorticoid to the inactive form. Glucocorticoids play a pivotal role in regulating fat metabolism, function and distribution. Evidence has accumulated that enzyme activity of 11beta-HSD1, which regenerates active glucocorticoids from inactive forms and plays a central role in regulating intracellular glucocorticoid concentration, is commonly elevated in fat depots from obese individuals. This suggests a role for local glucocorticoid reactivation in obesity and the Metabolic Syndrome. 11beta-HSD1 knockout mice resist visceral fat accumulation and insulin resistance even on a high-fat diet. In summary, 11beta-HSD1 is a promising pharmaceutical target for the treatment of the Metabolic Syndrome. Animal studies and pharmacological experiments suggest further unrelated target areas, for example improvement of cognitive function and treatment of glaucoma, osteoporosis due to the role of glucocorticoids and cellular activation by 11beta-HSD1 in these pathologies.

Keywords: 11 Beta-hydroxysteroid dehydrogenase inhibitors, metabolic syndrome, glucocorticoids, obesity.

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INTRODUCTION

Glucocorticoids (GCs) are steroid hormones secreted by the adrenal glands in a circadian fashion, further modulated by ectopic stress signals such as trauma, inflammation, psychological stress or physical exercise [1],[2],[3]. These hormones affect every tissue and organ in the body and thus contribute to maintain overall homeostasis and, importantly, are one of the most potent modulators of the stress response in mammals. Besides the stress mediated effects of the sympathetic nervous system on metabolic alterations that contribute to the etiology of diabetes mellitus, atherosclerosis and cardiovascular disease[4], GCs are among the critical components identified in metabolic disease.

Secretion of GCs from the adrenal cortex is controlled by negative feedback via the hypothalamic pituitary adrenal (HPA) axis. The main regulators of intracellular GC levels are 11 beta-hydroxysteroid dehydrogenase (11beta-HSD) enzymes. Two isoforms of 11beta-HSD have been cloned and characterized[5],[6]. 11beta-HSD1 is an NADP(H)-dependent enzyme that acts primarily as a reductase in intact cells, converting the inactive 11-keto metabolites cortisone (in humans) or 11-dehydrocorticosterone (in rodents) into the active GCs cortisol or corticosterone, respectively. 11beta-HSD1 is expressed in most tissue types and potentiates the action of endogenous GCs by increasing their local concentration. 11beta-HSD2 is an NAD (H)-dependent enzyme that catalyzes the reverse reaction, oxidizing active GCs to their inactive 11-keto forms. Although 11beta-HSD1 is widely expressed, 11beta-HSD2 expression is limited to tissues that express the mineralocorticoid receptor, such as the kidney and gut, as well as to the placenta. By inactivating cortisol, 11beta-HSD2 prevents it from binding to the mineralocorticoid receptor, thus conferring aldosterone specificity on the receptor. In the placenta, the enzyme prevents maternal GCs from reaching the fetal circulation.

The metabolic syndrome is a cluster of cardiovascular risk factors, including visceral obesity, insulin resistance, dyslipidemia, and hypertension. It has been suggested that metabolic syndrome may result from increased intracellular GC tone, as may occur with elevated 11beta-HSD1 activity, and that pharmacologic inhibition of 11beta-HSD1 may alter intracellular GC levels and be therapeutic option for metabolic syndrome[7],[8],[9].

Role of glucocorticoids in metabolic syndrome

The critical role of GCs for mammalian homeostasis is clearly highlighted by the phenotypical changes observed in deficiency to produce these steroids (Addison's disease) and those observed in situations of overproduction (Cushing's disease). Adrenal insufficiency to produce

GCs (caused by destruction of the adrenal gland e.g. by infection, autoimmune disorders, tumor metastases) leads to general weakness, pigmentation of the skin, weight loss and hypotension. In contrast, the systemic high levels of GCs observed in patients with Cushing's syndrome (usually with a pituitary tumor leading to overproduction of ACTH, the hormone controlling GC release and production from the adrenal gland or through pharmacological immunosuppressive treatment with synthetic GCs as in inflammatory disorders or in transplantation settings) show central obesity, insulin resistance, glucose intolerance, behavioral changes, dyslipidemia, and hypertension. The main metabolic effects of GCs in respect to the metabolic syndrome comprise (as the name implies) regulation of fasting blood glucose levels (through hepatic induction of gluconeogenesis enzymes, mainly glucose-6- phosphatase and phosphoenolpyruvate carboxykinase (PEPCK), control of adipocyte proliferation, differentiation and metabolism, control of skeletal muscle insulin sensitivity, and regulation of insulin secretion from the beta-cells of the endocrine pancreas.

The metabolic changes occurring in Cushing's disease are also observed in patients with the metabolic syndrome and constitute independent risk factors for the development of cardiovascular disease[10],[11],[12],[13], still among the most health threatening conditions in western societies and rapidly progressing in third world countries. Importantly, these symptoms are usually reversible in Cushing's disease, upon correction of the primary cause. However, despite extensive efforts, no systemic elevation of GC levels is observed in patients with the metabolic syndrome, an enigma that is solved by the discovery that the GC activating enzyme 11beta-HSD1 is present in adipose tissue or liver, an effect, which locally produces elevated tissue levels of GCs, in the light of normal systemic GC levels.

11beta-HSD1 as an Amplifier Of Glucocorticoid Action

More recently, the focus of attention has moved to 11beta-HSD1. Although this enzyme can catalyze dehydrogenase conversion of cortisol to cortisone *in vitro* when deprived of regeneration of reduced nicotinamide adenine dinucleotide phosphate (NADPH) cofactor, *in vivo* it functions as a predominant, if not exclusive, reductase converting cortisone to cortisol [14, 15,16]. 11beta-HSD1 is most highly expressed in liver, adipose tissue, lung, and areas of CNS [17]. In these sites it is associated with glucocorticoid, not mineralocorticoid, receptors. Because glucocorticoid receptors have relatively low affinity for cortisol, and cortisone levels in blood are relatively constant and even exceed the free levels of cortisol during the diurnal nadir, we hypothesized that the physiological role of 11beta-HSD1 is to maintain adequate activation of

glucocorticoid receptors in sites where this is vital to metabolic function [18].

It follows that increased 11beta-HSD1 activity may generate increased cortisol levels within adipose tissue and liver and thereby promote features of the metabolic syndrome, and that inhibition of 11beta-HSD1 may lower cortisol levels within these tissues and hence be beneficial in the metabolic syndrome. Such changes in tissue cortisol concentrations could occur without any changes in plasma cortisol levels provided the latter are maintained by normal feedback regulation of the HPA axis.

Potential of 11beta-HSD1 in metabolic syndrome

One of the most important discoveries in 11beta-HSD1 research was that the enzyme functions *in vivo* or in cell culture primarily as reductase thus amplifying intracellular cortisol levels [19],[20],[21],[22]. This was further elegantly corroborated by the 11beta-HSD1 knockout mouse (11beta-HSD1-/-) [23], showing that the enzyme is the sole 11-ketosteroid reductase, at least in mice. A logical translation of this concept into first clinical trials using the 11beta-HSD isozyme-unselective inhibitor carbenoxolone showed that 11beta-HSD inhibition indeed might lead to increased hepatic insulin sensitivity in healthy volunteers[24],[25] but also in a small set of diabetic patients. These initial analyses delivered for the first time substantial evidence that inhibition of 11beta-HSD1 might be a useful strategy in the treatment of metabolic disorders such as insulin resistance and possibly obesity. The 11beta-HSD1-/- animals are fertile, reproduce normally and exhibit a normal lifespan [23]. A diabetes-resistant phenotype is only apparent upon challenging by a high-fat diet or stress, showing attenuated responses to these stimuli, with altered glucose levels, fat accumulation and lipid profiles[23],[26],[27]. The hypothalamic-pituitary-adrenal (HPA) axis appears to be disturbed as shown by adrenal hyperplasia, indicating that cortisone reduction by 11beta-HSD1 is also important in the CNS feedback control and HPA axis regulation [23],[28]. Later on, transgenic mice were created with a rat 11beta-HSD1 gene under the control of the promoter of the adipocyte fatty acid binding protein 2 (aP2-11beta-HSD1 mouse;[29]), resulting in 2-3 fold elevated levels of 11beta-HSD1 in visceral adipocytes. This expression level is also observed in several[30],[31],[32],[33,[34]] but not all studies of obese patients[35],[37],[38], or in genetic rodent models of obesity such as the Zucker rat[24],[29]. Association studies suggest a correlation between GC metabolism and obesity markers such as body mass index or waist to hip ratio [40],[41].

A further indication for the significance of 11beta-HSD1 and GCs in visceral fat accumulation is a Cushing patient case with defective peripheral cortisone to cortisol conversion, displaying a non obese phenotype[42]. The aP2-11beta-HSD1 mice have an about 2-fold concentration level of adipose tissue corticosterone compared to wild-type animals, whereas plasma GC

levels are normal .Importantly, these aP2-11beta HSD1 animals show the cardinal symptoms of the metabolic syndrome. They are obese, predominantly through visceral fat accumulation achieved through differential GR distribution in visceral and subcutaneous adipocytes, and display insulin resistance, glucose intolerance, leptin resistance, have elevated free fatty acid and triglyceride levels, and are hypertensive[29],[43]. The arterial hypertension is an effect obtained through activation of the renin-angiotensin-aldosterone system, likely driven by elevated levels of adipocyte derived angiotensinogen [29],[43].

Altered expression levels compared to controls for key molecules such as leptin, adiponectin, resistin, TNF-alpha, UCP and Peroxisome proliferator-activated receptor (PPAR)-gamma were observed [29],[43]. A non-obese phenotype of the metabolic syndrome but with accompanying dyslipidemia and arterial hypertension, caused by hepatic activation of the renin-angiotensin system, was achieved through hepatic overexpression of 11beta-HSD1 using the apoE promoter (apoE-11beta-HSD1 mouse)[44]. These animals display fatty liver and increased hepatic fatty acid synthesis and fatty acid beta-oxidation by upregulation of LXR-alpha and PPAR-alpha mRNA levels, resulting in impaired lipid clearance[44]. This animal line might be useful as a model system for myotonic dystrophia or metabolically obese, but normal weight individuals[44],[45]. Hepatic inhibition of 11beta-HSD1 was achieved in several mouse models of insulin resistance by a first series of selective 11beta-HSD1 inhibitors developed by Biovitrum in Stockholm[46],[47],[48]. Down regulation of hepatic gluconeogenetic enzymes like PEPCK and glucose 6 phosphatase was accompanied by a significant decrease of insulin and glucose levels, as well as lowered cholesterol, triglyceride and free fatty acid levels [46],[47],[48]. Accordingly, these results demonstrated that enzyme inhibition in the liver leads to improved insulin sensitivity and lipid status in the ob/ob, db/db and KKAy animal model systems used [47],[48].

Expression of 11beta-HSD1 in skeletal muscle

The expression of 11beta-HSD1 not only in liver and adipose tissue, but also in skeletal muscle [49],[50],[51] and the endocrine pancreas[52] suggests a critical role of this GC activating system for regulation of overall insulin sensitivity. In skeletal muscle, the interplay between GR alpha and beta isoforms and the expression of 11beta-HSD1 in a study using human myoblast cultures, and the potential consequences for overall insulin sensitivity were presented[49],[50]. Interestingly insulin appears to upregulate 11beta-HSD1 expression level in the presence of unidentified serum factors[49],[50], thereby constituting a feedback control system, in contrast to the insulin effects observed on 11beta-HSD1 expression levels in

liver[21],[22]. Expression of 11beta-HSD1 in skeletal myoblasts was associated with insulin, increased body mass index (BMI) and blood pressure [49],[50] . Taken together, the studies supported the notion that skeletal muscle 11beta-HSD1 contributes to features of the metabolic syndrome and that pharmacological inhibition of 11beta-HSD1 might lead to increased insulin sensitivity mediated in part by increased triglyceride uptake in skeletal muscle.

11beta-HSD1 in pancreatic cells

The presence of 11beta-HSD in pancreatic islets and beta-cells was first established in the ob/ob mouse system[52]. The fundamental role of GC on beta-cell physiology was investigated in several studies, showing that increased glucocorticoid sensitivity leads to inhibition of insulin release[53],[54]. Transgenic mice, overexpressing the GR in beta-cells under the control of the insulin promoter show increased GC sensitivity, and animals ultimately develop diabetes with a decreased capacity in insulin secretion[53],[54] . In several cell culture systems, GCs display profound and complex effects on insulin secretion, with enhancing or inhibiting effects, depending on the experimental conditions [52],[53],[56],[57][58]. In ob/ob mice GCs inhibit insulin secretion[52],[59], further amplified by11 beta HSD1[52]. Blockade by CBX or synthetic selective 11beta-HSD1 inhibitors such as the aryl sulfonamide thiazole BVT2733 enhances glucose stimulated insulin secretion (GSIS) [52],[59].Therefore 11beta-HSD1 might constitute an essential factor for the ability of the endocrine pancreas to adequately secrete insulin, and accordingly could play a role in the pathogenesis of insulin resistance.

A convincing proof of concept that 11beta-HSD1 is a valid target for treatment of the metabolic syndrome was derived from animal models treated with a selective 11beta-HSD1 adamantyltriazol inhibitor developed by Merck[60],[61],[62] . The compound potently inhibits 11beta-HSD1 activity in liver and importantly also in adipose tissue. In diet induced obesity, the compound lowers weight gain, food intake and fat accumulation, and similar to the effects observed with other inhibitors improves insulin sensitivity and lipid profile, e.g. cholesterol, triglyceride and free fatty acid levels [62].Furthermore, in the apoE knockout mouse, the compound dramatically reduces atherosclerotic plaque formation, and for the first time suggests direct beneficial effects of enzyme disease [62]. Since the lipid effects observed were mainly a moderate decrease in lipid levels, these actions on plaque formation are likely to be mediated through direct effects on the complex artheriosclerotic process[62],[63]. Importantly, 11beta-HSD1 expression has been demonstrated in endothelial cells, activated macrophages and smooth muscle cells, and likely involves a yet to be defined role of 11beta-HSD1 in inflammatory mediation of plaque formation[62],[63]. Taken together, all animal and pharmacological

studies carried out thus far support the concept that blockade of 11beta-HSD1 might be a valid, novel approach in the treatment of all facets of the metabolic syndrome.

Potential Effects of 11beta-HSD1 Inhibitors beyond Adipose Tissue and Liver

The widespread distribution of 11beta-HSD1 raises the possibility that target related toxicity will occur in nonmetabolic tissues. For example, 11beta-HSD1 is increased in differentiation of monocytes to macrophages, [64] and lack of glucocorticoid action within macrophages may be deleterious in inflammation. 11beta-HSD1 is also expressed in vascular smooth muscle.[65] Although 11beta-HSD1 null mice have normal vascular contractile and relaxant function[66]. Recent findings shown lack of glucocorticoid regeneration within the vessel wall removes an angiostatic "brake."[67] As a result, enhanced angiogenesis may occur during 11beta-HSD1 inhibition which may be beneficial in healing of wounds, and may even improve myocardial recovery after ischemia,[67] but might also allow unrestrained angiogenesis, for example, in diabetic retinopathy. The expression of 11beta-HSD1 in the central nervous system, particularly in hippocampus, offers both opportunities and threats for the success of 11HSD1 inhibitors. The concern has been that inhibition of hippocampal 11beta-HSD1 may reduce negative feedback suppression of the HPA axis, resulting in a compensatory increase in plasma cortisol which overcomes the benefits of peripheral 11beta-HSD1 inhibition. However, although 11beta-HSD1 null mice do have a subtle elevation in plasma glucocorticoid levels,[68] they retain the beneficial effects of 11beta-HSD1 inhibition in peripheral tissues. 11beta-HSD1 null mice are protected from cognitive dysfunction with aging [69] and administration of carbenoxolone (100 mg, orally, three times per day for 4 weeks) to humans enhances cognitive performance [70] on balance, inhibition of 11beta-HSD1 in CNS appears to be beneficial rather than deleterious.

Role of 11HSD1 in Inflammatory Regulation

Inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor -α (TNF-α), upregulate 11beta-HSD1 expression in a number of different cells[14]. In monocytes, 11beta-HSD1 increases in association with differentiation into competent phagocytic macrophages [26]. These observations are consistent with 11beta-HSD1 playing a role in amplifying local glucocorticoid concentrations within the site of injury or infection, operating in addition to the activation of the HPA axis which accompanies systemically important inflammation. Obesity has been described as an inflammatory state, and it is possible that increased activity of immune cells within adipose tissue underlies the upregulation of 11beta-HSD1 which

accompanies obesity. This remains, however, a speculation.

Nutritional Regulation of 11beta-HSD1

A number of hormones which respond to nutritional status also influence 11beta-HSD1, including insulin,[78],[27] growth hormone and insulin-like growth factor-1 (IGF1)[28]. In addition, PPAR[30],[31] and liver X receptor (LXR) agonists[32] alter 11beta-HSD1 expression, consistent with a response to variations in fatty acids and/or oxysterols. Furthermore, variations in glucose flux may affect H6PDH activity and hence 11beta-HSD1 equilibrium. Few direct experiments to test the effects of nutritional status on 11beta-HSD1 *in vivo* have been published. Morton *et al*. showed that high fat feeding of mice down regulated 11beta-HSD1 in adipose tissue [33]. Leptin administration to ob/ob mice also upregulates liver 11beta-HSD1, although it is not clear whether this is a direct effect of leptin or an indirect effect of weight loss [79]. In humans, weight loss has variably been reported to increase [80] or decrease [81] adipose 11beta-HSD1; it is possible that this discrepancy reflects the different dietary exposure of subjects at the time that biopsies were taken. In mice, sensitivity of 11beta-HSD1 to regulation by dietary fat predicts susceptibility to diet-induced obesity [33]. It is an intriguing possibility that the primary purpose of 11beta-HSD1 is to facilitate appropriate adaptations to variations in diet, and that dysregulation of this response underlies increased 11beta-HSD1 in adipose tissue in obesity.

Further indications for selective 11beta-HSD1 inhibition

Besides the potential beneficial use of selective 11beta-HSD1 inhibitors to treat insulin resistance, obesity, dyslipidemia and cardiovascular disease, several studies suggest further potential applications, as outlined in the following subchapters. Some of these applications, namely the GC amplification effects by 11beta-HSD1 on the CNS and in glaucoma, appear to be rather validated, whereas several others, e.g. the role of 11beta-HSD1 in immunity and inflammatory processes clearly deserve further investigation and experimental efforts.

Glucocorticoids and the CNS: the Role of 11beta-HSD1 in Ageing and Neurodegeneration:

GCs exert a multitude of effects on the central nervous system affecting among others neurotransmitters, receptors, ion channels and metabolism[82],[83],[84]. Chronically elevated levels of GCs clearly impair neuropsychiatric functions and can lead to dysfunctions such as depression, anxiety, psychosis or euphoria. Thus considerable evidence exists which links GCs with cognitive functions and the neuroendocrine axis[82],[83],[84]. A highly sensitive site for GC effects is the hippocampus, a brain structure necessary to integrate multiple neuroendocrine,

cognitive and affective signals. Expression of 11beta-HSD1 in the central nervous system was shown to be mainly restricted to the hippocampus, cerebellum and the cortex[85],[86],[87]. The first experiments demonstrating a possible role of 11beta-HSD1 inhibition in blocking neurotoxicity were performed using primary cultured cells derived from fetal rat hippocampus, and it was shown that CBX inhibition of 11beta-HSD1 was able to prevent kainic acid induced neurotoxicity[88]. Further insight was obtained from 11betaHSD-/- animals, showing that aged wild-type animals show GC associated, hippocampal driven, significant learning and memory impairments in the water maze test[89] . Importantly, aged knock-out animals perform not significantly different in these tests than young wild-type or young knockout animals, suggesting that hippocampal 11beta-HSD1 inhibition might show significant effects and protects against ageing related loss of cognitive functions[89]. The potential benefit of 11beta-HSD1 inhibition in CNS relates to the fact that glucocorticoid action in the hippocampus and elsewhere impairs short-term memory. Indeed, in a double-blind, placebo controlled crossover study with healthy volunteers and diabetic patients (age matched, 52-75 years of age), administration of CBX (100 mg/ 3 times/day) resulted in significant improvement of verbal fluency and memory function after 4 weeks of treatment[90]. The recently described rare haplotype discovered in the regulatory region of the 11beta-HSD1 gene [91] was associated with a 6-fold increased risk for sporadic Alzheimer's disease, adding a further piece of evidence to the role of GCs and their metabolic activation in cognitive function. Importantly, an undisclosed compound from a recently developed selective inhibitor series by Merck (unpublished data) shows similar positive effects in animals subjected to passive avoidance or novel object recognition tests, suggesting that applications of selective 11beta-HSD1 inhibitors indeed go well beyond the treatment of the metabolic syndrome.

Role of 11beta-HSD1 in Glaucoma

Increase in intraocular pressure can be provoked by ocular or systemic administration of GCs, and furthermore, patients with primary open angle glaucoma exhibit increased GC sensitivity[92],[93]. Expression of 11beta-HSD1 has been shown in nonpigmented epithelial cells of the ciliary body, the site of aqueous humor production[92],[93], likely to be the reason for the observed increased cortisol:cortisone ratio in humor. Topical administration of the 11beta-HSD inhibitor CBX lowers intraocular pressure in healthy volunteers and patients with ocular hypertension, pointing to a potential novel application for 11beta-HSD1 inhibitors [92],[93].

Inflammation and Immunity: What is the Function of 11beta-HSD1 in the Immune System?

Since their introduction into clinical medicine GCs almost 50 years ago [94] GCs have been a cornerstone in the treatment of chronic inflammatory diseases such as rheumatoid arthritis, asthma bronchiale and autoimmune diseases or are used in transplantation settings to prevent graft versus host disease[1],[2],[3],[95],[96]. Consequently, much has been learned about the underlying pathophysiological mechanisms by the use of synthetic GCs. GCs exert potent effects on the immune system and it now appears to be oversimplified that GCs have merely an anti-inflammatory or immunosuppressive profile[97],[98]. The dogmatic viewpoint of immunosuppressive GC action appears to be supported by the fact that GCs have been mainly used in pharmacological i.e. supraphysiological doses. Many recent studies however suggest that the role of GCs on the immune system is extremely complex and shows a time, dose, compound and context dependent pattern of reactions on critical cells of the immune system[97],[98]. It appears that inflammatory processes are regulated in a time dependent manner and controlled by synergistic and antagonistic actions of GCs and cytokines. As discussed in two overviews [97],[98], GCs upregulate the expression of IL-6 receptors, the signal transduction component gp13, of IL-1 receptors or can promote release of inflammatory signals such as TNF α, IL-6 or macrophage migration inhibitory factor[97],[99]. Thus it appears that GC effects are rather immunoregulatory than only immunosuppressive. Furthermore GCs are intimately linked to their capacity to alter specifically the secretion pattern of cytokines associated with inflammatory and immune processes [97]. GCs modify the Th1-Th2 cytokine profile by favouring a Th2 profile and might represent an important determinant for the development of a specific Th1/Th2 pattern in inflammatory situations. Not unexpectedly, 11beta-HSD1 is expressed at important sites of inflammatory responses. Whereas peripheral lymphocytes appear to be devoid of 11beta-HSD isozymes [100], enzymatic activity and expression of 11beta-HSD1 was noted in stromal cells of lymphoid tissues[101], in activated monocytes or in dendritic cells[102]. Thus far the use of inhibitors of 11beta-HSD enhanced the local effects of GCs in patients with psoriasis or eczema[103] or decreased resistance to experimental Listeria infections[104]. Taken together, modulation of local activation of GC activation in immune tissues by 11beta-HSD inhibitors might offer the exciting possibility to selectively drive and direct immune responses [97],[98],[102], but final proof of concept for this hypothesis is still missing and experiments in several laboratories are currently underway.

Glucocorticoid Induced Osteoporosis: Does 11beta-HSD1 Play a Role?

Chronic exposure of endogenous and synthetic GCs has fundamental effects on bone structure and function [105], with osteopenia, osteoporosis and increased risk

for bone fractures as well recognized consequences. These detrimental effects are potentially reversible at least in part, and amenable to treatment e.g. by use of bisphosphonates [106]. GCs exert multiple effects on bone cells, by increasing bone resorption and decreasing bone formation, however the underlying mechanisms are at present far away from being completely understood. The potential impact of 11beta-HSD expression in bone cells[13],[107],[108],[109] was addressed in some studies. Short-term inhibition with CBX in healthy volunteers had no effect on bone formation markers, whereas a suppression of bone resorption markers was noted[108]. It was proposed that expression of 11beta-HSD1 in osteoblasts affects proliferation and differentiation and due to predominant reductase activity in intact cells constitutes a risk factor in age related decrease in bone formation and increased risk for GC induced osteoporosis [108]. Somewhat surprising was the lack of a clear bone phenotype in the 11beta-HSD1-/- mouse model. The animals exhibited no significant changes in cortical or trabecular bone mass, and aged animals show similar levels of bone loss compared to matched control animals[109], however, a complete absence of bone marrow adipocytes was noted. Clearly further studies are necessary to determine the role of 11beta-HSD isozymes and potential pharmacological intervention of 11beta-HSD inhibition in bone tissue.

RESULT AND DISCUSSION

As discussed in this overview selective inhibition of 11beta-HSD1 could in principle offer unprecedented and unique opportunities to improve all symptoms of the metabolic syndrome, which taken together, constitute independent risk factors for the development of cardiovascular disease. Due to the central role of GCs in control of metabolism and the function of 11beta-HSD1 as a pre-receptor control of the GR, tissue selective blockade could be a general principle to improve insulin sensitivity, lower lipid levels, regulate fat accumulation and decrease arterial hypertension, the cardinal features of the metabolic syndrome. Clearly, further innovative approaches are needed besides the established pharmacological principles of e.g. PPAR alpha and PPAR gamma agonists to lower lipids or increase insulin sensitivity in order to combat the consequences of the world wide dramatic increase in obesity and diabetes. In fact, several of the beneficial effects observed with fibrates or thiazolidine-diones might be due to their potential to down regulate 11beta-HSD1 in liver or adipose tissue. Moreover, the tight connection between lipid and glucose metabolism[72],[73] might be linked through the LXR-GR-11betaHSD1 axis[71]. Blockade of the hepatic GR to increase insulin sensitivity and lower blood glucose have been shown to be a valid concept in the treatment of diabetes[74],[75],[76],[77] and at least in several animal models a variation of this theme by

inhibition of hepatic 11beta-HSD1 has been shown effective[47],[48] .Targeting of hepatic 11beta-HSD1 might thus be a valid principle in lean diabetic individuals or in a subset of obese patients with elevated hepatic GC reamplification[27] .However, in several, but not all studies of human obesity hepatic expression of 11beta-HSD1 is apparently down regulated and might therefore not be the primary target for treatment of insulin resistance and hyperglycemia[77] . Immunogenic 11beta-HSD1 models, adipocyte 11beta-HSD1 plays the central role in mediating features of the metabolic syndrome and therefore might constitute the prime pharmacological target. Human idiopathic metabolic syndrome is undoubtedly more complex in terms of GC amplification [35],[36],[30],[38]. This is further corroborated by a recent mouse model of obesity and insulin resistance[27] ,with elevated hepatic 11beta-HSD1 activity but decreased adipose 11beta-HSD1 levels, indicating that such a pattern of GC amplification might exist in human idiopathic obesity as well. Hence it is clearly mandatory to investigate further patient populations to illuminate the role of GC amplification by 11beta-HSD1, determine the status of 11beta-HSD1 expression and address the suitability of 11beta-HSD1 inhibitor therapy.

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