REVIEW

Clinical implications of glucocorticoid metabolism by 11 β -hydroxysteroid dehydrogenases in target tissues

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Abstract

11 β -Hydroxysteroid dehydrogenases (11 β -HSD) are microsomal enzymes that catalyze the conversion of active glucocorticoids (GC) to their inactive 11-dehydro products and vice versa. Two isoenzymes of 11 β -HSD have been characterized and cloned in human tissues. The tissue-specific metabolism of GC by these enzymes is important for mineralocorticoid (MC) and GC receptor occupancy and seems to play a crucial role in the pathogenesis of diseases such as apparent MC excess syndrome, and may play roles in hypertension, obesity and impaired hepatic glucose homeostasis. This article reviews the literature and examines the role and importance of 11 β -HSD in humans.

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Introduction

Glucocorticoid (GC) and mineralocorticoid (MC) receptors (GR, MR) belong to the family of intracellular hormone-binding receptors. Whereas GR are expressed in nearly every organ (1, 2), MR were initially believed to be restricted to epithelial cells in organs regulating sodium transport, although they are also widely distributed throughout the body in many organs, such as kidney, intestine, salivary glands, arteries, lung, heart and parts of the brain (3–6). Due to their lipophilic structure, steroids can penetrate the cell membrane and reach intracellular receptors.

In the classical MC target organs, aldosterone, and only to a small extent GC such as cortisol or corticosterone, activate MR. When MR are isolated and purified, or expressed in COS cells, they show *in vitro* the same affinity for cortisol and corticosterone as for aldosterone (7). The unbound plasma cortisol concentration, which is approximately 100 times higher than that of aldosterone, suggests that there is a gatekeeper *in vivo* that excludes cortisol from MR and allows aldosterone to bind to MR.

The solution to this paradox is the tissue-specific steroid metabolism of GC by 11 β -hydroxysteroid dehydrogenases (11 β -HSD) (8, 9). These microsomal enzymes catalyze the conversion of 11-hydroxysteroids (e.g. cortisol) to 11-ketosteroids (e.g. cortisone) and vice versa (10). Steroids with a keto group at position 11 (e.g. cortisone) show low affinity for GR (11) or MR (12), and show little or no transactivation activity (13–16). The oxidation of cortisol to cortisone by 11 β -HSD is thus an inactivation of the steroid, while the

reduction of cortisone to cortisol is an activating step. Aldosterone is not metabolized by 11 β -HSD due to its aldehyde group at position C18, which, in aqueous solutions, forms an 11,18-hemiacetal or 11,18,20-hemiketal bridge (17).

This interconversion of 11-hydroxy- and 11-oxosteroids by 11 β -HSD explains the observation in the late 1940s that cortisone is not effective when injected directly into a joint, but is systemically effective in rheumatic diseases when given orally (18, 19). Cortisol, which was available shortly afterwards, had an effect following either topical or oral application. The intracellular cortisol/cortisone equilibrium regulated by 11 β -HSD seems thus to be as important as the plasma concentration of cortisol, which represents the extracellular supply of GC.

To date two 'isoenzymes' of 11 β -HSD, which belong to the superfamily of short-chain alcohol dehydrogenases, have been characterized and cloned in human tissues (20, 21). Due to their differences, they should be regarded as separate enzymes and not as isoenzymes. These enzymes differ from each other also in their tissue distribution and function and play a crucial role for the intracellular organ-specific GC concentration.

Tissue distribution, functions and regulation of 11 β -HSD isoforms

11 β -HSD-type 1

GR are expressed ubiquitously, and 11 β -HSD-type 1 enzyme is also localized in numerous tissues, such as the liver, testis, ovary and lung (1) (Table 1). In classical

MC target tissues like the kidney, salivary glands and distal colon, the expression of 11 β -HSD-type1 gene is low (22). The enzyme exhibits bidirectional catalytic properties (reduction and oxidation) *in vitro*, but *in vivo* it seems to function mainly as a reductase (Fig. 1) converting the inactive 11-dehydro-GC cortisone to the active 11-hydroxy-GC cortisol with NADPH as co-substrate (23–25). This leads to an increased GC activity in cells that express 11 β -HSD-type1 gene, and could thus be essential for cells which require high GC concentrations even during periods of low plasma cortisol. Hence, 11 β -HSD-type1 contributes to the supply of active GC for GR (26). On the other hand, 11 β -HSD-type1 is regulated itself by GC, which increase the enzyme activity (23, 27).

In the liver, 11 β -HSD-type1 activity is very high around the hepatic central vein, while in the areas of the hepatic artery, portal vein and bile duct the expression is low (1, 28). Catheterization studies in patients are in accordance with this distribution, finding a much higher cortisol/cortisone ratio in the hepatic vein compared with the portal vein. This activation of GC has pharmacological importance: inactive GC like cortisone and prednisone given orally are activated by the liver to the potent 11-hydroxy-GC cortisol and prednisolone (10). In situations that call for high amounts of active GC, such as stress, 11 β -HSD-type1 can be a second source of cortisol ‘production’ in addition to the adrenal glands. In the liver, 11 β -HSD-type1 regulates paracrine/autocrine effects of GC, such as the stimulation of gluconeogenic enzymes (29). In an 11 β -HSD-type1 knockout mouse, it was shown that homozygous mice could not activate GC, had an intrahepatic GC deficiency, and therefore demonstrated weaker activation of gluconeogenesis enzymes, resulting in blunted hyperglycemia provoked by stress or obesity (29).

A further important function of 11 β -HSD-type1 in the liver, but probably also in the lung, seems to be the detoxification of tobacco-specific nitrosamines (e.g. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) by carbonyl reduction as first-step metabolism followed by glucuronidation (30–32).

Recently it has been demonstrated that GC enhance the differentiation of preadipocytes into adipocytes. Mature adipocytes express 11 β -HSD-type1 activity, which leads to an increase in local GC concentration and further expansion of adipose tissue. This mechanism seems to be most effective in omental adipose tissue and may be important for the pathogenesis of central obesity (33, 34).

11 β -HSD-type1 is also expressed in placental decidua. In the mother, the enzyme seems to be important for guaranteeing enough active GC to maintain a local immunosuppressive effect for the blastocyst implantation and an immunological tolerance of the alien tissue (35–37).

In fetal lung, 11 β -HSD-type1 plays an important role in converting inactive to active GC, which are important for the induction of surfactant-phosphatidylcholine synthesis in type 2 pneumocytes in the process of lung maturation (38).

11 β -HSD-type1 is also expressed in adrenal cortex. The most intense staining is found in the inner zones, and it is not found in adrenal medulla. It has been suggested that the reduction of cortisone to cortisol at the adrenal cortico–medullary junction is important for the induction of adrenaline synthesis (28) (Table 1).

11 β -HSD-type2

11 β -HSD-type2 enzyme is expressed in classical MC target tissues, such as kidney, salivary glands, ileum and distal colon, and in placenta (22, 39, 40). The enzyme acts as an exclusive dehydrogenase for endogenous steroids (cortisol, corticosterone) (Table 1), metabolizing the active 11-hydroxysteroids to their inactive 11-ketosteroids, thus protecting MR from high GC concentrations (8, 9). When this protective mechanism is disrupted, cortisol can bind to MR and acts as a potent MC (Fig. 2).

In the kidney, cortical and medullary collecting ducts are the structures which show highest expression of 11 β -HSD-type2 (41), although the enzyme is also detectable by immunostaining in distal convoluted tubules, in thin and thick branches of Henle’s loop,

Table 1 Characteristics of 11 β -HSD isoenzymes type1 and 2.

	11 β -HSD-type1	11 β -HSD-type2
Enzyme kinetics	<i>In vitro</i> bidirectional, <i>in vivo</i> mainly reductase Low substrate affinity (K_m -value in the μ mol/l range) NADP/H preference	Only dehydrogenase activity for endogenous steroids High substrate affinity (K_m -value in nmol/l range) NAD ⁺ preference
High expression	Liver, lung, gonads, pituitary, brain	Kidney, colon, salivary glands, placenta
Molecular biology	Chromosome 1 Gene: 9 kb length, six exons Enzyme: 292 amino acids, 34 kDa Only 14% homology with 11 β -HSD-type2	Chromosome 16 Gene: 6.2 kb length, five exons Enzyme: 405 amino acids, 40 kDa 35% homology with 17 β -HSD/KSR-type2
Function <i>in vivo</i>	Alteration of intracellular GC concentration, organ-specific enhancement of GC effect	Protection of MC receptor from cortisol

KSR = ketosteroid reductase.

Figure 1 Redox equilibrium of corticosteroids catalyzed by human kidney 11 β -HSD-type2 (A) and liver 11 β -HSD-type1 (B). In the kidney (A), the preferred reaction for natural (unhalogenated) steroids (e.g. cortisol) is oxidation, whereas for fluorinated steroids (e.g. dexamethasone) it is reduction. In the liver (B), 11 β -reduction is preferred for natural and fluorinated steroids.

and in vascular smooth muscle cells (39, 40). In the latter, 11 β -HSD-type2 seems to modulate the response of resistance vessels to GC by regulating catecholamine sensitivity (42–44). Positive immunostaining for 11 β -HSD-type2 is found in surface and crypt colonic epithelial cells (41), and in striated ducts of the salivary glands (39). In the skin, 11 β -HSD-type2 is located only

in eccrine sweat glands, whereas sebaceous or apocrine glands are devoid of this 'gatekeeper enzyme' (45).

In the placenta, 11 β -HSD-type2 is located in the syncytial trophoblast cells (fetal origin) that protect the fetus from high maternal GC concentrations (4, 39, 46, 47), whereas the human decidual cells, formed from endometrial stromal cells (maternal origin), express

11 β -HSD-type1. Expression of 11 β -HSD-type2 in syncytial trophoblast cells seems to be ideal for this protective function, because they cover placental chorionic villi, thus forming an interface between the maternal and fetal circulation. Isotope studies have shown that the majority of circulating cortisol in the human fetus is derived from the fetal adrenal gland and not from maternal sources (48). As maternally administered dexamethasone is significantly less metabolized by 11 β -HSD-type2 than is cortisol (49–51), this synthetic steroid can be used successfully to enhance fetal lung maturation, because it crosses the placenta largely unmetabolized. In the past the placenta was not believed to express MR; very recently, however, new evidence for placental MR expression has been presented (52).

11 β -HSD-type2 is also detected in human lung epithelia and in epithelia of the trachea and bronchioli, where it seems to be co-localized with MR and may play a role in sodium and fluid transport of the airway epithelia, especially in the fetus (53).

11 β -HSD-type2 is expressed in only some brain areas, such as the commissural portion of the nucleus tractus solitarius, the subcommissural organ and the ventrolateral ventromedial hypothalamus. MR expression matches 11 β -HSD-type2 expression only in the ventrolateral ventromedial hypothalamus (54). The function of 11 β -HSD-type2 in regions without MR is not understood at present.

Recently it was shown that the enzyme is a strong reductase for synthetic 9-fluorinated 11-ketosteroids (dehydrodexamethasone and 9 α -fluorocortisone) (51, 55–57) (Fig. 1). These properties do not have physiological significance, but may be of pharmacological relevance.

11 β -HSD-type1: clinical implications

The function of 11 β -HSD-type2 is well understood, whereas the role of 11 β -HSD-type1 has been less well examined. The preferred reaction *in vivo* of 11 β -HSD-type1 is the reduction of 11-dehydro-GC to their active 11-hydroxy-GC (Fig. 1). This may be important for maintaining basal metabolic functions, especially at the diurnal nadir of GC secretion (58).

To examine the importance of this enzyme *in vivo*, mice with targeted disruption of 11 β -HSD-type1 gene were generated. These 11 β -HSD-type1 knockout mice were unable to convert 11-dehydrocorticosterone to corticosterone (29, 59). As compensation for this defective 'generation system', the homozygotic mice showed increased adrenocorticotrophic hormone (ACTH) and corticosterone levels, and developed adrenal hyperplasia. They showed lower fasting serum glucose concentrations and an expanded reservoir of hepatic glycogen (60). On starvation, they appeared to be deficient in hepatic gluconeogenic responses (attenuated activation of the key hepatic

gluconeogenic enzymes glucose-6-phosphatase and phosphoenolpyruvate carboxykinase), presumably because of relative intrahepatic GC deficiency. The knockout mice seemed to have an increased insulin sensitivity, similar to that of humans after inhibition of 11 β -HSD-type1 with carbenoxolone (61). 11 β -HSD-type1-deficient mice resisted hyperglycemia provoked by obesity or stress (29).

Abnormalities of 11 β -HSD-type1

Until now four patients with possible 11 β -HSD-type1 reductase deficiency have been described (62–66). They were all women with hirsutism and acne and adrenal androgen excess. Due to deficiency of 11 β -HSD-type1, reduction of cortisone to cortisol was impaired. Consequently, urinary excretion of cortisone metabolites was increased and urinary excretion of cortisol metabolites reduced. The lack of hepatic production of active GC seems to lead to a state of systemic GC deprivation and to increased hypophyseal ACTH production, which could explain adrenal enlargement and the increased androgen secretion in these patients. The patients were screened for mutations in the 11 β -HSD-type1 gene, but none were found, suggesting that the defect might not be in the coding region of the 11 β -HSD-type1 gene. The most sensitive parameter of this disorder is the urinary ratio of (5 α -tetrahydrocortisol (THF)+5 β -THF)/tetrahydrocortisone (THE), which is below 0.8–1.0 in 11 β -HSD-type1 reductase deficiency. After suppression of endogenous steroid secretion with dexamethasone, patients with 11 β -HSD-type1 deficiency showed decreased reduction of orally given cortisone, resulting in an impaired increase of plasma cortisol concentration (66).

Recently a patient with 21-hydroxylase deficiency (adrenogenital syndrome (AGS)) and 11 β -HSD-type1 reductase deficiency was described. 11 β -HSD-type1 deficiency was discovered when cortisone acetate treatment of the patient with AGS was not successful. Treatment with prednisolone and cortisol, however, was successful in decreasing the elevated 17-OH-progesterone and androgen plasma concentrations (67).

A mild defect in cortisone to cortisol conversion has also been described in some women with polycystic ovary syndrome and may play a role in the hyperandrogenemia in this syndrome (68).

Diabetes mellitus

Inhibition of hepatic 11 β -HSD-type1 increases insulin sensitivity in humans *in vivo*. Experiments in rats showed that hepatic 11 β -HSD-type1 inhibition by estradiol caused a reduced expression of GC-inducible genes such as phosphoenolpyruvate carboxykinase, the key enzyme of gluconeogenesis (69). This suggests that hepatic 11 β -HSD-type1 plays an important role in

maintaining expression of key GC-regulated hepatic genes and in hepatic glucose homeostasis.

On the other hand, an inappropriate increase in hepatic 11 β -HSD-type1 activity could be a contributing factor in central insulin resistance syndromes, including type 2 diabetes mellitus. An increased local hepatic cortisol concentration could lead to increased gluconeogenesis and attenuated insulin sensitivity. In contrast to the situation in patients with type 2 diabetes, Dullaart *et al.* (70) reported a decreased (5 α -THF + 5 β -THF)/THE urinary ratio in patients with type 1 diabetes, which indicates an attenuated 11 β -HSD-type1 activity. Furthermore, a reduced 5 α -reductase activity due to a decreased 5 α -THF/5 β -THF ratio was suggested.

Recently it was demonstrated that growth hormone (GH) inhibits hepatic 11 β -HSD-type1 via insulin-like growth factor-I (24, 71). If GH levels decrease, the hepatic reduction of cortisone to cortisol increases and could lead to an elevated glucose output by the liver and to central obesity. Approximately 25% of patients with acromegaly have impaired glucose tolerance that seems to be due to a post-insulin receptor effect of GH itself. However, patients with adult GH deficiency may also exhibit central obesity and insulin resistance (72), which may be caused by increased 11 β -HSD-type1 activity and enhanced conversion of cortisone to cortisol in the liver (71, 73).

The role of 11 β -HSD-type1 in the pathogenesis of diabetes mellitus is still unclear and needs further investigation.

Central obesity

GC regulate the differentiation and function of adipocytes, with expression of 11 β -HSD-type1 higher in omental than in subcutaneous adipocytes. The enzyme shows predominantly reductase activity, and its expression is increased by GC. As differentiation of stromal cells of adipose tissue into mature adipocytes is promoted by GC and insulin, it has been suggested that overactivity of 11 β -HSD-type1 in omental adipose tissue may be one factor that enhances central obesity (33, 34, 74), an important risk factor for premature mortality due to cardiovascular disease, diabetes mellitus, hypertension and hyperlipidemia. Although it has been suggested that patients with central obesity might benefit from selective inhibition of 11 β -HSD-type1 (33, 61), central obesity (visceral or omental obesity) is a more complex problem.

In gynoid obesity (hip and thigh fat) the urinary ratio of (5 α -THF + 5 β -THF)/THE shows a direct relation to the body mass index (BMI), supporting the hypothesis of an enhanced activity of 11 β -HSD-type1 in adipose tissue. In android obesity (scapular and waist fat), on the other hand, the urinary ratio of (5 α -THF + 5 β -THF)/THE is inversely related to BMI, suggesting an inhibited 11 β -HSD-type1 (73, 75).

The distribution of 11 β -HSD-type1 in adipose tissue and the autocrine generation of active cortisol by 11 β -HSD-type1 may therefore be of critical importance in explaining the different effects of GC on various adipose tissues. Furthermore, it is possible that 11 β -HSD-type1 of the omentum and the liver are regulated in different ways.

11 β -HSD-type2: clinical implications

Apparent MC excess syndrome

In the early 1970s, case reports were published describing children with the features of MC hypertension (hypokalemia, low plasma renin, very high blood pressure, plus successful treatment with spironolactone), plus weakness and failure to thrive (76, 77), with no elevated levels of aldosterone or deoxycorticosterone found (78). Therefore, this syndrome was named 'apparent MC excess' (AME) syndrome. The steroid analysis of this syndrome revealed a prolonged half-life of plasma cortisol (120–190 min compared with 80 min in healthy subjects) and an elevated ratio of cortisol metabolites over cortisone metabolites in the urine (79). It was concluded that AME is caused by a defect in 11 β -HSD-type2 leading to an unprotected MR and binding of cortisol to MR, resulting in a 'hyper-mineralocorticoid status by normal plasma cortisol concentrations'. After cloning of 11 β -HSD-type2, this hypothesis was proven by the discovery of mutations in the 11 β -HSD-type2 gene in patients with AME syndrome. Two mutations were compound heterozygotes with each allele coding for an enzyme devoid of activity (80, 81); all other mutations found were homozygous (82, 83). The autosomal-recessive AME syndrome is the third monogenic form of hypertension with Liddle's syndrome (84) and dexamethasone-suppressible hyperaldosteronism (85). To date approximately 50 patients with AME syndrome have been described. Because the syndrome is so rare, homozygous mutations of 11 β -HSD-type2 enzyme probably do not have an epidemiological relevance for the pathogenesis of 'essential' hypertension.

The characteristic urinary steroid metabolite profile is essential for the diagnosis of AME. The prolonged plasma cortisol half-life can be measured easily with 11 α -tritium-labeled cortisol, but this has not become routine. The urinary ratio of ring-A-reduced metabolites of cortisone and cortisol ((5 α -THF + 5 β -THF)/THE) is not a sensitive marker for 11 β -HSD-type2 deficiency, since this ratio largely reflects the activity of hepatic 11 β -HSD. In addition, in AME other unexplained abnormalities of cortisol metabolism are described (e.g. defective 5 β -reductase). Therefore, the urinary ratio of free cortisol to free cortisone seems to be the most sensitive and reliable parameter for AME.

AME can be treated with triamterene and/or amiloride, but most physicians and patients use

spironolactone. Dexamethasone has been reported to be effective in some patients, but not in others (58, 86). In a case report, Palermo *et al.* (87) described cure of AME by kidney transplantation. The main aim of therapy should be correction of hypokalemia and lowering blood pressure.

'Essential' hypertension

There are numerous clinical studies examining the role of 11 β -HSD-type2 in essential hypertension. Recently, a new polymorphic restriction site in exon 3 in the human 11 β -HSD-type2 gene was described. This was associated with end-stage renal disease in Caucasians, but not with hypertension (88). Another group used an 11 β -HSD-type2 polymorphic microsatellite marker and studied this polymorphism in normotensive and hypertensive subjects and hypertensive sibling pairs, but they found no connection to essential hypertension (89). Earlier studies examining urinary steroid metabolites (indicating an 11 β -HSD-type2 insufficiency) had given inconsistent results (90–92).

There are many publications on the association of decreased placental 11 β -HSD-type2 activity with an increased risk of adult hypertension. The placental 11 β -HSD-type2 seems to have a regulatory effect on fetoplacental growth and differentiation, supported by a direct correlation between 11 β -HSD activity and birth weight and an inverse relation between 11 β -HSD and placenta weight (93, 94). The hypothesis derived from these findings suggests that higher GC levels during fetal life, due to an impaired activity of placental 11 β -HSD-type2, could lead to programming of hypertension in adult life (95–97). This hypothesis was questioned by the finding that no correlation existed between 11 β -HSD-type2 mRNA concentrations in the placenta and fetal or placental weight (98).

Another possible mechanism of hypertension is the modulation of active GC concentration by 11 β -HSD in vascular smooth muscle cells (43). Topical application of GC to the skin causes a vasoconstriction of arterioles (42). This effect is enhanced by addition of 11 β -HSD inhibitors, suggesting an involvement of 11 β -HSD in the regulation of vascular tone by the amplification of responses to vasoconstrictors (44, 45, 99, 100).

In the brain, 11 β -HSD-type2 is not co-localized with MR in all areas, which suggests a different role for MR in the brain, such as in the central regulation of blood pressure; these receptors seem to be occupied by GC. Furthermore, it has recently been suggested that MC could be synthesized *de novo* in the brain (101). Further research and studies are necessary to evaluate the role of 11 β -HSD-type2 and MC in the brain and in hypertension.

Pre-eclampsia

Pre-eclampsia, defined as hypertension, edema and proteinuria in the third trimester of pregnancy, is

associated with enhanced sodium retention. Inhibition of 11 β -HSD-type2 by some unknown factor (102) and a subsequently increased intracellular cortisol concentration could be one explanation for MR downregulation (103), with decreased plasma renin substrate and serum aldosterone (104–106) in pre-eclampsia. Progesterone and its renal metabolites are inhibitors of 11 β -HSD-type2 (102). An altered progesterone metabolism in the kidney could play a role in the pathogenesis of pre-eclampsia. This hypothesis seems to be supported by the finding that the urinary free cortisol/free cortisone ratio is elevated in patients with pre-eclampsia, compared with women whose pregnancy is normal (107).

Licorice consumption

In the early 1950s, Molhuysen (108) described an MC-like effect of licorice consumption. Licorice, produced from the licorice plant (*Glycyrrhiza glabra*), contains glycyrrhetic acid and its glucuronide glycyrrhizin, which have a low affinity for MR (109), but a high affinity for 11 β -HSD enzymes (110). 11 β -HSD-type2 is inhibited by glycyrrhetic acid. The first recognizable effects on blood pressure, serum potassium and plasma renin appear if the daily consumption of glycyrrhetic acid ranges from a minimum of 225 mg (111) to 380 mg (112). Although the content of glycyrrhetic acid and glycyrrhizin varies in different licorice products, 200–400 mg glycyrrhetic acid roughly corresponds to about 100–200 g of 'normal' licorice. In Germany, the recommended maximum content is 200 mg/100 g, but some products contain 700 mg/100 g (113) or more (*Der Spiegel* 27/1998: up to 2650 mg/100 g). The clinical signs resemble those of AME: low renin and aldosterone, hypokalemia, increased sodium retention and an elevated cortisol/cortisone ratio in urine (113–115). Carbenoxolone, the hemisuccinate derivative of glycyrrhetic acid, has been used in the therapy of gastric ulcers and shows similar side-effects to licorice if used in concentrations above 300 mg/day.

Ectopic ACTH syndrome

More often than in other forms of Cushing's syndrome (10% of patients), the ectopic ACTH syndrome leads to hypokalemic alkalosis (95–100% of patients), and reveals higher plasma cortisol and ACTH concentrations (116, 117). Several investigations showed that ACTH infusions, but not cortisol infusions, elevated the cortisol/cortisone urine (118) and plasma ratio in healthy volunteers (119). It was shown that ACTH had no direct effect on 11 β -HSD-type2, but that the enzyme is overloaded by ACTH-dependent 11 β -HSD substrates such as cortisol, corticosterone and 18-hydroxycorticosterone (120, 121). Therefore, in severe hypercortisolism

Figure 2 The MC receptor (MC-R) binds aldosterone (Aldo) and cortisol (F) with equal affinity. The renal 11 β -HSD-type2 guarantees the selectivity of the MC-R for aldosterone. (A) In normal subjects cortisol is converted by 11 β -HSD-type2 into cortisone (E), which does not bind to the MC-R. Aldo is not metabolized by 11 β -HSD-type2 and binds to the MC-R. (B) In patients with AME syndrome or acquired 11 β -HSD-type2 deficiency (licorice, carbenoxolone), cortisol (F), whose plasma levels are nearly 100-fold higher than those of Aldo, becomes a potent MC.

(like ectopic ACTH syndrome), cortisol is the MC causing hypokalemia and hypertension.

Synthetic steroids and their metabolism by 11 β -HSD-type2

11 β -HSD regulate the access of active steroids to MR, but also to GR. During GC therapy they may play an

important role in the local regulation of the GC. To achieve an optimal local renal immunosuppression in renal transplant recipients, it would be necessary to use a GC that is not oxidized (= inactivated) by renal 11 β -HSD-type2. 9 α -Fluorinated steroids, such as 9 α -fluorocortisol and dexamethasone, are much less oxidized to 11-oxo-steroids than cortisol in the human kidney (51, 55, 56). Furthermore, 9-fluorination shifts the reaction

equilibrium of 11 β -HSD-type2 towards reduction. The consequence is a conversion of an inactive 9-fluorinated 11-dehydrosteroid (e.g. 11-dehydrodexamethasone (11-DH-D)) to an active 11-hydroxysteroid (dexamethasone) in the kidney (51, 56, 122). These observations explain the greatly enhanced MC effect of 9 α -fluorocortisol and the strong GC effect of dexamethasone. In the placenta, 11 β -HSD-type2 metabolizes dexamethasone to 11-DH-D, but also converts 11-DH-D back to dexamethasone (56, 57), which explains why 9 α -fluorinated synthetic steroids cross the placenta as active steroids (Fig. 2).

Conclusions

The tissue-specific metabolism of GC by 11 β -HSD is important for MR and GR activity. 11 β -HSD-type2 inactivates cortisol to cortisone in MC target cells, thus allowing almost selective binding of aldosterone to MR. Impaired 11 β -HSD-type2 leads to clinical symptoms of MC excess (hypokalemic hypertension), in which cortisol is acting as an MC.

11 β -HSD-type1 reduces cortisone to cortisol, producing active GC and regulating both intracellular GC concentration and GR occupancy. This tissue-specific regulation seems to be physiologically important, especially during the nadir of diurnal rhythmic alteration of plasma cortisol concentrations. In the liver, 11 β -HSD-type1 is involved in glucose homeostasis. The modulation of GC homeostasis by 11 β -HSD-type1 seems to play an important role in several disease processes, such as diabetes mellitus and obesity. Hopefully, further investigations will contribute to the understanding of these regulatory mechanisms.

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