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Review

The role of 11β-hydroxysteroid dehydrogenase in the pathogenesis of hypertension

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Abstract

The two 11β-hydroxysteroid dehydrogenase (11β-HSD) isozymes catalyze the interconversion of cortisol and cortisone. Type 1 11β-HSD (11β-HSD1) has bidirectional activity, while type 2 11β-HSD (11β-HSD2) mainly converts cortisol into cortisone. Of these two hormones only cortisol has affinity to mineralocorticoid receptors (MRs) and thus induces mineralocorticoid effects. A normal activity of 11β-HSD2 is crucial for prevention of mineralocorticoid activity of cortisol. Absent or decreased 11β-HSD2 activity results in cortisol-mediated hypermineralocorticoid hypertension. In several hypertensive syndromes a decreased 11β-HSD2 activity has been described as the pathogenetic mechanism of the increased blood pressure. In the apparent mineralocorticoid excess (AME) syndrome type 1, absence of 11β-HSD2 activity is caused by mutations in the gene coding for 11β-HSD2. In licorice-induced hypertension glycyrrhetinic acid, the active substituent of licorice, inhibits 11β-HSD2 resulting in an acquired hypermineralocorticoid state. 11β-HSD2 activity is not decreased in glucocorticoid hypertension (Cushing's syndrome). In essential hypertension some evidence for decreased systemic and skin activity of 11β-HSD1 and/or 11β-HSD2 has been found, while renal activity of both isozymes appears to be normal. 11β-HSD2 activity is also present in cardiovascular myocytes of humans and dogs, and inhibition of 11β-HSD potentiates the vascular response to catecholamines. Although MRs in the central nervous system have been incriminated in the pathogenesis of mineralocorticoid hypertension, a pathophysiological role for 11β-HSD2 has not yet been described. Finally, in the placenta 11β-HSD2 reduces fetal exposure to maternal glucocorticoids and a decreased activity of this isozyme may result in low birth weight and increased risk of high blood pressure at adult age. © 1998 Elsevier Science B.V.

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In the majority of patients with hypertension the cause is not known. In the last few years several studies have suggested a role for the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) in the pathogenesis of hypertension. In this paper we review the function of this enzyme under normal conditions and in various forms of secondary hypertension like the Apparent Mineralocorticoid Excess (AME) syndrome and licorice-induced hypertension. The potential role of 11β-HSD in the pathogenesis of glucocorticoid and, in particular, primary hypertension is discussed. Furthermore the relation between primary hypertension and the activity of 11β-HSD in cardiovascular tissues, the

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central nervous system and in the placenta will be reviewed.

1. Physiological function of 11β-hydroxysteroid dehydrogenase

The 11β-HSD isozymes catalyze the dehydrogenation of the naturally occurring glucocorticoids cortisol and corticosterone to their inactive 11-keto products cortisone and 11-dehydrocorticosterone as well as the reverse reductive reaction. The isozymes are present in many tissues, but their activity is not uniformly distributed [1]. Originally 11β-HSD was considered to be one single enzyme. Later two independent isozymes were identified, called 11β-HSD1 and 11β-HSD2 [2].

The isozyme 11β-HSD1 has first been cloned and sequenced in the rat [3] and later also in man [4]. It is ubiquitously present, e.g. in liver, lungs, gonads, hippocampus, cerebellum, pituitary gland and also in the proximal renal tubules [1,5,6]. The gene for 11β-HSD1 has been located on chromosome 1 [4]. This isozyme is NADP(H)-dependent and catalyzes both dehydrogenation and reduction [7,8]. In vitro both reactions are inhibited by glycyrrhetinic acid (GA), an important compound of licorice, and by its hemisuccinate carbenoxolone. A slightly higher GA concentration is necessary for inhibition of reductase- than for inhibition of dehydrogenase-activity [9]. In the liver 11β-HSD1 predominantly converts cortisone to cortisol.

The second isozyme, 11β-HSD2, is a high affinity NAD-dependent enzyme that is highly expressed in mineralocorticoid target tissues such as renal cortex, in particular distal tubules and collecting ducts [10], and medulla [8], rectal and sigmoid colon [8,11], salivary glands [12] and sweat glands [13]. It is also present in the adrenals and in the organs of the female reproductive system (ovary, oviduct, uterus, and placenta) [12,14]. The gene coding for 11β-HSD2 activity, HSD11B2, has been cloned in sheep [15], mouse [13], rabbit [16], rat [17] and in the human where it is located on chromosome 16 [11]. While the isozyme has generally been located in the microsomes, recent studies have also demonstrated presence of 11β-HSD2 in cell nuclei [18,19]. This isozyme has mainly dehydrogenase activity and is already active at very low cortisol concentrations. The Michaelis–Menten constant for 11β-HSD2 is 50–60 nmol [8,12], compared to 17 μmol for 11β-HSD1 [20].

11β-HSD2 plays a key role in regulating mineralocorticoid activity of glucocorticoid hormones. In-vitro experiments have shown that cortisol and aldosterone have similar affinities for mineralocorticoid receptors (MR) [21], so their functional aldosterone selectivity in vivo is apparently not mediated by the receptor structure. Yet, MRs are protected from exposure to cortisol by the isozyme 11β-HSD2. This isozyme rapidly metabolizes the active mineralocorticoid cortisol to its inactive metabolite cortisone. The physiological relevance of this enzyme for the regulation of blood pressure and potassium balance was demonstrated in studies in patients with apparent mineralocorticoid excess (AME) [22] and in licorice-induced hypertension [23]. In these patients renal activity of 11β-HSD2 is decreased.

In studies on *renal* 11β-HSD2 activity, analysis of urinary corticosteroid excretion played an important role. In the kidney cortisol is metabolised to cortisone. Cortisol can be reduced to tetrahydrocortisol (THF) and allo-tetrahydrocortisol (allo-THF), and cortisone to tetrahydrocortisone (THE) (Fig. 1: left panel). Therefore decreased renal 11β-HSD2 activity will result in an increased urinary (THF + allo-THF)/THE ratio and access of cortisol to the

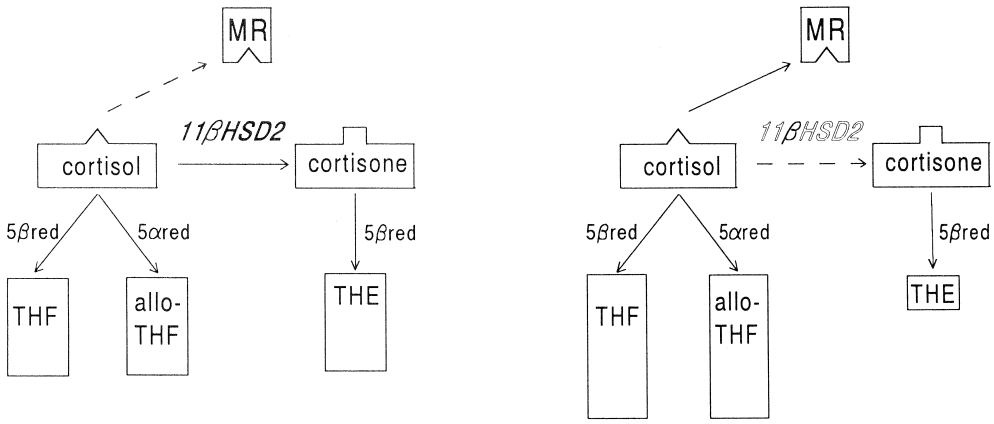

Fig. 1. Under physiological conditions (left panel) cortisol (F) is metabolised to cortisone (E) by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). As a consequence the mineralocorticoid receptor (MR) will not be exposed to relevant cortisol concentrations. When 11β-HSD2 activation is reduced, either congenitally (AME syndrome) or by inhibition by glycyrrhetinic acid, cortisol is not completely metabolised to cortisone and therefore activates the MR (right panel). Urinary excretion of cortisol and its tetrahydrometabolites (THF and allo-THF) is increased while excretion of cortisone and its tetrahydrometabolite THE is decreased. This results in increased ratio of (THF + allo-THF) to THE, reflecting decreased renal activity of 11β-HSD2. 5αred = 5α-reductase; 5βred = 5β-reductase.

renal MR (Fig. 1: right panel). Some of the studies involved will be discussed in more detail below

Conversion of cortisol to cortisone has also been demonstrated in cardiovascular cells [24]. In rats, activity of 11β-HSD is found in cardiac myocytes and fibroblasts, and in vascular smooth muscle cells, but not in endothelial cells [25–27]. The enzyme activity is NADP-dependent and bidirectional [28], indicating type 1 isozyme activity. While cardiac activity of 11β-HSD type 1 is high in species in which corticosterone is the predominant glucocorticoid (rats, pigs and rabbits), it is low in species in which cortisol is the major glucocorticoid (humans and dogs) [29]. Indeed, in human cardiomyocytes activity of 11β-HSD is mainly dependent on NAD, suggesting activity of type 2 isozyme [30]. Both vascular smooth muscle cells and skin arterioles express 11β-HSD2 [31,32].

Specific binding of aldosterone has been found in human heart [33] and cultured human arterial smooth muscle cells [34]. In more detailed immunohistochemical studies, MRs were localized in cardiac myocytes and fibroblasts, vascular smooth muscle cells and in cardiac and vascular endothelial cells [35,36]. These MRs can be activated by aldosterone. This hormone is not solely produced by the adrenals. Recently, synthesis of aldosterone has also been described in cultured human vascular endothelial and smooth muscle cells [37,38]. In both species aldosterone production was increased by AngII and potassium, and decreased by angiotensin-converting enzyme (ACE) inhibition. Adrenocorticotropic hormone (ACTH) regulates adrenal aldosterone synthesis, but it does not affect vascular aldosterone production [39]. This is explained by the finding that mitochondrial P-450 scc (the enzyme that regulates conversion of cholesterol to pregnenolone in an ACTH-dependent way) is absent in vascular cells, while it is the key enzyme for regulating corticosteroid synthesis in the zona glomerulosa of the adrenals [40].

Activity of 11β-HSD has also been demonstrated in the central nervous system. In studies in rat brains the highest NADP-dependent (type 1) enzyme activity was described in hippocampus, cortex, pituitary, hypothalamus, brain stem and spinal cord [41,42]. Expression of 11β-HSD type 2 mRNA was clearly found in the commissural portion of the nucleus tractus solitarius, the subcommissural organ and the ventrolateral ventromedial hypothalamus [43], areas in the brain that are known to be involved in cardiovascular regulation mechanisms [44]. It is not clear whether MRs in the brain are protected by 11β-HSD2. Although the isozyme is present in the brain and administration of inhibitors of 11β-HSD2 activity results in hypertension, intracerebroventricular (icv) infusion of corticosterone does not increase but decrease blood pressure, and blood pressure does not change during administration of RU28318, a specific mineralocorticoid antagonist [45,46].

Finally, expression of 11β-HSD2 mRNA and isozyme activity have been demonstrated in the placenta of rats and humans [12,14]. In contrast to the 11β-HSD2 expressing tissues that have been discussed previously, mineralocorticoid receptors have not been demonstrated in the placenta. Therefore the isozyme does not serve as a protector against cortisol-mediated activation of MR, but it regulates fetal exposure to maternal glucocorticoids [47].

2. Apparent mineralocorticoid excess syndrome

In the 1970s a new hypertensive syndrome consisting of hypertension, hypokalaemia, low renin activity and *low* aldosterone production was described [22]. Additional clinical features were short stature, polyuria, polydipsia and failure to thrive. More than 20 cases with this syndrome, mainly children, have been published [48,49]. Sometimes hypertensive retinopathy and cardiomegaly were already discovered at a very young age, and four patients died before the age of 15 as a result of complications of hypertension or hypokalaemia [48,50]. Clinical and biochemical findings suggested overproduction of an (unknown) adrenal mineralocorticoid, but circulating cortisol was normal and no other steroid could be identified. Therefore the syndrome was described as the Apparent Mineralocorticoid Excess (AME) syndrome [51]. Administration of hydrocortisone (= cortisol) aggravated the condition [52], while dexamethasone administration [suppression of adrenocorticotropic hormone (ACTH)] normalized hypokalaemia and blood pressure. The AME syndrome responded to spironolactone, a MR blocker. Amiloride had some effect but potassium supplements were still required [53]. Further studies showed that conversion of plasma 11α[^{3}H]cortisol to tritiated water and cortisone was reduced and urinary (THF + allo-THF)/THE ratio was increased [54]. These data suggested that the syndrome was caused by decreased activity of 11β-HSD resulting in activation of the MR by cortisol. This form of AME was called type 1. Apart from the decreased 11β-HSD activity it seems that 5β-reductase activity [measured by ratio of 5α- (including 5α-THF) to 5β-metabolites in urine] is also decreased in this syndrome [50]. The clinical relevance of the decreased 5β-reductase activity is however not clear.

In recent years studies on HSD11B2, the gene coding for 11β-HSD2 activity, confirmed that type 1 AME syndrome is caused by reduced 11β-HSD2 activity. Genetic analysis has been done in 22 patients out of 17 families. In 15 families homozygote mutations in HSD11B2 were found. In one family a compound heterozygote was found while in the remaining family no mutation was identified [55,56]. The mutations result in a premature stop codon or a change in amino acid sequence. When genes carrying the mutations were expressed in cultured chinese hamster ovary cells the activity of 11β-HSD2 in these cells was considerably decreased ranging from 0.4 to 82% of activity in cells transfected with a normal gene [57]. The inheritance of AME1 is autosomal recessive. Studies in parents of a child with AME1 revealed that in the heterozygote state blood

pressure is not increased and urinary steroid profiles were normal [58]. The gene for 11β-HSD1 is normal in patients with AME1 [59]. The AME type I syndrome is one of the few examples of human hypertension caused by a single gene defect.

Ulick and colleagues described a second form of AME, called AME type 2. In four patients with this variant no evidence for severely impaired activity of 11β-HSD2 or 5β-reductase was found [60]. As the total amount of THF + allo-THF in urine was low compared to urinary cortisol it was concluded that in these patients the metabolic inactivation of cortisol by ring A reduction is impaired [61]. Walker et al. have suggested that in AME type 2 both 11-dehydrogenase and 11-reductase activity are reduced [62]. No molecular analysis of this syndrome has been published.

An other inheritable hypertensive syndrome with signs of hypermineralocorticoid activity that can also be relieved by dexamethasone is glucocorticoid-remediable aldosteronism (GRA) [63,64]. In contrast to the AME syndrome, aldosterone secretion rate is increased in GRA and is regulated by ACTH [65]. Severe hypertension is most commonly discovered in infancy or early adulthood. Usually many family members are affected due to autosomal dominant inheritance [66]. GRA is probably caused by a mutation in chromosome 8q, resulting in fusion of the regulatory region of 11β-hydroxylase to the coding sequences of aldosterone synthase [67]. Thus aldosterone synthase is expressed in the ACTH regulated zona fasciculata, explaining the increased synthesis of aldosterone and two abnormal adrenal steroids, 18-oxocortisol and 18-hydroxycortisol [68]. The resulting mineralocorticoid excess state suppresses physiological aldosterone synthesis in the zona glomerulosa.

3. Licorice-induced hypertension

Excessive consumption of licorice or its active component GA may result in severe hypertension, hypokalaemia and other signs of mineralocorticoid excess [69]. In some cases the hypokalaemia has resulted in rhabdomyolysis and/or tetraparesis [70,71]. In the Netherlands the average yearly licorice consumption is 2.2 kg per person (approximately 450 mg GA), but individual consumption probably varies considerably, just as reported in Denmark [72] and New Zealand [73]. The effects of licorice become visible after 3–10 days and are usually reversible in several weeks. However, suppression of the renin angiotensin-system has been described for up to four months after cessation of consumption [71]. Just as in AME syndrome, licorice-induced hypertension and hypokalaemia are cortisol-dependent and respond to spironolactone [74]. Further, consumption of GA or licorice results in increased cortisol/cortisone ratio in plasma and urine [23,75]. This suggested that licorice-induced hypertension is caused by decreased 11β-HSD2 activity. In in vitro studies both GA and carbenoxolone inhibit activity of this isozyme in a dose-dependent manner. In rat kidney microsomes 70% inhibition of isozyme activity was found after addition of GA 20 nM or carbenoxolone 16 nM. However, in intact renal cortical tubules substantially higher GA concentrations (10^{-4} to 10^{-6} M) were required for 11β-HSD2 inhibition [76]. In contrast to GA, carbenoxolone also inhibits 11β-HSD1 [77].

In a study in volunteers no change of plasma potassium, aldosterone and PRA was found during GA intake of 217 mg/day, but a decrease of these parameters was clearly present at 813 mg/day. Increased blood pressure was only found in 2 out of 12 volunteers in the high dose group [78]. This study suggests that licorice-induced effects in humans are dose-dependent, but a direct relation between plasma GA concentration and changes in blood pressure, plasma cortisol/cortisone ratio or potassium has not been published. A review by Størmer et al. shows that adverse effects of licorice have been reported after daily GA intake ranging from 0.01 to 4 g. A daily intake of 10 mg GA (±5 g licorice) is regarded as a safe dose for most healthy adults [79]. The wide variability of GA effects may be explained by individual variation in the effects of mineralocorticoids, the renal mineralocorticoid escape [80,81], variation in bioavailability of GA or by individual variation in sensitivity of 11β-HSD2 to GA. In conclusion licorice consumption can result in decreased 11β-HSD2 activity resulting in hypertension and hypokalaemia due to cortisol-mediated activation of the MR.

4. Activity of 11β-HSD in glucocorticoid induced hypertension

Hypertension occurs in approximately 75% of patients with Cushing's syndrome [82]. In 20% of patients treated with oral glucocorticoids hypertension was found [83], the incidence of hypertension probably being dose-dependent. Several studies were done to investigate the activity of 11β-HSD2 in patients with Cushing's syndrome. The urinary ratio of (THF + allo-THF)/THE was increased in these patients, suggesting decreased 11β-HSD2 activity. The ratio was highest in patients with Ectopic ACTH syndrome [84,85]. Further, infusion of ACTH in dexamethasone-treated normal volunteers resulted in increased cortisol/cortisone ratio. However, an inhibitory effect of ACTH on 11β-HSD2 could not be confirmed by in vitro experiments in human kidney slices [86]. Further it was shown that while the (THF + allo-THF)/THE ratio was increased in patients with Cushing's syndrome, the total THE excretion was not decreased, but increased, suggesting that 11β-HSD2 is quite active [84,85]. Therefore it seems that in patients with Cushing's syndrome absolute 11β-HSD2 activity is not decreased, but that the enzyme

capacity is overwhelmed by the increased cortisol concentration resulting in only relatively reduced renal conversion of cortisol to cortisone.

5. The possible role of 11β-HSD2 in the pathogenesis of primary hypertension

Already 35 years ago it was described that in hypertensive patients plasma cortisol levels and urinary excretion of cortisol are normal [87], so cortisol was thought not to play a significant role in the pathogenesis of essential hypertension. However, while treatment with the synthetic glucocorticoid dexamethasone in a dose of 0.5 mg/day (suppressing adrenal corticosteroid production) did not change blood pressure in normotensive volunteers, it resulted in a fall in supine blood pressure in patients with essential hypertension [88]. In the absence of increased circulating concentrations of adrenal corticosteroids, the tissue effects of these hormones may be increased due to reduced 11β-HSD2 activity. Therefore the possible role of decreased 11β-HSD, in particular type 2, activity in the pathogenesis of essential hypertension was investigated in several studies.

Analysis of the corticosteroid excretion pattern in a group of 68 hypertensive patients provided evidence for small but significantly decreased activities of both 11β-HSD2 and 5β-reductase compared to a control group [89]. In another study in 128 patients with essential hypertension and 39 normotensive controls analysis of urinary glucocorticoid metabolites suggested normal renal 11β-HSD2 activity in the hypertensive group [90]. Takeda et al. studied 30 patients with low-renin essential hypertension and 20 normotensive controls. Plasma aldosterone and urinary (THF + allo-THF)/THE ratio were not different between both groups [91]. In a study on the plasma half-life of 11α[^{3}H]cortisol, no difference was found between 20 patients with essential hypertension and 19 matched healthy controls. The plasma half-life of 11α[^{3}H]cortisol was prolonged in a subgroup of patients, suggesting decreased 11β-HSD activity [92]. However, the urinary (THF + allo-THF)/THE ratio was normal and no hypokalaemia or other signs of increased renal mineralocorticoid receptor activation were found. Therefore, the decreased 11β-HSD activity in this subgroup of patients with essential hypertension is probably extra-renal. The half-life of 11α[^{3}H]cortisol was also prolonged in 4 patients continuing effective antihypertensive medication, thus it is unlikely that the decrease in 11β-HSD activity was induced by the hypertension per se. It seems that renal activity of 11β-HSD2 is normal in patients with essential hypertension.

Other studies focused on 11β-HSD activity in the skin. Vasoconstriction by glucocorticoids in the skin can be measured by applying glucocorticoids to the forearm skin and measuring the intensity of the vasoconstriction the next day. In a study using this assay in healthy normotensive volunteers, the skin vasoconstrictor sensitivity to glucocorticosteroids was increased by oral administration of GA, probably mediated by inhibition of 11β-HSD activity [93]. Compared to a group of healthy volunteers, skin dermal vasoconstriction on topical glucocorticoids was increased and mean half-life of 11α[^{3}H]cortisol was prolonged in a group of hypertensive patients. However the increased skin vasoconstrictor response was not significantly correlated to the increased half-life of 11α[^{3}H]cortisol and was also present on beclomethasone, a glucocorticoid that is not metabolized by 11β-HSD [94].

Corticosteroids have been reported to potentiate vascular responses to catecholamines [95]. In volunteers carbenoxolone, an inhibitor of 11β-HSD type 1 and 2, orally for 7 days potentiated vascular reactivity to noradrenaline (NA). Both forearm vasoconstriction to intra-arterial NA and the pressor response to systemic NA were enhanced [96]. The effect of inhibition of 11β-HSD on vascular reactivity has not been studied in patients with essential hypertension. Also no studies have been performed to compare the vascular activity of 11β-HSD in hypertensive patients with that in healthy volunteers.

As mentioned before, both 11β-HSD activity and MRs have been found in the brain. In rats icv infusion of aldosterone for 14 days resulted in elevation of systolic blood pressure, while no pressor effect was found when the same dose of aldosterone was infused subcutaneously [97]. A similar effect of aldosterone was found in both salt-replete and salt-depleted dogs [98]. Administration of carbenoxolone, both orally and icv, and oral GA also increased blood pressure. This could be completely prevented by RU28318 icv [45]. Interestingly, the development of hypertension in rats receiving aldosterone icv was prevented by bilateral adrenalectomy but could be restored by systemic administration of corticosterone [99]. This indicates that mineralocorticoid receptors in the central nervous system may participate in the pathogenesis of mineralocorticoid hypertension. A pathogenetic role of cerebral 11β-HSD2 remains to be established.

Some studies focused on the relation between 11β-HSD2 activity in the placenta and primary hypertension. As already mentioned, 11β-HSD2 activity in the placenta regulates fetal exposure to maternal glucocorticoids. Increased fetal exposure to glucocorticoids inhibits fetal growth in rats and humans [100]. In epidemiologic studies an inverse relation between birth weight and adult blood pressure was found [101,102]. Thus it was hypothesized that decreased placental 11β-HSD2 activity results in increased fetal exposure to maternal glucocorticoids, low birth weight and subsequent hypertension at adult age [103]. Indeed in both rats and humans a positive correlation between placental 11β-HSD2 activity and fetal weight was found [104,105]. Administration of dexamethasone (which is not metabolised by 11β-HSD2 and passes the placenta) to pregnant rats resulted in 20% reduction in

birth weight and significantly increased systolic blood pressure in offspring, while blood pressure of the mothers was not changed [105]. Further, administration of carbenoxolone to pregnant rats also reduced birth weight and elevated blood pressure in offspring [106]. Thus, decreased placental 11β-HSD2 activity may result in glucocorticoid-mediated reduction in birth weight and in an increased risk of hypertension at adult age.

Finally some evidence for a role of 11β-HSD2 in the pathogenesis of essential hypertension was found in a study on genetic markers in black subjects. An association was found between D16S496 (a microsatellite marker flanking 11β-HSD2) and essential hypertension [107]. These results have not been confirmed by other studies and the clinical relevance needs to be established.

In conclusion, activity of 11β-HSD2 is crucial for prevention of mineralocorticoid activity of cortisol. Absent or decreased renal 11β-HSD2 activity results in mineralocorticoid hypertension both in AME syndrome type 1 and during excessive consumption of licorice. The isozyme does not play a role in glucocorticoid hypertension. In patients with essential hypertension some evidence for decreased systemic and skin activity of 11β-HSD has been found, while renal activity seems normal. In vascular myocytes inhibition of the enzyme results in increased vascular response to catecholamines, but this has not been studied in patients with essential hypertension. MRs in the central nervous system may participate in the pathogenesis of mineralocorticoid hypertension, but a role of cerebral 11β-HSD2 is unknown. Finally in the placenta 11β-HSD2 does not protect mineralocorticoid receptors but reduces fetal exposure to maternal glucocorticoids. Decreased isozyme activity may result in low birth weight and high blood pressure at adult age.

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