

Hypertension and the Cortisol-Cortisone Shuttle

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11 β -Hydroxysteroid dehydrogenase type 2 (11 β -HSD2) plays a crucial role in converting hormonally active cortisol to inactive cortisone, thereby conferring specificity on the mineralocorticoid receptor. Mutations in the gene encoding 11 β -HSD2 (HSD11B2) account for an inherited form of hypertension, the syndrome of apparent mineralocorticoid excess, in which cortisol induces hypertension and hypokalemia. A similar clinical picture to apparent mineralocorticoid excess occurs after the ingestion of licorice and carbenoxolone, which are competitive inhibitors of 11 β -HSD2. Reduced 11 β -HSD2 activity may explain the increased sodium retention in preeclampsia, renal disease, and liver cirrhosis. Substrate sat-

uration of 11 β -HSD2 occurs in Cushing's syndrome and explains the mineralocorticoid excess state that characterizes ectopic ACTH syndrome. Polymorphic variability in the HSD11B2 gene in part determines salt sensitivity, a forerunner for adult onset hypertension. Furthermore, reduced placental 11 β -HSD2 expression might underpin the Barker hypothesis, the epidemiological link between reduced birth weight and adult hypertension. At a prereceptor level, 11 β -HSD2 plays a key role in normal physiology in the corticosteroid regulation of sodium homeostasis and pathophysiology of hypertension. (*J Clin Endocrinol Metab* 88: 2384–2392, 2003)

CIRCULATING LEVELS OF adrenal corticosteroids are involved in blood pressure regulation. Their importance is highlighted by pathophysiological situations such as Cushing's syndrome with increased cortisol secretion resulting in hypertension and Addison's disease with inadequate corticosteroid production causing life-threatening hypotension.

Over the last decade, it has emerged that cortisol can also exert deleterious effects on the cardiovascular system at an autocrine level. This occurs despite normal circulating cortisol concentrations in the setting of an alteration in cortisol metabolism.

Two distinct isozymes of 11 β -hydroxysteroid dehydrogenase (11 β -HSD) catalyze the interconversion of hormonally active cortisol and inactive cortisone (Fig. 1; Refs. 1–3). In human tissues, the type 1 enzyme (11 β -HSD1) is widely distributed but most abundant in liver and adipose tissue. It functions mainly as an oxidoreductase converting cortisone to cortisol. Conversely, in adult tissues the type 2 isozyme (11 β -HSD2) is found predominantly in mineralocorticoid target tissues, kidney, colon, and salivary gland, where it serves to protect the mineralocorticoid receptor (MR) from glucocorticoid excess (Fig. 1). The MR has the same affinity for cortisol and aldosterone *in vitro* (4), and the inactivation of cortisol to cortisone by 11 β -HSD2 at the site of the MR enables aldosterone to bind to this receptor *in vivo* (Fig. 2; Refs. 5 and 6). Aldosterone is not metabolized by 11 β -HSD2 because it forms a C₁₁-C₁₈ hemi-ketal group in aqueous solution.

This review discusses the role of the cortisol-cortisone shuttle in human hypertension.

The syndrome of apparent mineralocorticoid excess (AME)

Clinical features. In the 1970s, case reports emerged of children with features of mineralocorticoid hypertension (low-renin, hypokalemia) but low levels of aldosterone and deoxycorticosterone (7–9), hence the term "apparent mineralocorticoid excess." Worldwide, less than 100 cases have been reported (10, 11). Presentation is usually in childhood with low birth weight, failure to thrive, short stature, and severe, often fatal, hypertension with hypokalemic metabolic alkalosis. The profound hypokalemia may cause rhabdomyolysis and nephrogenic diabetes insipidus manifesting as thirst and polyuria. Other renal abnormalities include renal cysts and nephrocalcinosis and can lead to renal insufficiency. The severe hypertension is associated with end organ damage of retina, kidney, central nervous system, and cardiovascular system, including left ventricular hypertrophy. Several cases with affected siblings have been reported, and the condition is inherited as an autosomal recessive condition.

Biochemical abnormalities comprise suppressed plasma renin activity, undetectable serum aldosterone levels and hypokalemia. Urinary steroid metabolite profiles indicate that the majority of cortisol metabolites are excreted as A-ring reduced metabolites of cortisol itself [5 β -tetrahydrocortisol (THF) and 5 α -THF or allo-THF] with very low or absent levels of tetrahydrocortisone (THE) in the urine (Fig. 3). The excretion of 5 α -cortisol metabolites exceeds that of 5 β -cortisol metabolites and results in a high urinary allo-THF/THF ratio, suggesting an additional defect in 5 β -reductase activity (12, 13). The incremental increase in the THF+allo-THF/THE compared with the allo-THF/THF ratio, however, is much larger, with typical THF+allo-THF/THE ratios ranging from 6 to greater than 70 in AME (normal ratio is approximately 1). The THF+allo-THF/THE ratio has historically been used in the diagnosis of AME (12, 13), but probably provides an index of global 11 β -HSD activity within the body, *i.e.* principally 11 β -HSD1 in the liver and

Abbreviations: AME, Apparent mineralocorticoid excess; 11 β -HSD, 11 β -hydroxysteroid dehydrogenase; icv, intracerebroventricular; MR, mineralocorticoid receptor; THE, tetrahydrocortisone; THF, 5 β -tetrahydrocortisol; UFE, urinary free cortisone; UFF, urinary free cortisol.

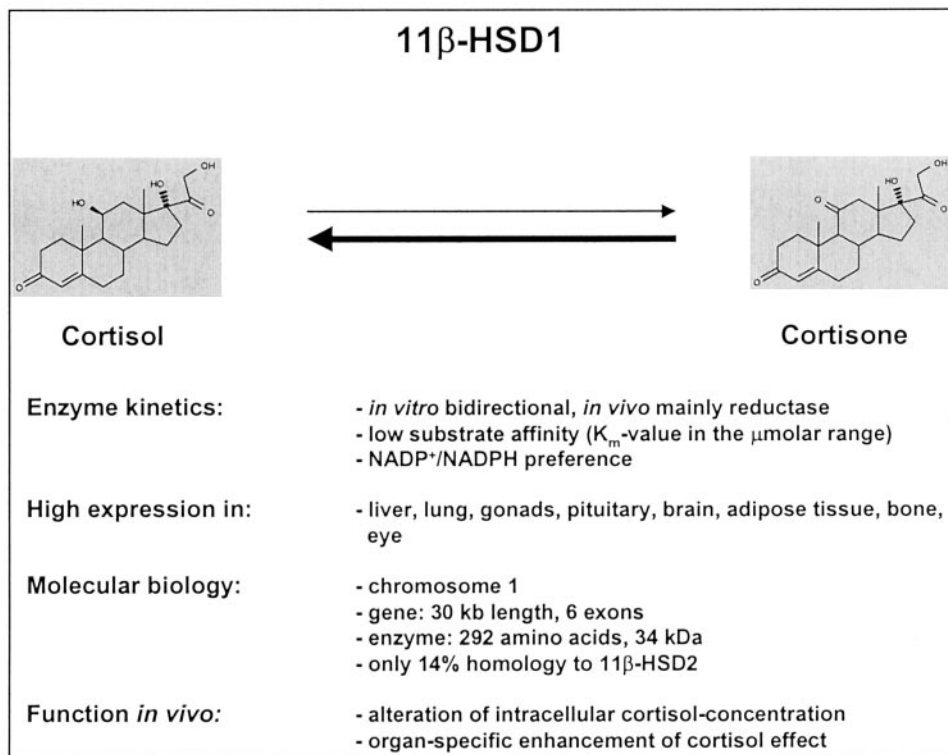
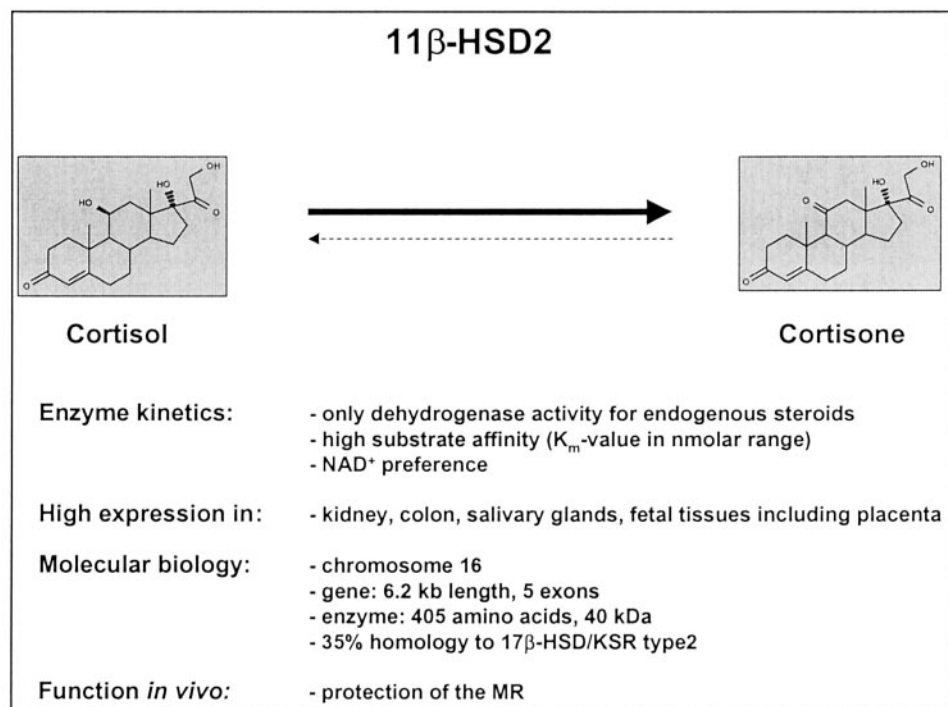


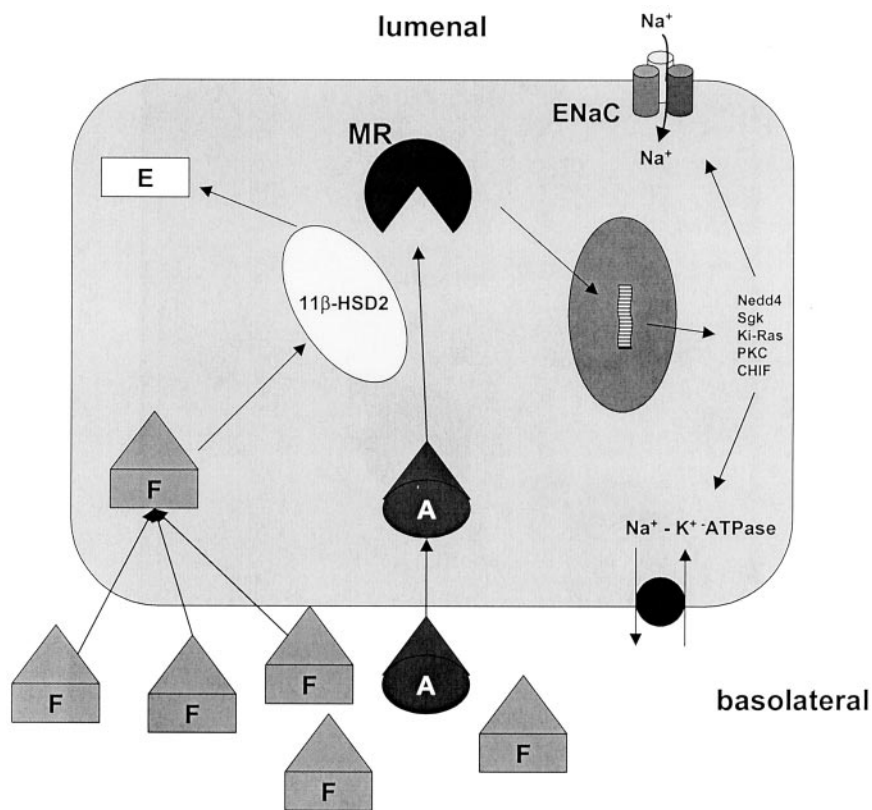
FIG. 1. Characteristics of 11 β -HSD isoenzymes.



11 β -HSD2 in the kidney. The conversion of cortisone to cortisol mediated by 11 β -HSD1 is normal in AME (9, 14). The plasma half-life of [11-³H]cortisol (which when metabolized by 11 β -HSD yields tritiated water and cortisone) may more accurately reflect renal 11 β -HSD2 activity (9, 14), as may the ratio of urinary free cortisol (UFF)/urinary free cortisone (UFE) (15). Normal subjects excrete 2- to 3-fold more UFE

than UFF, reflecting the significant activity of renal 11 β -HSD2. In AME, however, UFE excretion is virtually undetectable (15), resulting in a high UFF/UFE ratio. Plasma cortisol half-life is prolonged (120–190 min *vs.* 70–90 min in controls), but patients with AME are not cushingoid; the cortisol secretion rate falls often to very low levels due to a normal intact negative feedback mechanism. This maintains

FIG. 2. Schematic depiction of 11 β -HSD2 function. The MR binds aldosterone (A) and cortisol (F) with equal affinity. Plasma F concentrations exceed those of A by 100-fold. 11 β -HSD2 guarantees the selectivity of the MR for A by converting F to its inactive metabolite cortisone (E). (E does not bind to the MR.) After binding of A to the MR, the A-MR complex binds to DNA hormone response elements and increases transcription of target genes, e.g. the epithelial sodium channel (ENaC) and the basolateral sodium potassium (Na^+/K^+) ATPase. In the case of impaired 11 β -HSD2 activity, F binds inappropriately to the MR and increases transcription of MR target genes, leading to sodium resorption and potassium excretion. The potassium loss results in metabolic alkalosis.



normal circulating concentrations in the face of impaired cortisol metabolism.

A variant of AME, so-called type II AME, has been documented in several patients (16, 17). This variant is characterized by a milder phenotype, with onset in late adolescence or early adulthood and only a mildly deranged urinary THF+allo-THF/THE ratio. However, the UFF/UFE excretion is high in the type II variant, and the metabolism of 11-tri-ated cortisol (directly reflecting 11 β -HSD2 dehydrogenase activity) is grossly deranged, confirming deficiency of 11 β -HSD2 (17).

Therapeutic options. The main aim of treating patients with AME should be to correct life-threatening hypokalemia and control blood pressure. Dexamethasone has been very effective in many cases, but not all. This may relate to inadequate suppression of cortisol secretion. As is the case with all secondary forms of hypertension, however, removal of the source (in this case by suppressing cortisol) only restores blood pressure to normal in approximately 60% of cases, and additional antihypertensive medication may be required. Patients have been successfully treated with triamterene and/or amiloride. Thiazide diuretics are indicated when hypercalciuria and/or nephrocalcinosis are present. Spironolactone, a MR antagonist, has been of variable benefit, presumably because very high doses are required to block the mineralocorticoid effects of cortisol on the MR. Cure of AME was reported in one patient after kidney transplantation due to the normal 11 β -HSD2 activity of the transplanted kidney (18).

Molecular basis for AME types I and II. Information on the structure and sequence of the HSD11B2 gene has enabled the identification of mutations in AME patients. HSD11B2 is 6.2 kb in length, containing five exons, and is located on chromosome 16q22 (19). At present, 33 different mutations have been defined within the HSD11B2 gene in approximately 60 affected kindreds (Fig. 4; Refs. 10 and 20–22).

Most type I AME patients are homozygous for HSD11B2 mutations, causing full or partial loss of activity. In one case (mutation R374Stop), affected placental tissue was obtained from an AME kindred, and absent conversion of cortisol to cortisone was confirmed *in vitro* (22). This same R374X mutation is also seen in an unrelated case reported in The Netherlands (23). Although two mutations (R337C and P227L) were found to exhibit significant activity, the elevated K_m values suggest that intracellular cortisol would not be lowered to levels that would preclude occupancy of the MR.

AME is most commonly found in consanguineous families (10, 20–22). A founder effect is evident in three families homozygous for the R337H Δ 3nt mutation. One of these families are Zoroastrians from Iran, and the others come from the Bombay area to which the religious group emigrated in the seventh century (20). This mutation also appears to have arisen independently in a compound heterozygote from Japan (24). Homozygosity in AME is thought to result from endogamy or a founder effect in the Native American families with the R208C and E356 Δ 1nt mutations and the L250S,L251P mutation. The fact that six kindreds are of Native American origin has prompted speculation as to a possible selective advantage of heterozygotes. Such individuals

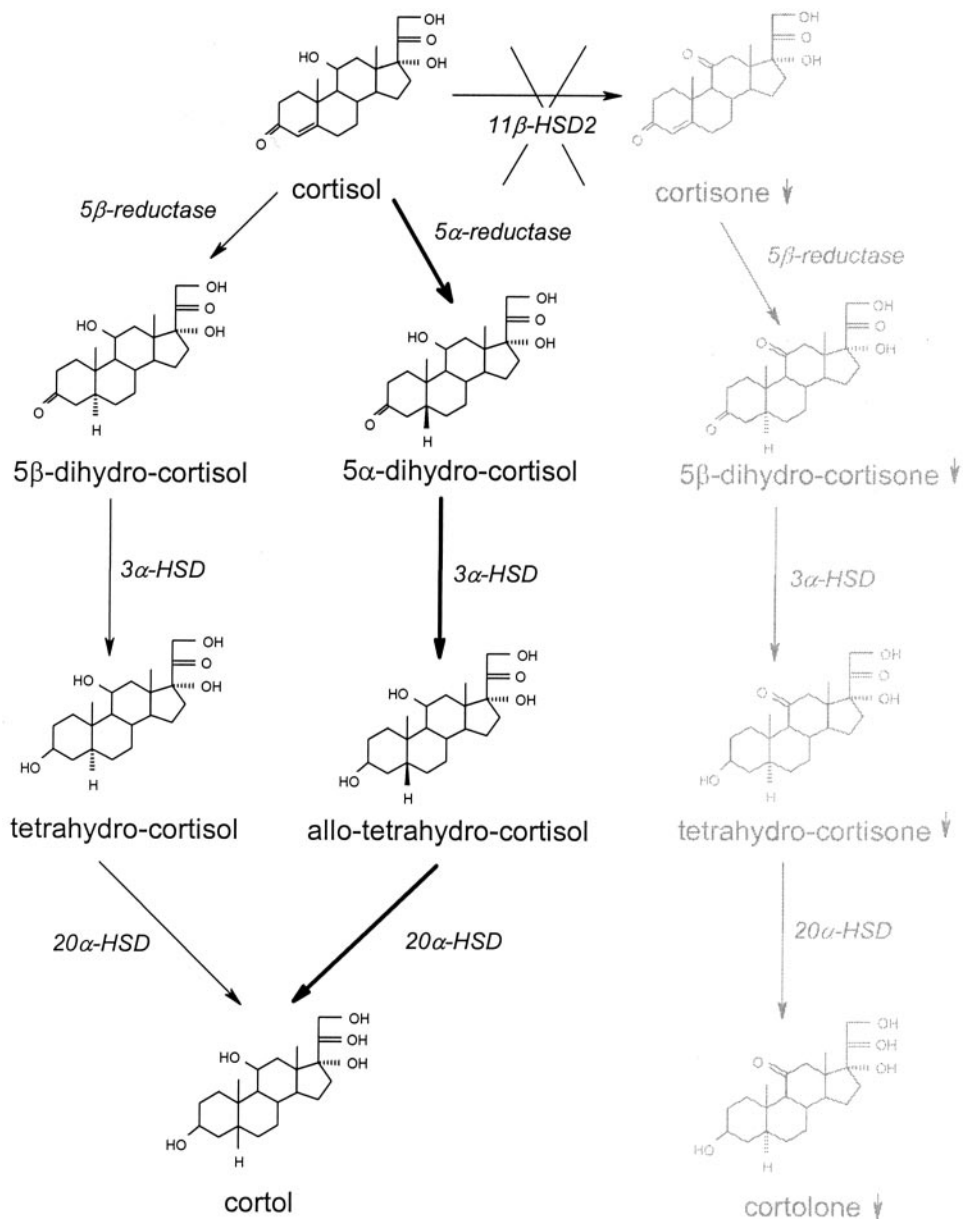


FIG. 3. Effect of 11 β -HSD2 deficiency on the pathways of cortisol ring A metabolism. Despite normal circulating cortisol levels, patients with AME show a decrease in the total urinary excretion of cortisol metabolites, reflecting a reduction in secretion rate consequent on a prolonged plasma half-life. Cortisone and its metabolites are greatly diminished due to 11 β -HSD2 deficiency. In addition, 5 α -reduced cortisol metabolites predominate over 5 β -reduced cortisol metabolites consistent with a reduction of 5 β -reductase activity in patients with AME.

may have an increased ability to conserve salt under conditions of extreme sodium deprivation (10).

Up to nine patients are compound heterozygotes, with each allele coding for an enzyme devoid of activity (24, 25). Compound heterozygosity for mutations in the HSD11B2 gene demonstrates a prevalence of novel mutations outside founder populations.

Type II AME is also explained on the basis of mutations in the HSD11B2 gene (26, 27). In an extensive Sardinian kindred, a novel homozygous mutation (R279C) was found in all four affected cases. In keeping with the mild phenotype, the mutation resulted in a mutant enzyme with only minor disturbances in activity. Classification of AME into distinct variants is therefore inappropriate. In keeping with this, a close correlation is reported between disease phenotype (as measured by the THF+allo-THF/THE ratio, serum potassium, and blood pressure) and genotype (25). Patients with

mutant 11 β -HSD2 cDNAs that demonstrate little or no activity *in vitro* present in early life with severe, often life-threatening, hypertension and hypokalemia. In contrast, patients presenting in late adolescence or early adulthood with so-called mild forms of AME (earlier referred to as AME type II) have been found to have mutations that result in an 11 β -HSD2 protein with only attenuated activity.

In one report, both parents were found to be mildly hypertensive and had evidence of mineralocorticoid-based hypertension (14), whereas in another family the father of an affected case, who in turn was heterozygous for a A328V mutation, developed hypertension at age 38 yr and displayed a moderately elevated THF+allo-THF/THE ratio of 2.47 (26). Because AME is usually diagnosed in childhood, prolonged follow-up of the relatively young parents into late adulthood is required to define the full functional significance of the heterozygote state.

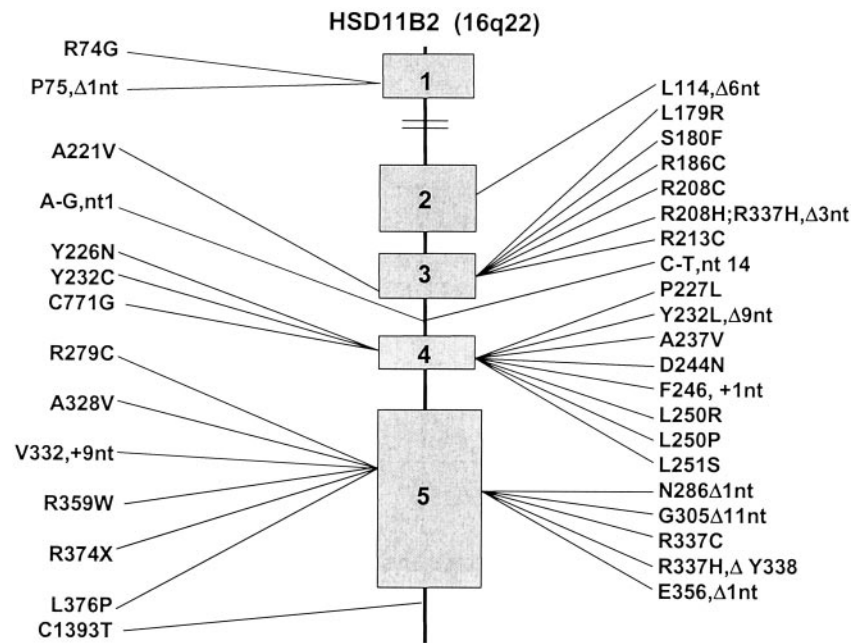


FIG. 4. Mutations in the HSD11B2 gene leading to AME syndrome. Gray squares represent exons.

Licorice and carbenoxolone ingestion

Licorice has been used medically for several thousand years, but its mineralocorticoid effect was first documented in the 1940s. A preparation of the root of the licorice plant (*Glycyrrhiza glabra*), was successfully used to treat patients with peptic ulceration. Such observations were the basis for the development of the effective antiulcer drug, carbenoxolone, which is a hemisuccinate derivative of 18 β -glycyrrhetic acid. However, both licorice and carbenoxolone induce mineralocorticoid side effects (edema, shortness of breath on exertion, and increased blood pressure) in up to 50% of patients consuming these compounds. In Europe, licorice is mainly ingested as a confectionery sweet, with as little as 50 g/d required to induce mineralocorticoid hypertension. In North America, glycyrrhizin is found in some confectioneries, but is also a sweetener in chewing gums and tobacco.

Patients consuming excessive quantities of licorice present with hypertension and hypokalemia that may be severe enough to cause myopathy and cardiac arrhythmias (28). Both plasma renin activity and aldosterone levels are suppressed, and exchangeable sodium levels are increased. The condition responds to spironolactone and is reversible on stopping licorice ingestion. The active components in licorice are glycyrrhizic acid, its hydrolytic product glycyrrhetic acid, and the 3-monoglucuronyl metabolite of glycyrrhetic acid. Glycyrrhizic and glycyrrhetic acids have a very low affinity for the MR, but are very potent competitive inhibitors of 11 β -HSD2 ($K_i \sim 5\text{--}10\text{ nM}$; Ref. 29). Licorice administration to normal volunteers results in a mineralocorticoid excess state, an increase in the urinary THF+allo-THF/THE ratio, an increase in plasma cortisol half-life, and a decrease in circulating cortisone values, indicative of inhibition of 11 β -HSD2 *in vivo* (30, 31). Similar changes in cortisol metabolism were reported in patients presenting with licorice-induced mineralocorticoid excess (32). Thus, it is now established that licorice induces an acquired and milder form of AME, caus-

ing its mineralocorticoid effects through inhibition of 11 β -HSD2.

Glycyrrhetic-acid-like factors

The excretion of endogenous compounds in the urine that inhibit 11 β -HSD2 activity and might elevate blood pressure have been identified in some studies. These so called glycyrrhetic-acid-like factors are elevated during pregnancy, especially during the second and third trimester (33), suggesting that they might be progesterone metabolites. It has not been possible to correlate glycyrrhetic-acid-like factor excretion with blood pressure (34), and their characterization and biological significance are poorly understood.

Ectopic ACTH syndrome

Eighty percent of patients with Cushing's syndrome have hypertension, and in the subgroup of patients with ectopic ACTH syndrome this increases to over 95%. The severity of hypertension is a key factor in predicting morbidity and mortality from the disease, yet its pathogenesis had been poorly understood. The ectopic ACTH syndrome is characterized by mineralocorticoid excess, with hypokalemic alkalosis found in 95–100% of cases, in contrast to less than 10% in other forms of Cushing's syndrome. Although elevated plasma levels of deoxycorticosterone have been postulated to play a role, it is the level of cortisol secretion that correlates best with the degree of mineralocorticoid excess.

ACTH has no direct effect on 11 β -HSD2, but the enzyme is saturated in ectopic ACTH syndrome by very high concentrations of ACTH-dependent 11 β -HSD substrates, such as cortisol and corticosterone. Both the urinary ratio of THF+allo-THF/THE and UFF/UFH are elevated, not because of impaired 11 β -HSD2 activity, but simply because of substrate saturation. In severe hypercortisolism, all available cortisol cannot be inactivated to cortisone and spills over onto the MR to cause mineralocorticoid hypertension (35–37).

Renal disease

The human kidney is the principal site of cortisol to cortisone metabolism *in vivo*. Patients with chronic renal failure have a prolonged plasma cortisol half-life (2.9 h, compared with 2.1 h in controls; Ref. 38). The same is true for prednisolone, but not for dexamethasone, no doubt reflecting the observation that cortisol and prednisolone are better substrates than dexamethasone for 11 β -HSD2. Plasma cortisone concentrations are reduced in patients with renal disease (39, 40) with an inverse correlation between cortisone values and plasma creatinine. Because of the negative feedback mechanism and concomitant fall in cortisol secretion rate, plasma cortisol concentrations remain unchanged. Impaired 11 β -HSD2 activity in patients with renal disease might underpin the increased sodium retention observed in some pathologies, notably nephrotic syndrome (41). ACE inhibitors are known to increase renal 11 β -HSD2 activity, and this, in part, may explain their natriuretic effect (42).

Liver disease

Renal sodium retention and potassium loss in patients with liver cirrhosis is caused by activation of the MR. Patients with both alcoholic and nonalcoholic chronic liver disease or bile duct obstruction have an increase in their urinary THF+allo-THF/THE ratio, suggesting a reduction in renal 11 β -HSD2 activity (43, 44). This could be explained by the inhibitory action on 11 β -HSD2 of bile acids, notably chenodeoxycholic acid and deoxycholic acid (45, 46).

Essential hypertension

The discovery of AME and other forms of mineralocorticoid-induced monogenic forms of hypertension (47) has focused attention on the role of adrenocorticosteroids in the pathogenesis of essential hypertension (Fig. 5). Regarding 11 β -HSD2, studies have demonstrated variations in 11 β -HSD activity in hypertensive subjects with increases in either

the plasma [11-³H]cortisol half-life (48) or the THF+allo-THF/THE ratio (49), but mineralocorticoid excess in patients with impaired 11 β -HSD2 activity could not be demonstrated.

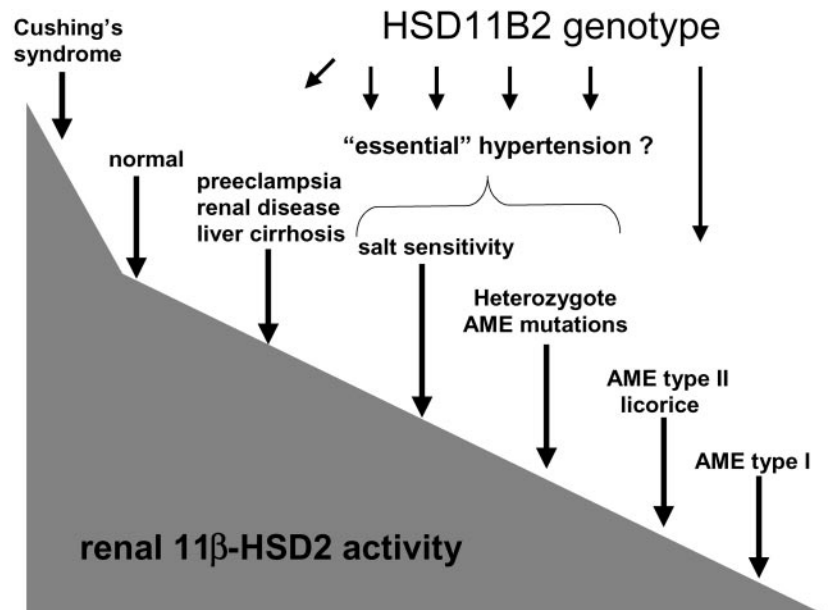
More recently, association and linkage studies have been performed. One study has reported an association between a microsatellite marker close to the HSD11B2 gene and hypertension in African-Americans with hypertensive end-stage renal disease (50). These data were confirmed using a polymorphic restriction site in exon 3 of the HSD11B2 gene. In terms of hypertension *per se*, however, linkage and/or association studies have been negative (51, 52).

Increased sensitivity to salt is a forerunner to essential hypertension. Salt-sensitive individuals appear to have impaired 11 β -HSD2 activity as measured by increased urinary cortisol/cortisone ratios (53). Studies have evaluated a microsatellite within intron 1 of the HSD11B2 gene and documented association with salt sensitivity in both normal subjects and patients with hypertension (53, 54). Short microsatellite alleles were more common in salt-sensitive compared with salt-resistant subjects. The same phenomenon was observed in Blacks compared with Caucasians (55), in keeping with the predisposition to low-renin, salt-sensitive hypertension in this ethnic group.

In addition to enhanced renal sodium retention, the modulation of active glucocorticoid concentration by 11 β -HSD in vascular smooth muscle cells could be an additional factor underlying hypertension (56). *In vitro* and *in vivo* studies indicate that 11 β -HSDs regulate vascular tone at an autocrine level through the amplification of responses to vasoconstrictors (57). Inhibition of 11 β -HSD2 in vascular smooth muscle cells resulted in increased responses to angiotensin-II (58) and phenylephrine (59). 11 β -HSD2 knockout mice demonstrate increased arterial reactivity to norepinephrine and a decreased endothelium-derived nitric oxide synthase activity (60).

The brain may be another important site of blood pressure regulation by corticosteroids. In some areas, the MR is oc-

FIG. 5. Spectrum of 11 β -HSD2 activity leading to different phenotypes. Whereas complete loss of 11 β -HSD2 activity is seen in AME syndrome type I, only attenuated activity is suspected in cases of low renin hypertension.



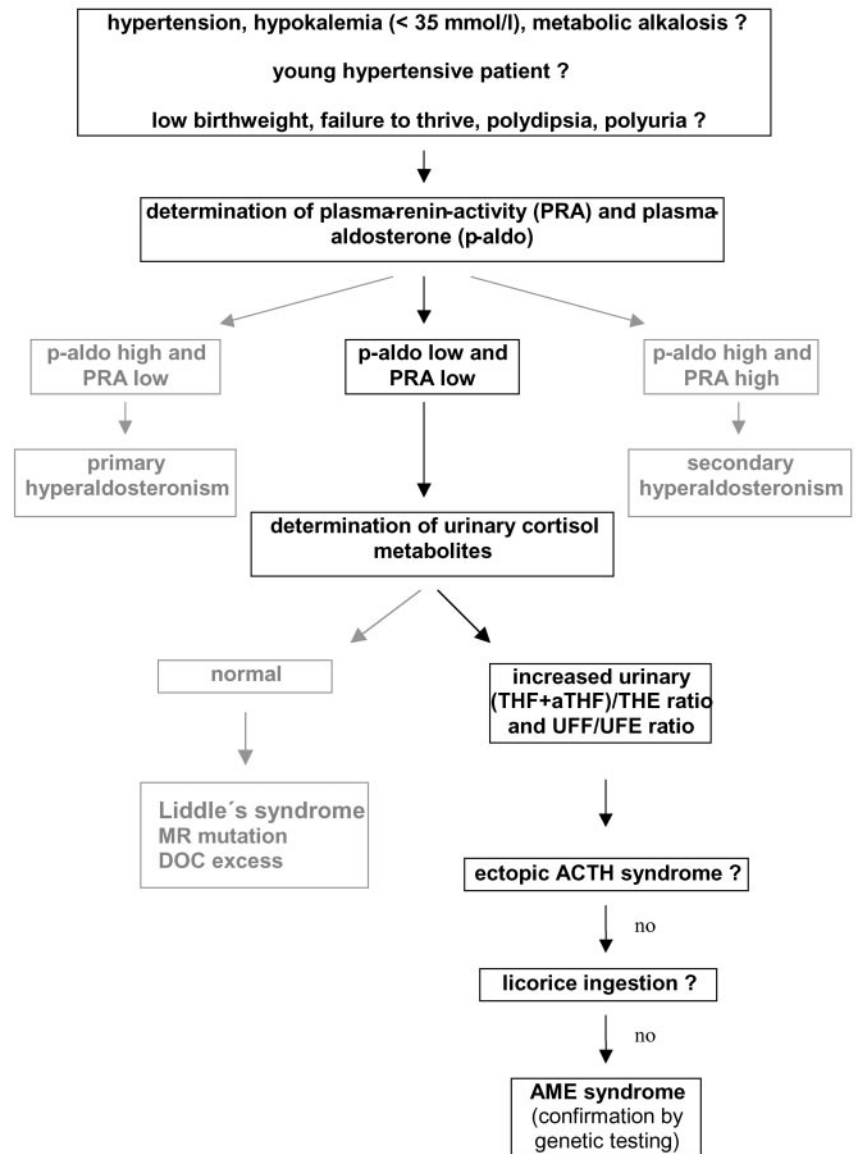


FIG. 6. Flowsheet with guidelines for detecting AME syndrome. aTHF, Allo-THF.

cupied by cortisol because of a lack of 11 β -HSD2 expression. Chronic intracerebroventricular (icv) infusion of aldosterone elevated blood pressure at doses far below those that produce hypertension systemically. This effect was mediated by the MR because it could be blocked by icv infusion of an antimineralocorticoid. In rats with hypertension induced by systemic carbenoxolone or high-sodium diet, the blood pressure was lowered by icv infusions of a MR antagonist (61). These studies provide evidence of the importance of the central nervous system and its effects on salt appetite, baroreceptor function, and autonomic nerve regulation in the pathogenesis of hypertension produced by systemic mineralocorticoid excess (62).

Fetal growth retardation

Barker's epidemiological studies indicate a strong correlation between low birth weight at term and cardiovascular disease risk in adulthood, and this has prompted speculation

that factors involved in regulating fetal growth might in some way program the subsequent development of hypertension (and other cardiovascular risk factors) in adulthood (63). 11 β -HSD2 is widely expressed in fetal tissues, including placental syncytiotrophoblasts, the barrier between maternal and fetal circulation (64, 65). Glucocorticoid excess *in utero* decreases fetal growth, and the high levels of placental 11 β -HSD2 activity may protect the fetus from maternal glucocorticoid excess. The poor growth rate seen in many children with AME is possibly due to glucocorticoid excess *in utero* consequent on absent or impaired 11 β -HSD2 activity (66, 67). Impaired placental 11 β -HSD2 activity has been associated with intrauterine growth restriction and with programming of hypertension in adult life (68, 69).

Preeclampsia and pregnancy-induced hypertension

Increased sodium retention is a feature in preeclampsia and pregnancy-induced hypertension caused probably by

activation of the MR. This may be due to inhibition of 11 β -HSD2 by some unknown factor or by progesterone and its metabolites (70). Reduced 11 β -HSD2 expression has been reported in placentas of women with preeclampsia and pregnancy-induced hypertension (71, 72).

Our understanding of an unusual form of hypertension, AME, has defined an important prereceptor pathway in the analysis of corticosteroid hormone action. 11 β -HSD2 serves to protect the MR from glucocorticoid excess through its inactivation of cortisol to cortisone in kidney and other tissues. Licorice inhibits 11 β -HSD2, and its ingestion results in a similar, though milder phenotype, as AME. Mineralocorticoid excess is also a feature of the ectopic ACTH syndrome, because 11 β -HSD2 is overwhelmed by its substrate cortisol. Figure 6 illustrates how these conditions might be diagnosed in a patient presenting with mineralocorticoid excess. Polymorphic variability in the HSD11B2 gene determines salt sensitivity and might play a role in patients with essential hypertension. Impaired 11 β -HSD2 activity in patients with renal or hepatic disease or in preeclampsia might be involved in sodium retention in these diseases. In summary, the cortisol-cortisone shuttle remains an exiting mechanism underpinning human cardiovascular disease.

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