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Editorial Comment

Mineralocorticoid receptor malfunction: further insights from rare forms of hypertension

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Introduction

Monogenic diseases enhance the understanding of mechanisms for arterial hypertension. All genetic forms so far identified induce hypertension by increased renal sodium reabsorption [1,2]. Recently a novel form of genetically determined renal sodium retention due to a gain-of-function mutation of the mineralocorticoid receptor (MR) has been described. This mutation causes activation of the MR in the absence of aldosterone [3]. Therefore, this disease potentially provides a clue to understand the pathomechanisms in the large number of patients with low renin-low aldosterone hypertension [4].

Mechanisms for enhanced sodium retention in the cortical collecting duct

The mechanism of sodium reabsorption in the principal cells of the cortical collecting duct is depicted in Figure 1. Sodium enters the cell via the epithelial sodium channel (ENaC). Gain-of-function mutations of the ENaC cause a prolongation of the time the channel resides in the plasma membrane, thus increasing the effective channel number, causing enhanced renal sodium retention and hypertension. This entity is known as Liddle syndrome (Table 1) [5–7].

The driving force for sodium delivery to the basolateral side is a Na^+-K^+-ATPase (Figure 1). The overall effect of this sodium transport is controlled by activated MR. The MR translocates from the cytoplasm to the nucleus after binding to its cognate ligand [8]. In the nucleus the steroid–MR–receptor complex binds to defined response elements (MRE) on the DNA and modulates transcription which ultimately enhances by not completely understood mechanisms, the net transport of sodium from the tubular lumen to the basolateral side of the principal cell [9].

The normal MR recognizes two naturally occurring ligands with the same affinity, aldosterone and cortisol (Figure 1) [10]. In undisturbed mammalian principal cells cortisol is inactivated into cortisone, a steroid with virtually no affinity to the MR [10]. This transformation is brought about by an enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). Therefore, the specificity of aldosterone for MR is given as long as there is no loss-of-function mutation of 11β-HSD2 [11] or no endogenous or exogenous inhibitors such as bile acids or liquorice are present [12–14]. An activation of the MR by increased intracellular cortisol concentrations can only be diagnosed indirectly by the finding of an augmented ratio of (tetrahydrocortisol + 5α-tetrahydrocortisol)/tetrahydrocortisone in the urine [15].

Besides an excessive activation of the MR by increased intracellular cortisol concentrations high serum concentrations of aldosterone, deoxycorticosterone, 18-hydroxycortisol or cortisol can cause increased occupation of the MR, thus inducing abnormal renal sodium retention with hypertension (Table 1) [16,17]. More recently, another entity has been described in which abnormally high gluco- or mineralocorticosteroid concentrations are not found to be the cause of excessive activation of the MR. Rather the naturally occurring steroid progesterone exhibits an unusual high affinity for the receptor as a result of a gain-of-function mutation of the MR. This entity is discussed below.

Activating mineralocorticoid receptor mutation

Several splice variants of the human MR have been detected or hypothesized in different tissues [18–20]. The human MR consists of 10 exons [21]. Exons 1b and 1a are arranged in reverse order and are not

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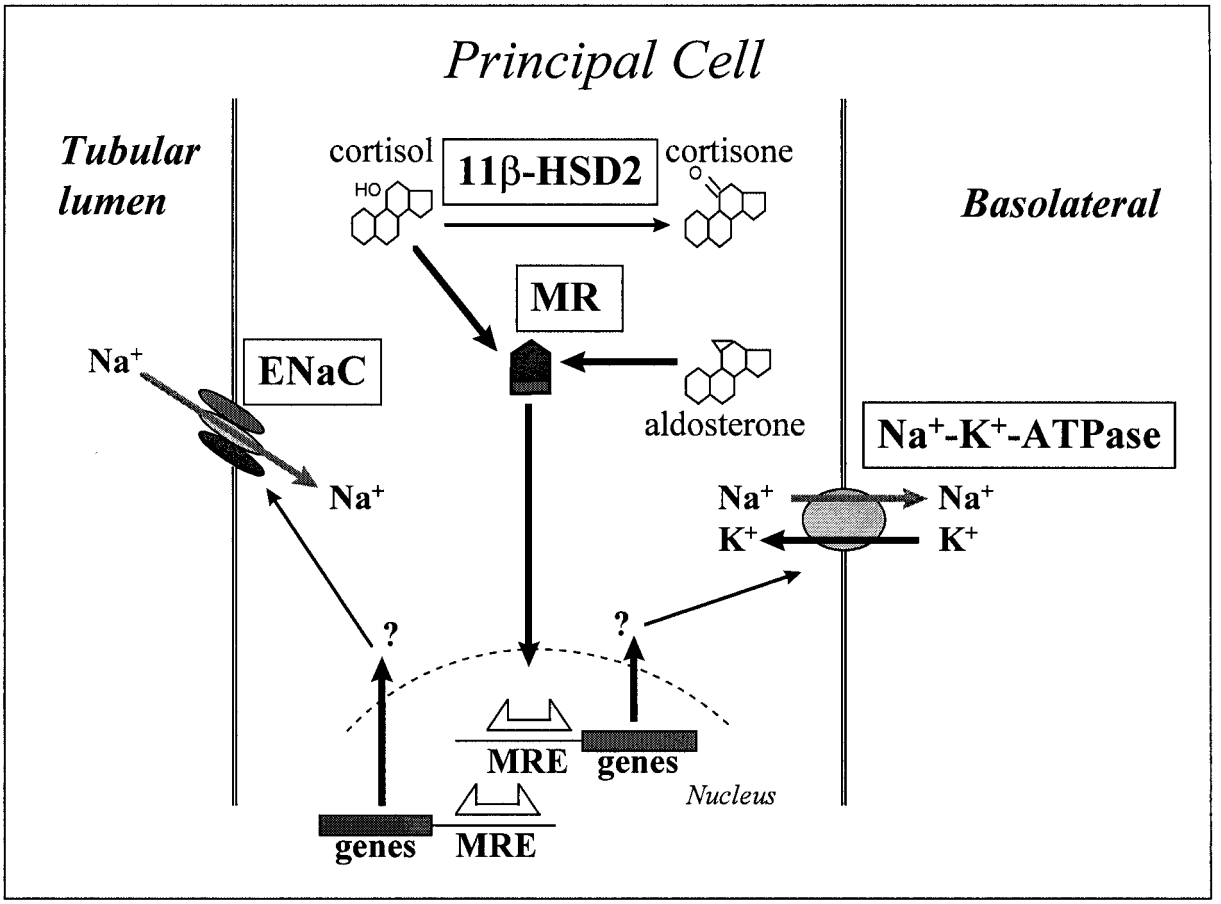

Fig. 1. Mechanisms of sodium reabsorption in the cortical collecting duct.

Table 1. Mechanisms for enhanced sodium retention in the cortical collecting duct

Basic mechanisms		Clinical entities
Gain-of-function mutation of the ENaC	Prolongation of the cell surface half-life of channels	Liddle's syndrome
Increased concentrations of ligands for the MR	*Systemic concentrations are increased*:	
	Aldosterone	M. Conn, bilateral hyperplasia, adrenal carcinoma, high renin states
	Cortisol	M. Cushing, adrenal carcinoma
	Deoxycorticosterone	Adrenal adenoma/carcinoma, loss-of-function mutation of 11β-hydroxylase or 17α-hydroxylase
	18-hydroxycortisol	Chimeric gene of 11β-hydroxylase/aldosterone synthase: glucocorticoid-remediable hyperaldosteronism
	Intracellular concentrations are increased:	
	Cortisol	Loss-of-function mutation or inhibition by endo- or xenobiotics of 11β-hydroxysteroid dehydrogenase: apparent mineralocorticoid excess
Gain-of-function mutation of the MR	Enhanced affinity of the MR for:	
	Progesterone	
	Spironolactone	Hypertension exacerbated in pregnancy

translated [21]. The coding region starts at exon 2. The two small exons 3 and 4 encode for two zinc fingers of the DNA-binding domain of the receptor. The hormone-binding domain is encoded by exons 5 to 9. Among the glucocorticoid/mineralocorticoid/androgen/progesterone receptor superfamily [22] the length of the exons is identical for those encoding the second zinc finger (exon 4 in the human MR)

and the ligand-binding domain (exon 6 to 8 in the human MR) [20], indicating a highly conserved DNA sequence.

Geller *et al.* [3] screened 75 patients with low renin-low aldosterone arterial hypertension for potential mutations within the mineralocorticoid system and detected an individual with a missense mutation in exon 6 of the human MR. This mutation led to an amino acid exchange at position S810L [3]. Further work-up of this mutation in the ligand-binding domain of the human MR identified an identical clinical picture in eight out of 23 members of the index patient's family. The patients presented with an early-onset hypertension with a high systolic and diastolic blood pressure, reduced serum potassium and aldosterone concentrations, features not present in family members without such mutations. The transmission of the trait suggested an autosomal dominant heredity. Of interest, in two affected female individuals five pregnancies were complicated by a marked exacerbation of hypertension during pregnancy. Delivery was between the 24th and 34th week of gestation due to uncontrolled hypertension, yet without signs of pre-eclampsia. Interestingly, three family members died of early-onset congestive heart failure.

Biochemical testing of the mutated human MR L810 revealed an activation of this receptor even in the absence of a natural ligand [3]. Maximal stimulation by aldosterone was similar when compared to the wild type. This observation of a gain-of-function mutation explained a mineralocorticoid effect even when aldosterone concentrations are low or aldosterone is absent, however, it did not account for the pregnancy-induced exacerbation of hypertension. Therefore, Geller *et al.* [3] investigated *in vitro* the action of steroid hormones which are increased in pregnancy, such as estradiol and testosterone with 17-keto groups and the 21-carbon steroid progesterone, for their ability to activate the mutated human MR. Of these steroids only progesterone activated the mutated MR. The concentrations of progesterone found to activate the MR were in the range of concentrations observed in pregnant women [23]. Interestingly, progesterone acts as a MR antagonist on the wild-type MR. Furthermore, spironolactone, the model compound for antagonizing aldosterone action, acts as an agonist for the abnormal receptor. Thus, the mutation of the MR in the ligand-binding domain altered the binding characteristics of the receptor, phenotypically presenting as low potassium-low aldosterone hypertension, exacerbated during pregnancy or presumably after administration of spironolactone. Structurally, the mutation resulted in a change in the ligand-binding domain, which led to similarities between the human MR and the progesterone receptor.

Conclusion and perspectives

What is the clinical relevance of activating mutations of the MR? Blockade of the MR reduces cardiovascular morbidity independent of lowering blood pressure in animals and humans [24,25]. In line with these observations is the appearance of early-onset congestive heart failure in three family members with the gain-of-function mutation of the MR [26].

In normal pregnancies an enhanced sodium retention with volume expansion, increased cardiac output, and peripheral vasodilatation is observed [27–30]. This haemodynamic state requires an augmented aldosterone availability relative to angiotensin II generation, reflected by the known elevated aldosterone to renin ratio in normal pregnancy [31,32]. An enhanced response of the mutated MR to aldosterone or other steroids as a novel mechanism for hypertension in pregnancy with low renin activity has now been shown in a few women [3]. In the future it has to be established whether the commonly observed low renin-low aldosterone constellation of hypertension in pregnancy is often related to such MR mutations, or whether the mutations described by Geller *et al.* [3] remain a marvelous piece of molecular medicine without relevance in clinical practice.

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