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Inherited forms of mineralocorticoid hypertension

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Aldosterone plays an essential role in the maintenance of fluid and electrolyte homeostasis in the distal nephron. Monogenic forms of mineralocorticoid hypertension result from genetic defects leading to excessive production of aldosterone (or other mineralocorticoids) from the adrenal cortex or to illegitimate mineralocorticoid effects in the kidney. They are characterized in the majority of cases by early onset, severe or resistant hypertension and associated with suppressed renin levels. Depending on their causes, these diseases are distinguished at the clinical and biochemical level and differently affect aldosterone levels and kalemia. The diagnosis is confirmed by genetic testing, which allows in many cases targeted treatment to prevent severe cardiovascular consequences of high blood pressure or aldosterone excess. In this review we describe the different forms of inherited mineralocorticoid hypertension, providing an overview of their clinical and biochemical features, their underlying genetic defects and specific therapeutic options.

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Introduction

Aldosterone is the principal mineralocorticoid hormone in human. It is synthesized by the zona glomerulosa of the adrenal gland. Aldosterone acts on epithelial cells, particularly in the renal collecting duct, but also in colon, and salivary and sweat glands. Aldosterone production from the adrenal cortex is tightly controlled to maintain electrolyte and fluid homeostasis by the kidney. Aldosterone and the mineralocorticoid receptor (MR) play a major role in regulating blood pressure; more recently they have emerged as major cardiovascular risk factors mediating end organ damage [1].

Sodium reabsorption in the kidney is essential for maintaining fluid and electrolyte homeostasis as well as regulation of blood pressure. Aldosterone and the mineralocorticoid receptor (MR) play a key role in fine tuning renal sodium reabsorption in the distal parts of the nephron as well as regulating potassium and hydrogen secretion. The aldosterone-sensitive distal nephron (ASDN) comprises the late distal convoluted tubule (DCT), the connecting tubule (CNT) and the collecting duct (CD) and plays an important role in fine-tuning the renal excretion of sodium by reabsorbing about 5–10% of the filtered sodium load [2,3].

The majority of effects of aldosterone on sodium and potassium balance is mediated by its binding to the MR, a ligand-dependent transcription factor belonging to the nuclear receptor superfamily [4]. In the distal tubule of the kidney, aldosterone stimulates the activity of several proteins involved in transepithelial sodium transport, including the epithelial sodium channel ENaC and the Na^+-K^+-ATPase [5]. Aldosterone rapidly increases mRNA levels of the serum- and glucocorticoid-inducible kinase (sgk) 1, which directly stimulates ENaC activity by phosphorylating Nedd4-2, thus reducing its role in ubiquitylation, retrieval, and degradation of ENaC [6]. In addition, aldosterone increases the expression of glucocorticoid-induced leucine zipper protein (GILZ) which acts in parallel with sgk1 to increase ENaC plasma membrane localization by inhibition of extracellular signal–regulated kinase (ERK) [7]. Thus, cell surface expression of ENaC is controlled via ubiquitylation which is itself regulated by aldosterone-induced proteins [8]. Some studies suggest that sgk1 could mediate the effect of aldosterone on renal K^+ secretion by enhancing the export of ROMK channels from the endoplasmic reticulum and by suppressing the inhibitory effect of serine/threonine protein kinase WNK4 on ROMK channels [9–11]. In addition, aldosterone directly stimulates vacuolar H^+-ATPase activity by a signaling cascade via small G proteins, phospholipase C, protein kinase C, ERK1/2 kinases as well as elements of the protein kinase A-dependent pathway [12–14].

The MR binds with the same affinity aldosterone and cortisol, which circulates at 100–1000 fold higher concentrations. In epithelial target tissues, specific binding of aldosterone to the MR is made possible by the action of an enzyme, the corticosteroid 11-beta-dehydrogenase isozyme 2 (11-beta-HSD2, encoded by *HSD11B2*), which converts cortisol into its inactive metabolite cortisone. The late part of DCT, CNT and CD express MR, ENaC and 11-beta-HSD2, allowing for mineralocorticoid selectivity in these nephron segments [15–17]. In non-epithelial target tissues, like the brain and the adipose tissue, the MR is to be considered a high affinity receptor for glucocorticoid hormones.

Aldosterone is synthesized from cholesterol in the zona glomerulosa of the adrenal cortex by a series of specific enzymatic reactions, whereas cortisol is synthesized in the zona fasciculata [18]. The final steps of aldosterone biosynthesis are catalyzed by the aldosterone synthase (AS, encoded by *CYP11B2*) whereas 11β-hydroxylase (encoded by *CYP11B1*) is responsible for the final steps of cortisol biosynthesis. These enzymes are highly homologous and their genes are located in tandem on the chromosome 8q21-q22. Aldosterone biosynthesis is tightly regulated mainly by the renin-angiotensin system and extracellular potassium concentration. AngII signals through the AngII type 1 receptors (AT1R) to stimulate inositol trisphosphate dependent Ca^{2+} release from the endoplasmic reticulum. Stimulation by potassium (K^+), but also by angiotensin II (AngII), results in depolarization of the zona glomerulosa cell membrane and opening of voltage-dependent Ca^{2+}-channels. These signals converge to increase intracellular Ca^{2+} concentrations. Activation of the calcium signaling pathway triggers a phosphorylation cascade that leads to the positive regulation of *CYP11B2* transcription and increased aldosterone biosynthesis [19].

Several monogenic disorders, displaying Mendelian inheritance, affect mineralocorticoid function. Mineralocorticoid excess leading to hypertension may result from any abnormality that increases aldosterone production or function. This includes adrenal diseases leading to autonomous aldosterone

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