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Review

Aldosterone resistance: Structural and functional considerations and new perspectives

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ABSTRACT

Aldosterone plays an essential role in the maintenance of fluid and electrolyte homeostasis in the distal nephron. Loss-of-function mutations in two key components of the aldosterone response, the mineralocorticoid receptor and the epithelial sodium channel ENaC, lead to type 1 pseudohypoaldosteronism (PHA1), a rare genetic disease of aldosterone resistance characterized by salt wasting, dehydration, failure to thrive, hyperkalemia and metabolic acidosis. This review describes the clinical, biological and genetic characteristics of the different forms of PHA1 and highlights recent advances in the understanding of the pathogenesis of the disease. We will also discuss genotype–phenotype correlations and new clinical and genetic entities that may prove relevant for patient's care in neonates with renal salt losing syndromes and/or failure to thrive.

Contents

1. Introduction

Sodium reabsorption in the kidney is essential for maintaining fluid and electrolyte homeostasis as well as regulation of blood pressure. Aldosterone plays 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 integrity of the mineralocorticoid axis is particularly relevant in the neonatal period,

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where renal regulation of water and electrolyte balance is impaired owing to immature tubular function, as the abundance and activity of salt and water transporters are developmentally regulated (Holtback and Aperia, 2003). In this setting, intercurrent events such as prematurity or infections may precipitate salt loss and dehydration, further promoted by a physiological partial aldosterone resistance in the neonatal period (Martinerie et al., 2009). A rare genetic disease of mineralocorticoid resistance, pseudohypoaldosteronism type 1 (PHA1), results from defects affecting two central molecules involved in aldosterone-dependent regulation of water and electrolyte balance, the mineralocorticoid receptor (MR) and the epithelial sodium channel ENaC. Here we review different forms of aldosterone resistance and discuss their underlying pathogenetic mechanisms, genotype–phenotype correlations and possible implications stemming from knowledge of PHA1 for sodium handling and blood pressure regulation in the general population.

2. The aldosterone-sensitive distal nephron – key regulator of volume and electrolyte homeostasis

While two-thirds of filtered sodium is reabsorbed in the proximal tubule and a further 20–25% in the loop of Henle, the aldosterone-sensitive distal nephron (ASDN) plays an important role in fine-tuning the renal excretion of Na^+ by reabsorbing about 5–10% of the filtered Na^+ load. The ASDN includes the late distal convoluted tubule (DCT), the connecting tubule (CNT) and the collecting duct (CD) and activity along this segment is controlled by hormones and dietary sodium intake (Campean et al., 2001; Loffing et al., 2001). The late DCT, CNT and CD express MR, ENaC and the 11-β hydroxysteroid dehydrogenase type 2 allowing for mineralocorticoid selectivity in these nephron segments (Bostanjoglo et al., 1998; Farman and Rafestin-Oblin, 2001; Loffing and Kaissling, 2003).

Sodium reabsorption is mediated at the apical membrane by the thiazide-sensitive Na–Cl cotransporter (NCC) in DCT cells, and by ENaC in late DCT, CNT and principal cells of the CD (Biner et al., 2002; Loffing and Kaissling, 2003; Reilly and Ellison, 2000). Sodium exits distal nephron cells across the basolateral membrane to the interstitial fluid via the ubiquitous Na^+–K^+-ATPase, providing the primary driving force for Na^+ transport. Na^+–K^+-ATPase contributes to making the inside of the cell electronegative with respect to the outside generating large ion concentration gradients that drive potassium and hydrogen ion secretion (Reilly and Ellison, 2000) (Fig. 1). In the ASDN basolateral K^+ channels (Kir4.1 and Kir5.1) participate in generating cell membrane potential and in K^+ recycling, while apical K^+ channels, mainly the renal outer medullary potassium channel (ROMK1 or Kir1.1), the activity of which increases with high dietary potassium intake (Meneton et al., 2004; Palmer, 1999), are responsible for K^+ secretion (Wang et al., 2010). Acid–base transport occurs in intercalated cells (ICs) in CNT, CCD and medullar collecting duct (MCD). Type A ICs secrete protons into urine via an apically expressed vacuolar H^+-ATPase, coupled with the basolaterally expressed chloride-bicarbonate exchanger AE1, that releases bicarbonate into blood. Type B ICs express an apical chloride–bicarbonate exchanger excreting bicarbonate into urine, while protons are secreted into blood by basolateral H^+-ATPases (Wagner et al., 2006). Proton secretion through vacuolar H^+-ATPases is thought to be indirectly coupled to Na^+ reabsorption by ENaC, which creates a lumen-negative potential that enhances H^+ secretion (Kovacikova et al., 2006; Rubera et al., 2003).

Aldosterone confers the main hormonal regulation of sodium, potassium and hydrogen balance in the ASDN via its effects on MR. In the CD, aldosterone stimulates activity of several proteins implicated in transepithelial sodium transport, including ENaC and Na^+–K^+-ATPase (Stockand, 2002). Aldosterone rapidly increases mRNA levels of the serum- and glucocorticoid regulated kinase (sgk) 1, which stimulates ENaC activity by phosphorylating Nedd4-2, thus reducing its role in ubiquitylation, retrieval, and degradation of ENaC (Bhalla et al., 2006). On the other hand, short-term transcriptional regulation of the deubiquitylating enzyme Usp2-45 leads to increased ENaC surface expression and activity (Verrey et al., 2008). 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) (Soundararajan et al., 2005). Thus, cell surface expression of ENaC is controlled via ubiquitylation which is itself regulated by aldosterone-induced proteins (Verrey et al., 2008). 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 (Ring et al., 2007; Vallon et al., 2005; Wang et al., 2010). 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 (Wagner et al., 2006; Winter et al., 2004).

3. Pseudohypoaldosteronism type 1: classification, diagnosis and treatment

PHA1 is a rare disease of mineralocorticoid resistance first reported by Cheek and Perry (1958) who described a male infant with severe salt wasting and failure to thrive in the absence of any renal or adrenal defect. Patients exhibit hyponatremia, hyperkalemia and metabolic acidosis despite extremely high levels of plasma renin and aldosterone (Zennaro and Lombès, 2004). Two different forms of PHA1 have been described (Hanukoglu, 1991) that can be distinguished at the clinical and genetic level (Table 1).

3.1. Renal PHA1

Renal PHA1 (MIM#177735, also called autosomal dominant PHA1, (Geller, 2005)) is a mild form of mineralocorticoid resistance, with a phenotypic expression restricted to the kidney. It represents the most frequent form of the disease with a prevalence, as estimated from recruitment through a national reference centre for rare diseases (PHA1.NET, coordinator MC. Zennaro; MARHEA, http://www.asso.orpha.net/MARHEA/cgi-bin), of ∼1 per 80,000 newborns (MC Zennaro, unpublished results). Patients generally present with a salt losing syndrome in the neonatal period, with weight loss, failure to thrive, vomiting and dehydration. Biological findings are hyponatremia, hyperkalemia, metabolic acidosis and inappropriately high urinary sodium excretion. In contrast, urinary potassium excretion is low, with reduced fractional potassium excretion and transtubular potassium gradient (Rodriguez-Soriano et al., 1990; Zettle et al., 1987). The diagnosis is confirmed by the presence of high plasma and urinary aldosterone and high plasma renin levels. Symptoms of renal PHA1 usually improve in early childhood; afterwards, patients compensate for their defective MR by up-regulating their mineralocorticoid axis. Indeed, high plasma aldosterone levels persist into adulthood, while plasma renin activity decreases into normal range ((Speiser et al., 1986) and references therein; (Geller et al., 2006; Hanukoglu, 1991; Hanukoglu et al., 2008; Kuhnle et al., 1990; Zennaro et al., 1992)). Kidney maturation, access to dietary salt and tubulo-glomerular