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Aldosterone-induced signalling and cation transport in the distal nephron

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ABSTRACT

Aldosterone is an important regulator of Na^+ and K^+ transport in the distal nephron modulating the surface expression of transporters through the action of the mineralocorticoid receptor as a ligand-dependent transcription factor. Aldosterone stimulates the rapid activation of protein kinase-based signalling cascades that modulate the genomic effects of the hormone. Evidence is accumulating about the multi-factorial regulation of the epithelial sodium channel (ENaC) by aldosterone. Recent published data suggests that the activation of a novel PKC/PKD signalling pathway through the c-Src-dependent trans-activation of epidermal growth factor receptor contributes to early ENaC trafficking in response to aldosterone.

1. Introduction

Salt conservation through re-absorption is a vital function of the kidney in terrestrial animals. The movement of electrolytes between the renal ultra-filtrate and the blood is subject to precise hormonal regulation that is essential to maintain whole body homeostatic balance. The mineralocorticoid hormone aldosterone is released by the adrenal cortex as the last stage in the rennin–angiotensin cascade in response to decreased blood pressure or directly in response to hyperkalaemia. The net effect of aldosterone release is to promote Na^+ conservation though re-absorption from the renal ultra-filtrate, which can be coupled to simultaneous elevation of K^+ secretion. The re-absorption of Na^+ facilitates the osmotic movement of water from the renal ultra-filtrate back into the blood resulting in increased blood pressure. It has long been proposed that excessive salt conservation through aldosterone action leads to the development of hypertension with pathophysiological consequences including the development of cardiovascular disease [1].

Clinical trials demonstrating the efficacy of the mineralocorticoid receptor (MR) antagonists spironolactone and eplerenone in reducing blood pressure and enhancing cardiovascular disease outcomes [2,3] did not demonstrate a link between the beneficial cardiovascular effect and reduced Na^+ re-absorption. This has been interpreted as evidence that the renal effects of aldosterone are largely homeostatic, and that occupancy of MR by glucocorticoids in the cells of the cardiovascular system such as cardiomyocytes contributes to the distinct effects of MR antagonism on reducing hypertension [4]. Liddel's syndrome patients present with symptoms resembling hyperaldosteronism: hypertension and hypokalaemia [5]. This phenotype is due to a gain in epithelial sodium channel (ENaC) activity that results in excessive Na^+ conservation, strengthening the view that dysregulation of aldosterone sensitive transport in the kidney can have pathophysiological

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consequences. The degree of contribution made by the renal effects of aldosterone to the development of cardiovascular disease is thus still unclear.

Aldosterone acts through a specific nuclear receptor, MR that is expressed in the epithelial cells of the distal nephron and other target tissues. MR bound by aldosterone translocates to the nucleus and acts as a ligand-dependent transcription factor that regulates the expression of a large repertoire of responsive genes. Aldosterone responsive genes include the membrane transporters that transport ions across the renal epithelium such as the subunits of the ENaC and the Na^+/K^+ ATPase pump [6,7]. In the kidney MR is expressed along the aldosterone sensitive distal nephron (ASDN), which represents the principal regulatory site for salt conservation in the body. The ASDN comprises the thick ascending limb (TAL) of the loop of Henle; the distal convoluted tubule (DCT); the connecting tubule (CNT) and the cortical collecting duct (CCD). It was believed that Na^+ re-absorption mainly occurred through ENaC located at the apical surface of the principal epithelial cells of the CCD. The DCT and connecting tubule are now regarded as the major sites of Na^+ re-absorption in the kidney with the CCD playing a lesser role [8]. Na^+ is subsequently transported across the basolateral membrane of the epithelium by the Na^+/K^+ ATPase pump and into the blood, which in turn maintains a gradient for apical Na^+ uptake.

I addition to its direct effects on transporter expression, aldosterone also stimulates the activation of signalling cascades that in turn modulate the activity of these transporters. Some of the signalling cascades activated by aldosterone are dependent on the transcriptional effects of MR such as the up-regulation of serum and glucocorticoid regulated kinase (SGK-1), while other, more rapid signalling events stimulated by aldosterone are independent of its effects on transcription (reviewed in [9]). Determining the interaction between these genomic and nongenomic events is crucial in understanding the full scope of aldosterone's effects on renal physiology.

2. Aldosterone and K^+ transport in the distal nephron

Aldosterone stimulated K^+ transport in the epithelial cells of the distal nephron can be a process of either apical secretion or basolateral recycling. The switch over between secretion and recycling is dependent upon the plasma K^+ concentration. The Na^+/K^+ ATPase pump is located in the basolateral membrane of the epithelial cells and provides the electrochemical driving force for the influx of Na^+ from the lumen of the nephron. Na^+ is pumped from the cytoplasm of the epithelial cells across the basolateral/blood side of the epithelium in exchange for K^+. Potassium ions are recycled back into the blood through basolateral K^+ channels or secreted into the lumen of the nephron by apical K^+ channels. Na^+/K^+ ATPase activity is regulated by aldosterone at the level of transcription and through the activation of signalling cascades. MR promotes the expression of pump subunits and the recruitment of pre-expressed pump subunits to the cell membrane through the up-regulation of SGK-1 [10]. Na^+/K^+ ATPase activity is also sensitive to intracellular pH [11,12], which affects the cation binding specificity of the pump [13]. Since the elevation of intracellular pH through increased Na^+/H^+ exchanger type 1 (NHE1) activity is an early response to aldosterone in the renal epithelium, this may contribute to the earliest phase in aldosterone-induced Na^+/K^+ ATPase activity [14–16]. Aldosterone suppresses the activity of the apical Na^+/H^+ exchanger type 3 (NHE3) in the medullary thick ascending limb of the loop of Henle (TAL) through a nongenomic, MR-independent mechanism to block HCO_3^- re-absorption in this part of the nephron [17,18]. These observations suggest divergent roles for the NHE isoforms in aldosterone-stimulated ion transport processes. NHE1 stimulation modulates the transcriptional effects of the hormone through pH-sensitive signalling and transporter activity, while NHE3 activity contributes to the aldosterone-sensitive re-absorption of HCO_3^- from the renal ultra-filtrate.

The stimulation of NHE1 activity by aldosterone to raise intracellular pH also contributes to the activation ATP-sensitive K^+ (K^+_{ATP}) channels that promote K^+ recycling in the distal nephron [19]. K^+_{ATP} channels facilitate K^+ recycling across the basolateral membrane to balance the activity of the Na^+/K^+ ATPase pump. Aldosterone treatment of frog skin principal cells stimulated a pH-sensitive K^+_{ATP} channel activation within 2 min [19]. Aldosterone also modulates the activity of the renal outer medullary K^+ (ROMK) channel to promote K^+ secretion. The regulation of ROMK determines whether K^+ secretion or recycling occurs in response to aldosterone. Studying the rare condition of pseudohypoaldosteronism type II (PHAII) has elucidated the precise mechanism of this physiological switch [20]. PHAII patients possess a mutation in the protein kinase with no lysine (WNK) types 1 and 4 resulting in excessive K^+ secretion [21]. It has now been established that WNK4 suppresses both ROMK and ENaC but phosphorylation of WNK4 by SGK-1 relieves this inhibition to promote Na^+ re-absorption and promote K^+ secretion. The PHAII mutation mimics the combined effect of aldosterone and angiotensin II on WNK4 to promote ENaC activity while suppressing ROMK activity to conserve salt and raise blood pressure without loosing K^+. Recent research proposes that the aldosterone-induced up-regulation of the ROMK channel activity in murine TAL cells relies upon activation of the cystic fibrosis trans-membrane conductance regulator (CFTR) Cl^- channel [22] and expression of ENaC [23]. This emphasizes the integrated nature of aldosterone control over responsive membrane transporters. Since CFTR has multiple potential PKA phosphorylation sites it has been proposed that CFTR acts as a PKA-dependent switch for the up-regulation of K^+ secretion by the distal nephron through CFTR-dependent coupling to ROMK [22]. A rapid increase in adenylate cyclase activity was detected in isolated inner medullary collecting duct cells treated with aldosterone that could potentiate PKA activity in this model [24].

3. Aldosterone and ENaC activity

While it is the Na^+/K^+ ATPase pump that provides the driving force for Na^+ re-absorption, it is the activity of ENaC that is the effective rate-limiting step for the trans-epithelial movement of Na^+ [7]. ENaC activity is stimulated by aldosterone and results in the electrogenic transport of Na^+ across the apical membrane of the epithelial principal cells of the