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Rapid aldosterone actions on epithelial sodium channel trafficking and cell proliferation

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ABSTRACT

Aldosterone regulates blood pressure through its effects on the kidney and the cardiovascular system. Dysregulation of aldosterone signalling can result in hypertension which in turn can lead to chronic pathologies of the kidney such as renal fibrosis and nephropathy. Aldosterone acts by binding to the mineralocorticoid receptor (MR), which acts as a ligand-dependent transcription factor in target tissues such as segments of the distal nephron including the connecting tubule and cortical collecting duct (CCD). Aldosterone also promotes the activation of protein kinase signalling cascades that are coupled to growth factor receptors and act directly on specific substrates in the cell membrane or cytoplasm. The rapid actions of aldosterone can also modulate gene expression through the phosphorylation of transcription factors. Aldosterone is a key regulator of Na^+ conservation in the distal nephron, largely through multiple mechanisms that modulate the activity of the epithelial Na^+ channel (ENaC). Aldosterone transcriptionally up-regulates the ENaCα subunit and also up regulates serum and glucocorticoid-regulated kinase-1 (SGK1) that indirectly regulates the ubiquitination of ENaC subunits. Aldosterone promotes the activation of protein kinase D1 (PKD1) which can modify the activity of ENaC and other transporters through effects on sub-cellular trafficking. In M1-CCD cells, early sub-cellular trafficking causes the redistribution of ENaC subunits within minutes of treatment with aldosterone. ENaC subunits can also interact directly with phosphatidylinositide signalling intermediates in the membrane and the mechanism by which PKD isoforms regulate protein trafficking is through the control of vesicle fission from the trans Golgi network by activation of phosphatidylinositol 4-kinaseIIIβ (PI4KIIIβ).

Contents

1. Introduction

Steroid hormones influence electrolyte balance within the body through their action on epithelial transport processes in different organs. Aldosterone regulates Na^+ homeostasis through activation of the mineralocorticoid receptor (MR) in epithelial cells of target tissues that express the receptor including the kidney and colon. Aldosterone is a critical hormone regulating normal renal functionality, particularly Na^+ conservation in the distal nephron. The impact of aldosterone action is most strongly emphasized when the aldosterone–epithelial Na^+ channel (ENaC) axis is excessively challenged leading to physiological effects on the performance of the renal system [1] and the development of hypertension which can lead to car-

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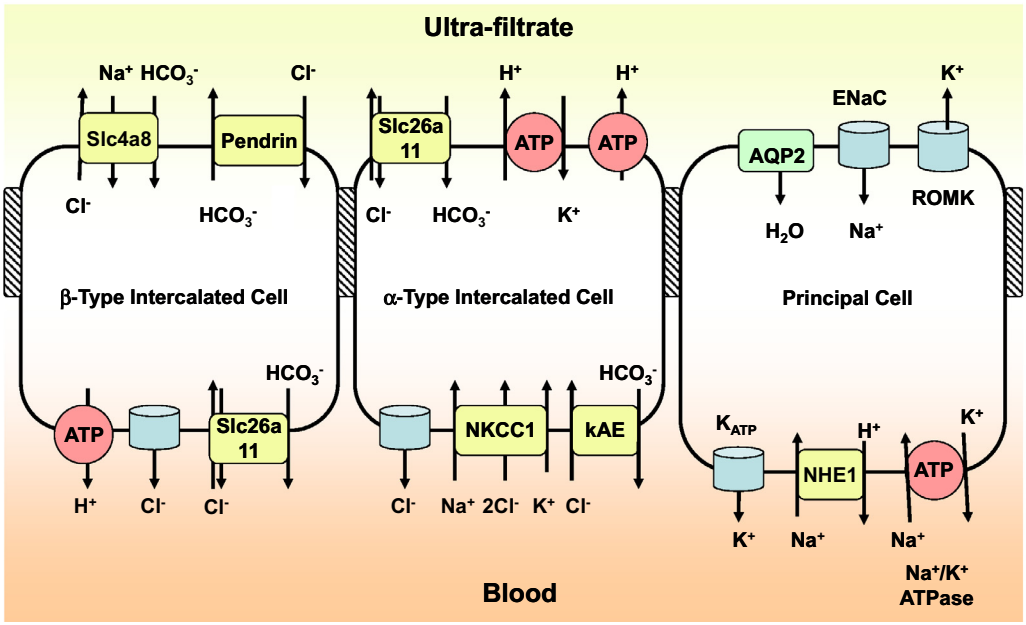

Fig. 1. Membrane transport molecules in cortical collecting duct cells. The cortical collecting duct (CCD) cells play a critical role in whole body electrolyte balance. Under conditions of hyperkalemia, K^+ is secreted by the principal cells through the renal outer medullary K^+ (ROMK) channel. Na^+ is reabsorbed through the epithelial Na^+ channel ENaC, driven by the basolateral Na^+/K^+ ATPase. Water is recovered by osmosis either through paracellular transport or via apical water channel aquaporin 2 (AQP2). The α- and β-type intercalated cells regulate blood acid/base homesostasis. α-Type intercalated cells secrete protons via apical H^+ ATPase and H^+/K^+ exchangers, while bicarbonate is reabsorbed by anion exchangers at the apical (Slc26a11) and basolateral (kAE) membranes. The β-type intercalated cells secrete bicarbonate via the anion exchangers Slc26a4 (Pendrin) and Slc4a8, and reabsorb protons via a basolateral H^+ ATPase.

diovascular disease and stroke [2], or where rare genetic pathologies dysregulate the effectors of aldosterone action, such as in pseudohypoaldosteronism type I [3] and Liddle's Syndrome which presents itself with hypertension and hypokalemia [4]. A common feature of these pathologies is an increase in the activity of ENaC which subsequently drives the excessive conservation of Na^+. Na^+ in the renal ultra-filtrate is reabsorbed at the apical or the luminal surface of the aldosterone sensitive distal nephron (ASDN) principal epithelial cells through the ENaC and Na^+/Cl^- co-transporter under the influence of circulatory levels of aldosterone [5]. The ASDN, which is the principal site for the regulation and conservation of salt, is comprised of the distal convoluted tube (DCT), the connecting tubule (CNT), the thick ascending limb (TAL) of the loop of Henle and the cortical collecting duct (CCD) which all show MR expression [6]. The principal and intercalated cells of the CCD (Fig. 1) operate as a functional unit in ion transport but the principal cells exhibit much higher expression of MR when compared to the intercalated cells [1]. The DCT and the CNT are the key sites of Na^+ re-absorption in the kidney by absolute quantity, but the lesser fraction recovered by the CCD is subject to the most stringent hormonal control [7].

In common with other steroid hormone receptors, MR operates as a ligand-dependent transcription factor. In the distal nephron the expression of ENaC is tightly regulated by aldosterone, which promotes the MR-dependent transcription of ENaCα. MR activation also suppresses the activity of Nedd 4-2 ubiquitin ligase to promote the stability of pre-expressed ENaC. The earliest transcriptional change initiated by aldosterone is the up-regulation of serum and glucocorticoid-regulated kinase (SGK)-1 expression. The measurable effects on the transportation of electrolytes in the kidney are usually detected a few hours following treatment [8]. The earliest physiological effect of aldosterone on ion transport has been linked to an increase in SGK expression that impacts upon transporter stability. Changes in SGK-1 mRNA abundance can be detected within 20 min of aldosterone treatment. It is now becoming clear that rapidly activated signalling cascades also contribute to the modulation of renal ion transport by aldosterone. The early, non-genomic effects of aldosterone can produce rapid changes such as the activation of protein kinase C (PKC) and protein kinase D (PKD) [9]. How the stimulation of such signalling cascades augments the activity of key aldosterone-modulated effectors including ENaC, Na^+/K^+-ATPase, SGK and the renal outer medullary K^+ (ROMK) channel is crucial to establishing the physiological relevance of processes that are initiated in advance of transcriptional control [10–12]. At present, MR is the only widely recognised receptor specific to aldosterone and considerable effort has been exerted in understanding how nuclear receptors like MR can initiate protein kinase signalling cascades in the manner of membrane associated receptors [13].

2. MR and rapid signalling cascades

A number of strands of evidence point to MR as being the receptor responsible for initiating the aldosterone-induced rapid signalling cascades. The activation of protein kinases such as PKD and extracellular stimulus-regulated kinase (ERK1/2) by aldosterone for example can be inhibited with the use of MR-specific antagonists such as spironolactone and eplerenone [14–16]. The ability to exhibit the rapid actions of aldosterone in MR-null cells can be conferred through exogenous expression of the receptor in CHO and HEK cells [17]. MR can be considered to be a multifunctional receptor. If recombinant MR which lacks its DNA-binding and coactivator-binding domains is expressed, signalling events can be instigated by a rapid response to aldosterone independent of transcriptional activity [18]. In terms of the intermediate phases that couple the aldosterone-MR interaction with the rapid activation of protein kinases, there are still some questions to be addressed. It is well established that the trans-activation of the epidermal growth factor receptor (EGFR) is a fundamental step in linking this initiation signal to the aldosterone-responsive downstream signalling intermediates [19]. It has yet to be determined by which molecular mechanism EGFR and its activation is coupled to MR but it is thought that it is EGFR ligand independent. EGFR is phosphorylated by a small tyrosine kinase, c-Src, within 5 min of treatment with aldosterone and this c-Src phosphorylation could be a