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Rapid responses to aldosterone in the kidney and colon☆

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Abstract

Aldosterone is a crucial modulator of ion transport across high resistance epithelia and regulates whole body electrolyte balance through its effects on the kidney and colon. The net consequence of aldosterone release is to promote salt conservation. The genomic mechanism of aldosterone action is relatively well characterized and the role of the classical mineralocorticoid receptor as a ligand-dependent transcription factor is well established. The rapid effects of aldosterone on target tissues are less well understood and there is still controversy over the identity of the aldosterone non-genomic receptor. Greater understanding of the physiological consequences of aldosterone's rapid responses in the kidney and colon has been achieved through the identification of definite and putative membrane targets and their signaling regulators.
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1. Introduction

The kidney and distal colon are the principal target organs for aldosterone regulation of whole body electrolyte balance. The classical mechanism for aldosterone to elicit its effects is to increase the expression of membrane transporters in target epithelia through the action of the classical mineralocorticoid receptor (MR) as a ligand dependent transcription factor [1,2]. Rapid physiological responses to aldosterone may also be observed well in advance of transcriptional changes, however it is the genomic effects of aldosterone that have been most intensively studied. The earliest investigation of rapid responses to aldosterone almost 50 years ago, described the hormone's effects on Na^+ and K^+ excretion into the urine within 5 min following its intra-arterial administration [3]. The critical role for aldosterone in the regulation of Na^+, K^+ and H^+ fluxes across high resistance epithelia both rapidly and over extended periods of time has subsequently been confirmed by many investigators [4]. In general terms, aldosterone promotes Na^+ absorption and net K^+ secretion in the distal nephron and distal colon, additionally since water follows Na^+ by osmosis the net effect of aldosterone release is to increase extracellular fluid volume and to raise blood pressure [5]. Consequently, the effects of aldosterone on the kidney and colon not only modulate whole body, homeostatic, electrolyte balance but can also contribute to pathophysiological effects on tissues including the kidney and vasculature through the development of hypertension [6,7].

2. Kidney

In the kidney, aldosterone exerts its most pronounced physiological effects on the epithelial cells of the distal, reabsorbative region of the nephron. The aldosterone sensitive distal nephron is comprised of the thick ascending limb (TAL) of the loop of Henle; the distal convoluted tubule; the connecting tubule and the cortical collecting duct (CCD). This region of the nephron is the principal site for regulating the rate of Na^+ efflux from the body. Na^+ is reabsorbed at the apical surface of the principal epithelial cells from the renal ultrafiltrate through the epithelial sodium channel (ENaC). Na^+ is transported out of the epithelium at the basolateral membrane by the Na^+/K^+ ATPase pump and into the blood, which in turn maintains a gradient for apical Na^+ uptake. The Na^+ mem-

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brane transporters and others such as the Na^+/H^+ exchangers (NHE) are regulated by aldosterone at the transcriptional level over a number of hours after treatment and some are also activated rapidly, within a few minutes through the stimulation of cell signaling cascades that modulate the activity and subcellular distribution of pre-expressed transporters.

2.1. Membrane targets

2.1.1. NHE

The eight known mammalian NHE sub-types mediate the electroneutral exchange of Na^+ for H^+ across the cell membrane. In polarized epithelia NHE1 is located at the basolateral membrane and contributes to homeostatic processes such as cell volume regulation and cytoplasmic pH modulation. NHE3 is located at the apical surface of cells from the proximal nephron, the distal nephron and the colorectal epithelium where it mediates $NaHCO_3$ and NaCl reabsorption. Trans-membrane Na^+/H^+ exchange was identified as responding rapidly to aldosterone in the MDCK canine, renal cell line [8]. The rise in cytoplasmic pH associated with this activation was preceded by, and dependent upon, a rise in $[Ca^{2+}]_i$ within 1 min of aldosterone treatment [9]. NHE3 activation in proximal tubule cells was sensitive to the classical MR antagonist spironolactone [10] and was dependent on ERK1/2 MAP kinase activation [11]. Aldosterone stimulated NHE1 activity in the M1-CCD cells was also preceded by a calcium influx, and was PKC and ERK1/2-dependent, but was spironolactone-insensitive [12]. It has recently been proposed that aldosterone inhibits the activity of apical NHE3 in the medullary TAL through a non-genomic, MR-independent mechanism to block HCO_3^- reabsorption [13,14]. This effect is contrary to aldosterone's stimulatory effect on NHE3 activity in the proximal tubule [10]. The stimulation of NHE1 by aldosterone may mediate the hormone's transcriptional effects through the activation of pH sensitive signaling processes while NHE3 activity contributes to the aldosterone sensitive absorption of HCO_3^- from the renal ultrafiltrate. The pH shift generated by NHE1 stimulation contributes to the activation of other membrane transporters that promote K^+ recycling in the distal tubule such as K^+_{ATP} channels [15].

2.1.2. K^+ channels

Active transport of Na^+ across the basolateral membrane requires activation of Na^+/K^+ ATPase to export Na^+ in exchange for K^+. The ATP sensitive K^+ channels facilitate K^+ recycling across basolateral membrane. Stimulation of K^+_{ATP} channel activity was detected within 2 min of aldosterone treatment of A6 amphibian renal principal cells [15]. This effect was blocked by amiloride, an inhibitor of NHE activity and could be mimicked by a cytosolic pH shift from pH 7.15 to 7.4 [15]. More recent work has shown that the aldosterone induced up-regulation of the Kir1.1/ROMK K^+ channel in murine TAL cells relies upon cystic fibrosis trans-membrane conductance regulator (CFTR) Cl^- channel activation [16] and is also dependent on ENaC expression [17]. Complex regulatory mechanisms therefore integrate the different aldosterone responsive membrane transporters. CFTR is regulated through multiple potential phosphorylation target sites for PKA and PKC. The coupling of CFTR activation to Kir1.1 confers ATP sensitivity on Kir1.1 and CFTR may act as a PKA-dependent switch for the regulation of K^+ secretion by the distal nephron [16]. Rapid PKC but not PKA activation has been identified as a consequence of aldosterone treatment in the M1-CCD cell line [18]. However, increased cAMP production has been detected in isolated inner medullary collecting duct cells within 4 min of aldosterone treatment that could potentiate PKA activity [19]. It may prove to be that the increase in cytosolic pH stemming from increased NHE activity is the switch that initially engages K^+ recycling but other factors later feed into the regulation once the expression of transporters such as ENaC and CFTR in the cell membrane has been adjusted.

2.1.3. Na^+/K^+ ATPase

The basolateral Na^+/K^+ ATPase pump by reducing intracellular Na^+ and raising K^+ provides the main electrochemical driving force for the luminal influx of Na^+ and the basolateral efflux of K^+ in the distal nephron. The activation of Na^+/K^+ ATPase is generally regarded to occur in two phases early (1–4 h) where pre-existing pump subunits are recruited to the cell membrane and late (+4 h) when there is a detectable change in Na^+/K^+ ATPase expression through the transcriptional effects of activated MR. Aldosterone also stimulates Na^+/K^+ ATPase activity in isolated CCD tubules within 30 min of treatment [20]. The serum and glucocorticoid-induced kinase 1 (SGK-1) is the only kinase identified which directly regulates Na^+/K^+ ATPase in response to aldosterone in the kidney [21]. The prominent role of SGK-1 as an intermediate in aldosterone's early effects (1–2 h) on Na^+ transport is well established. This kinase is however regulated at the transcriptional level and its effects on Na^+/K^+ ATPase activity are only observed after an extended period [21]. The Na^+/K^+ ATPase also has a PKC phosphorylation site on the α subunit, residue Ser-23 [22] and mutation of this site compromises its capacity to transport Na^+ [23]. Phosphorylation of Na^+/K^+ ATPase by PKA has been observed at Ser-943 and phosphorylation at this site potentiates activation by PKC [24]. Many investigators have also observed the pH sensitivity of Na^+/K^+ ATPase activity in different experimental systems including renal cells [25,26]. This has been attributed to the effect of intracellular pH on ion binding specificity of the transporter [27]. Since PKC activation and changes in intracellular pH are early events in the rapid responses stimulated by aldosterone in the kidney, these may contribute to the early phase in aldosterone induced Na^+/K^+ ATPase activity in advance of changes in SGK-1 expression.

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