On the Pleotropic Actions of Mineralocorticoids

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Introduction

Mineralocorticoids are key hormones regulating extracellular volume homeostasis [1, 2]. Their release is up-regulated in extracellular volume depletion, they enhance salt intake by upregulating salt appetite [3, 4] and they decrease renal salt loss by stimulating salt reabsorption in the aldosterone-sensitive nephron segments [1, 2]. Moreover, mineralocorticoids curtail salt loss by stimulating salt (re)absorption in colon [5, 6], sweat glands and salivary glands [6]. At least in part due to extracellular volume expansion, mineralocorticoids enhance cardiac output and blood pressure [7, 8]. However, the mineralocorticoid receptor [9–11] is expressed in a wide variety of tissues [10]. The mineralocorticoid receptor binds aldo-
sterone, cortisol and corticosterone with similar affinity [10, 12] but the inactivation of glucocorticoids by 11β-hydroxysteroid dehydrogenase 2 (HSD2) in aldosterone-target cells confers some aldosterone specificity in those cells [10, 12, 13]. More recent research revealed further functions of mineralocorticoids, which are seemingly unrelated to extracellular volume regulation. This brief overview will address some of those functions. Moreover, several of those functions are amplified in separate short reviews of this special issue.

**Effects of Mineralocorticoids**

Mineralocorticoids are powerful regulators of renal tubular salt transport [1, 2]. They upregulate the epithelial Na⁺ channels, the apical K⁺ channels and the Na⁺/K⁺ ATPase and thus stimulate renal tubular Na⁺ reabsorption and K⁺ secretion in the aldosterone-sensitive nephron segments [1, 2]. The aldosterone-induced renal Na⁺ retention in the distal nephron leads to extracellular volume expansion, which inhibits Na⁺ reabsorption in the proximal tubule and thick ascending limb resulting in reduced Ca²⁺ and Mg²⁺ reabsorption in those nephron segments [14, 15]. As a result, aldosterone leads to magnesuria and calciuria [14, 15]. Mineralocorticoids further stimulate renal tubular H⁺ secretion and thus generate alkalosis [16–18]. Aldosterone modifies renal acid excretion in part by upregulating both H⁺ pumps and Cl⁻/HCO₃⁻ exchanger pendrin [18]. Mineralocorticoids upregulate pendrin in a variety of further tissues [19]. The functional significance of mineralocorticoid-sensitive pendrin regulation in those tissues remained elusive.

Mineralocorticoids further enhance salt appetite [2, 4] and thus foster salt intake, as amplified in separate reviews of this special issue [20, 21]. Enhanced salt intake and renal salt retention lead to extracellular volume expansion with increase of blood pressure [7, 8, 22]. The effect of mineralocorticoids on blood pressure does, however, not depend on the effect of mineralocorticoids on the distal nephron [23] but is attributed in part to vascular inflammation [24, 25], to enhanced endothelial stiffness, which compromises the release of nitric oxide [26–30] and direct effects of the mineralocorticoid receptor in vascular smooth muscle [31]. Besides leading to systemic hypertension, mineralocorticoids could foster pulmonary hypertension [32].

Moreover, mineralocorticoids increase vascular stiffness [33, 34] and vascular as well as soft tissue calcification [25, 35, 36], as amplified in a separate contribution to this special issue [37]. Mineralocorticoids influence tissue calcification in part by downregulation of klotho [38, 39].

Mineralocorticoids further stimulate cardiac and renal fibrosis [33, 40–56], as discussed in a further contribution to this special issue [57].

The increase of blood pressure following aldosterone action affects the heart, which is further affected by direct effects of mineralocorticoid receptors on cardiac function, electrical conduction, oxidative stress, inflammation and fibrosis [43, 58, 59]. Mineralocorticoid receptors are further involved in the regulation of adipogenesis as well as adipose tissue expansion and may contribute to insulin resistance and obesity [60–63]. Mineralocorticoids affect neuronal function and survival [3, 64–67] as amplified in a separate review of this special issue [21].

Mineralocorticoids upregulate the pore-forming Ca²⁺ channel protein Orai1 [68] and thus increase the Ca²⁺ concentration [69] in blood platelets. Activation of Orai1 contributes to store-operated calcium entry (SOCE) [70, 71], thus leading to platelet activation [72–74], cytoskeletal reorganization with respective shape changes [75] and cell membrane scrambling with phosphatidylinerine translocation to the outer platelet membrane surface [76–80]. Phosphatidylinerine at the platelet surface enhances in turn thrombin formation and platelet procoagulant activity [77–79, 81]. Moreover, increased Ca²⁺ concentration triggers platelet degranulation, integrin α IIb β 3 activation and adhesion of platelets [72]. Orai1 protein abundance and thus Ca²⁺ entry are upregulated by the serum- and glucocorticoid-inducible kinase isoform SGK1 [82, 83], a kinase strongly upregulated by mineralocorticoids [84]. Orai1 is further upregulated by the isoform SGK3 [85]. SGK1 upregulates in megakaryocytes the transcription factor NF-κB, which in turn stimulates Orai1 expression [82]. Mineralocorticoids thus enhance the sensitivity of platelets to activators and mineralocorticoid excess is thus expected to foster thrombosis and vascular occlusive disease [82]. On the other hand, specific activation of the endothelial mineralocorticoid receptor may counteract thrombosis [86].

**Mechanisms Involved in Mineralocorticoid Effects**

Mineralocorticoids are, at least partially, effective by binding to the mineralocorticoid receptor, which acts as a ligand-dependent transcription factor regulating gene expression.
expression [9, 34, 36, 46, 48, 87–89]. The receptor is similar to the glucocorticoid receptor and may be activated by glucocorticoids [90]. Activation of the mineralocorticoid receptor upregulates a wide variety genes involved in transport such as channels, carriers and transport-regulating signaling molecules including the serum- and glucocorticoid-inducible kinase SGK1 [91, 92].

Mineralocorticoid receptor activation further triggers inflammation in part due to stimulation of reactive oxygen species generation by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and mitochondria [43]. In the heart, activation of mineralocorticoid receptors leads to activation of the Na⁺/H⁺ exchanger NHE-1 with subsequent increase of cytosolic Na⁺ and Ca²⁺ entry through reversal of the Na⁺/Ca²⁺ exchanger [93]. Notably NHE1 is upregulated by oxidative stress [93] and SGK1 [94, 95].

The effects of mineralocorticoids are augmented by Ras-related C3 botulinum toxin substrate 1 (Rac1), a Rho-family small GTPase [96].

Besides their effect on gene expression, mineralocorticoids could exert nongenomic effects [3, 33, 56, 66, 67, 97–104], which are, at least partially, mediated by angiotensin-II receptor and G protein-coupled receptor 30 [43]. Signaling involved in nongenomic mineralocorticoid action includes stimulation of phosphatidylinositol-3-kinase (PI3K) [105, 106].

As apparent from blood platelets [68], mineralocorticoids may further influence protein translation, which is regulated by the translation initiation factors eIF-4E and eIF-2α eIF-4E [107, 108] as well as the inhibitory 4E-binding protein 4E-BP1 [107]. 4E-BP1 is phosphorylated by PI3K [109] and subsequently binds eIF-4E, thus inhibiting translation [109]. Mineralocorticoids activate PI3K leading to redistribution of the initiation factors to the proximity of mRNA [107]. Initiation of translation requires both actin polymerization and PI3K activation [110].

**Pathophysiology of Mineralocorticoid Excess**

Excessive mineralocorticoid action is associated with enhanced risk of vascular disease, such as hypertension, heart failure, cardiac electrical remodeling, atrial fibrillation, atherosclerosis and fibrosis [33, 58, 111–116]. The cardiovascular disease in mineralocorticoid excess is the result of extracellular volume expansion with hypertension [7, 8, 41], endothelial stiffness with compromised NO release [26–30], cardiovascular inflammation and fibrosis [43, 57, 117, 118] as well as calcification with enhanced vascular stiffness [35–37]. Moreover, vascular events may result from enhanced Ca²⁺ entry into blood platelets [69] with enhanced degranulation, aggregation and adhesion [68] and eventually acute thrombotic occlusion following atherosclerotic plaque rupture [82, 119] and ischemic cardiovascular events such as myocardial infarction or ischemic stroke [120]. In the kidney, excessive mineralocorticoid action leads to renal inflammation, fibrosis, podocyte injury, and mesangial cell proliferation [121]. The pathophysiological consequences of mineralocorticoid action could be reversed by mineralocorticoid receptor antagonists [58, 63, 116, 122–140]. The therapeutic potential of mineralocorticoid receptor antagonists is thus not only confined to their diuretic action, but involves prevention of tissue fibrosis, vascular calcification and vascular occlusive disease.

**Disclosure Statement**

The author has no conflicts of interest to disclose.

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**References**


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Mineralocorticoid Actions


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