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Review Article

Aldosterone's impact on kidney health: exploring the benefits of mineralocorticoid receptor antagonists for renal protection

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Abstract: Aldosterone, a hormone synthesized by the adrenal cortex, plays a crucial role in regulating sodium and potassium levels in the kidneys through interaction with the mineralocorticoid receptor (MR) in the distal tubules and collecting ducts. While aldosterone aids in maintaining fluid balance by promoting sodium reabsorption and potassium secretion, elevated levels can lead to inflammation, oxidative stress, and organ damage. Experimental evidence highlights aldosterone's involvement in renal inflammation, collagen deposition, and fibrosis, often exacerbating the effects of therapies like angiotensin-converting enzyme inhibitors (ACEIs) by increasing proteinuria and vascular damage. Conversely, mineralocorticoid receptor antagonists (MRAs) show promise in mitigating these harmful effects. This review integrates current knowledge on aldosterone and MRAs, emphasizing their roles in renal health from both clinical and experimental perspectives. Additionally, the novel drug finerenone has shown favorable renal and cardiovascular outcomes in patients with diabetes and chronic kidney disease (CKD), warranting exploration of its potential use in other disease populations in future research.

Keywords: Aldosterone, chronic kidney disease, mineralocorticoid receptor antagonists, kidney injury, renin-angiotensin system

Introduction

Kidney disease is a prevalent and critical global health concern impacting millions of individuals worldwide [1]. Excessive production of aldosterone, a key contributor to kidney disease, can result in hypertension, electrolyte imbalances, and renal fibrosis. Despite extensive research efforts in recent years, a satisfactory method for managing this condition has yet to be developed. Hypertension and proteinuria are recognized as primary drivers of CKD progression, underscoring the essential role of effective antihypertensive therapy in treatment [2]. Notably, certain antihypertensive medications, such as ACEIs and angiotensin II (Ang II) receptor blockers (ARBs), have demonstrated protective effects. Experimental evidence has elucidated that activation of the renin-angiotensin system (RAS) can contribute to intra-glomerular and systemic hypertension, leading to hemodynamically induced renal injury [3]. Furthermore, Ang II, the principal mediator of RAS, can directly and indirectly promote the proliferation of mesangial cells and renal tubular cells, potentially resulting in stromal production and tubulointerstitial fibrosis. Many studies have highlighted the beneficial impact of ACEIs or ARBs in mitigating RAS-related effects, improving proteinuria, and slowing CKD progression [4-6].

Recent research insights suggest that aldosterone, whether produced systemically or locally, plays a significant role in kidney disease, alongside the adverse effects of Ang II [7]. Hyperactivation of the MR can induce endothelial dysfunction, fibrinolytic disorders, oxidative

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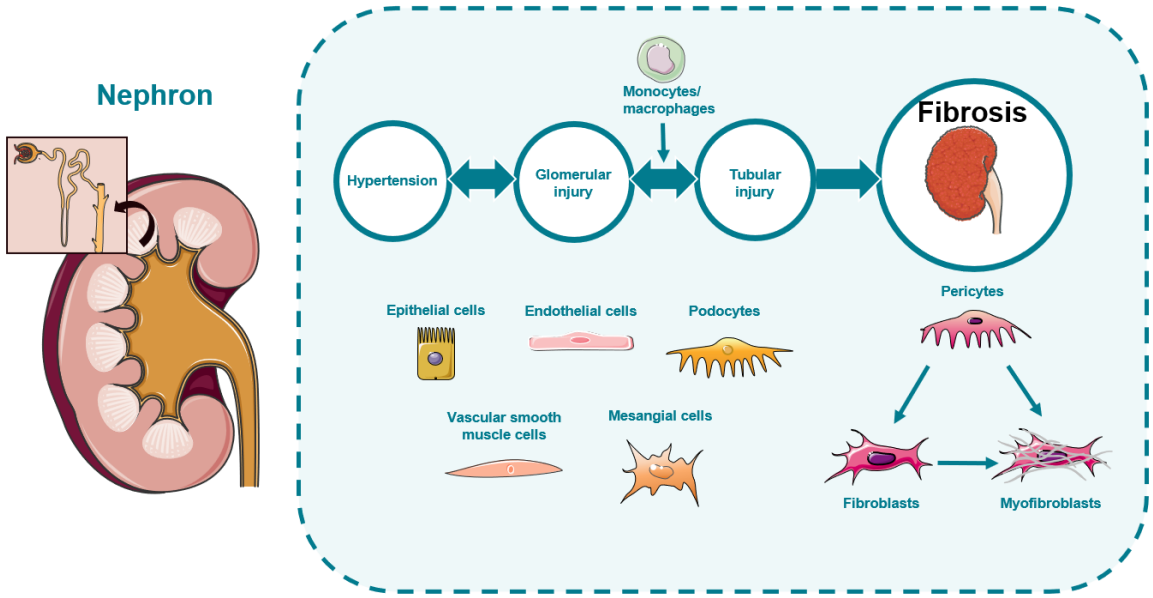

Figure 1. Role of aldosterone in kidney damage and clinical benefits of aldosterone blockade by mineralocorticoid receptor antagonists.

stress, and cardiovascular and renal fibrosis, culminating in organ dysfunction, damage, and failure. However, the utilization of MRAs can offer cardiorenal protection by inhibiting inflammation and fibrosis triggered by MR activation. This advancement has opened avenues for employing MRAs in CKD treatment. Several clinical trials have underscored the impact of MRAs on kidney disease progression and development. Notably, recent studies on a novel MRA named finerenone have been published [8, 9]. Finerenone, a novel nonsteroidal MRA with high selectivity and potent MR blockade, exhibits definitive cardiorenal protective effects, further underscoring the therapeutic potential of this drug class. This review delves into the influence of aldosterone on kidney disease progression and explores the potential role of MRAs in managing kidney disease (**Figure 1**).

Synthesis and secretion of aldosterone

Aldosterone, a steroid hormone, was initially identified in the 1950s and is produced and released by the adrenal cortex [10]. It plays a pivotal role in maintaining fluid and electrolyte balance in the body. The synthesis and secretion of aldosterone are primarily governed by RAS, as well as the levels of sodium and potassium ions. Renin, an enzyme, is synthesized by granular cells in the glomerular parietal apparatus and is influenced by factors such as reduced renal blood flow, renal hemorrhage, dehydration, and salt intake. Subsequently, Ang II binds to the angiotensin II receptor type 1 (AT1R), enhancing the transcriptional activity of the aldosterone synthase gene, leading to aldosterone production and release. Potassium also plays a role in regulating aldosterone independent of the RAS by affecting calcium channels. Activation of calcium-regulated protein kinases by calcium influx promotes the expression of transcription factors and calcium-binding proteins, further stimulating aldosterone synthase gene expression and aldosterone secretion. Notably, aldosterone is not only produced in the adrenal gland but also in extrarenal tissues such as the heart, blood vessels, and brain [11, 12]. The local RAS in vascular smooth muscle cells generates Ang II, which in turn stimulates aldosterone production and secretion. Adipocytes can also synthesize aldosterone through calcium-regulated neuro-phosphatase signaling pathways, influencing cell differentiation and vascular function in an autocrine and paracrine manner [13].

Recent research has dramatically transformed our understanding of aldosterone secretion in the past few decades. It is now recognized that aldosterone release is not solely driven by

angiotensin, as various other factors can stimulate its production. Increased sympathetic nervous system activity can trigger aldosterone secretion, potentially contributing to elevated aldosterone levels during stress [14]. Additionally, factors such as low plasma sodium levels, high potassium levels, hypovolemia, hypoglycemia, and atrial natriuretic peptide can also stimulate aldosterone synthesis [15]. Inflammation and certain medications like nonsteroidal anti-inflammatory drugs may impact aldosterone levels as well [16]. These discoveries have reshaped our comprehension of aldosterone, underscoring the intricate interplay of multiple factors in its regulation. This complex regulatory network shifts the perception of aldosterone secretion from being solely controlled by the RAS to being comprehensively influenced by various internal and external stimuli. Furthermore, aldosterone serves not only as a primary ligand for the MR but also plays a crucial role in regulating sodium reabsorption to maintain fluid balance. Its influence on blood pressure regulation extends beyond fluid balance to involve vascular and central nervous system modulation. Moreover, aldosterone is intricately linked to a spectrum of disease-related pathophysiological processes, beyond its role in fluid and electrolyte regulation.

Pathways of action of aldosterone: genomic and non-genomic

Historically, the effects of aldosterone were predominantly attributed to genomic pathways, where it binds to the MR to modulate gene expression. The carboxy-terminal structural domain of MR, CT-LBD, and its specific interaction with heat shock proteins (HSPs) are pivotal for its functionality [17]. In its inactive state, MR associates with HSP70, HSP90, and various immunoaffinity proteins. Upon aldosterone binding, these molecules dissociate from CT-LBD, activating MR and facilitating its translocation to the nucleus. Within the nucleus, MR binds to hormone response elements in the promoter region of target genes, leading to either gene activation or repression, contingent upon the recruitment of co-activators or repressors in the gene transcription initiation complex.

Aldosterone's modulation of gene expression occurs promptly, within hours of aldosterone stimulation, or delayed, promoting the synthesis of new proton pumps, ion channels, and transporters, thereby enhancing their abundance on the plasma membrane [18]. Epithelial sodium channels (ENaC) act as the final effectors of renal aldosterone activation and its receptor system, facilitating sodium-water reabsorption and regulating body fluid volume and blood pressure. The circulating glucocorticoid-regulated kinase 1 (SGK1) serves as a crucial downstream molecule, a serine-threonine kinase activated approximately thirty minutes post-aldosterone stimulation, correlating with an elevation in cell surface ENaC density [19]. SGK1 phosphorylates and inhibits the ubiquitin ligase Nedd4-2, preventing ENaC degradation. Furthermore, aldosterone stimulation upregulates the expression of pro-fibrotic genes like connective tissue growth factor in cardiomyocytes, indicating the influence of aldosterone and its receptors on extrarenal tissues [20]. Additionally, MR in cardiomyocytes triggers the atrial natriuretic peptide pathway by interacting with p300 and GATA4, fostering myocardial hypertrophy [17].

Aldosterone possesses the capability to activate both genomic and non-genomic pathways, leading to target organ injury (Table S1). The non-genomic effects of aldosterone can occur through MR binding or independently of MR via crosstalk mechanisms. Notably, aldosterone triggers a rapid and transient elevation in intracellular calcium levels in renal epithelial cells, dependent on c-Src tyrosine kinase activation and transactivation of the epidermal growth factor receptor (EGFR) [21]. This EGFR signaling activation subsequently impacts other pathways such as mitogen-activated protein kinases (ERK), protein kinase C (PKC), and phosphatidylinositol-3 kinase (PI3K), with c-Src playing a pivotal role in this cascade. In vascular smooth muscle cells, aldosterone-induced c-Src activation leads to p38 mitogen-activated protein (MAP) and nicotinamide adenine dinucleotide phosphate oxidase (NOX) 2 and NOX4 activation, culminating in collagen synthesis and reactive oxygen species production [22]. Inhibition of AT1R can impede ERK activation, suggesting potential crosstalk between aldosterone and Ang II pathways [23]. Moreover, studies have indicated that the MR/AT1R system activation is associated with both genomic

and non-genomic effects linked to aldosterone stimulation [24]. Additionally, aldosterone prompts nuclear translocation of the G protein-coupled receptor via the MR/AT1R system, with G protein-coupled receptor kinase 5 being a key player in aldosterone-mediated genomic effects leading to cellular hypertrophy. While some evidence suggests that aldosterone can activate the estrogen receptor in myocytes and non-myocytes, further research is warranted to comprehensively elucidate its potential impact on cardiac and vascular smooth muscle cells [25].

It is evident that the effects of aldosterone can manifest through both genomic and non-genomic pathways. While aldosterone-MR binding regulates fluid and electrolyte balance, its non-genomic pathways play a critical role in mediating target organ damage through swift and direct effects.

Pathways of aldosterone-induced kidney damage: inflammatory and fibrosis

In the early 2000s, animal studies indicated that targeted blockade of aldosterone mitigated glomerulosclerosis and reduced urinary protein levels in spontaneously hypertensive rats. Administration of ACEIs and ARBs also suppressed proteinuria and glomerulosclerosis, but co-infusion of aldosterone reinstated these indications of damage [26]. These results strongly suggest the involvement of aldosterone in kidney damage. Subsequent research has increasingly demonstrated a close relationship between aldosterone, MR, and the advancement and onset of kidney damage, which may occur through the stimulation of an inflammatory response and fibrosis (Table S2).

During the development of the inflammatory response, various causes first induce the production of pro-inflammatory factors, chemotaxis, recruitment of immune cells, and promotion of local tissue damage; then active inflammation and further infiltration of inflammatory cells occur, which, if left unchecked, lead to remodeling, extracellular matrix production, collagen deposition, and eventually fibrosis. Tissue/organ remodeling and fibrosis represent the ultimate manifestation of the inflammatory response. In the 1990s, Brilla et al. [27] reported that aldosterone injection induced interstitial and perivascular fibrosis in rats, while an aldosterone antagonist, spironolactone, mitigated the rise in blood pressure and improved left ventricular hypertrophy. These findings led to the hypothesis that aldosterone is associated with inflammation in the heart and that its effects are primarily mediated through MR binding. Subsequently, numerous studies have demonstrated that aldosterone not only contributes to the ultimate manifestation of fibrosis but also stimulates the production of inflammatory factors. Aldosterone has been shown to play a role in the development of inflammation and fibrosis in the cardiovascular system and cardiac damage [28]. The genomic pathway regulates gene expression, affecting gene transcription and protein synthesis within cells, thereby influencing cell function and organ physiological activities. Infusion of aldosterone in a rat model upregulated the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), as well as inflammatory markers such as cyclooxygenase 2 (COX-2), monocyte chemotactic protein 1 (MCP-1), and osteopontin (OPN) prior to inflammatory cell infiltration [29, 30]. Pathological examination of cardiac tissue revealed signs of coronary artery inflammation, local ischemia, and necrosis.

As investigations progressed, the connection between aldosterone and renal inflammatory and fibrotic responses became increasingly evident. Terada et al. [31] reported that in mouse kidneys, aldosterone contributed to renal tract fibrosis and inflammation by stimulating the transcription of ICAM-1 and CTGF through the activation of SGK-1 and NF-κB. Furthermore, MRAs notably alleviated glomerular injury. Hao et al. [32] also revealed that aldosterone promoted renal inflammatory responses by upregulating NF-κB expression. In rats injected with aldosterone, the expression of pro-inflammatory factors was elevated in the kidneys, and MR knockdown mitigated this effect. Macrophages were found to play a key role in mediating MR activation-induced injury. Another study discovered increased levels of IL-6 and tumor necrosis factor alpha expression in perirenal tissues of patients with aldosteronism compared with those with essential hypertension, further supporting the role of aldosterone in the renal inflammatory response [14]. In addition, renal podocytes were found to activate NLRP3 inflammatory vesicles in response to aldoste-

rone, thereby promoting the development of proteinuria [33].

The non-genomic pathway, on the other hand, involves aldosterone interacting with receptors on the cell membrane or other signaling molecules, directly affecting intracellular signaling pathways, rapidly regulating cell function and metabolic activities. In terms of vascular regulation, aldosterone exerts its effects mainly by binding to HRE and activating the ERK1/2 signaling pathway, promoting vascular smooth muscle cell proliferation and expression of vascular collagen components [34]. This, in turn, decreases vascular compliance, constricts small inlet and outlet glomerular arteries, elevates glomerular pressure, and ultimately leads to renal fibrosis. In this process, the mediators of aldosterone-induced renal fibrosis include fibrinogen activator inhibitor 1 (PAI-1) and nitric oxide. Moreover, aldosterone induces an increase in OPN expression through activator protein 1 (AP-1) and NF-κB activation, which also contributes to the development and progression of renal fibrosis [35, 36].

Furthermore, aldosterone can induce increased expression of inflammatory factors and infiltration of renal inflammatory cells through multiple pathways, as demonstrated by cellular and animal experiments. This, in turn, leads to renal fibrosis and ultimately manifests as renal injury. *In vivo* studies have also shown that aldosterone antagonists can attenuate the damaging effects of aldosterone on the kidney to some extent.

Clinical study of aldosterone and kidney disease

Association between aldosterone and kidney disease in the general population

Numerous clinical studies have investigated the link between circulating aldosterone levels and kidney injury across diverse populations in recent years [37, 38]. As our understanding of kidney disease has advanced, it has become evident that conventional risk factors may not entirely account for the occurrence and progression of kidney disease, suggesting the involvement of additional unidentified factors. For instance, Fox et al. [39] explored the predictive value of aldosterone levels for CKD development in the Framingham Offspring Cohort. They observed that baseline aldosterone levels were associated with CKD onset during a 9.5-year follow-up of 2345 subjects (OR=1.17, P= 0.047). However, this study did not adjust for confounding factors like age, sex, hypertension, and diabetes in the multifactorial regression model, potentially introducing bias. Subsequent studies in various populations yielded mixed results. A US study [40] involving 9498 subjects found no significant association between plasma aldosterone levels and CKD prevalence, while the Japanese Ohasama study [41] reported no correlation between baseline aldosterone levels and CKD after a median follow-up of 9.1 years. Conversely, a German general population study revealed a negative association between plasma aldosterone levels and glomerular filtration rate, with a positive correlation with CKD [42]. Buglioni et al. [43] conducted a study in 1674 individuals, observing a significant association between aldosterone and CKD in the cross-sectional analysis; however, this association was not sustained in the longitudinal follow-up after four years.

The existing literature on the relationship between circulating aldosterone levels and kidney disease in the general population exhibits inconsistencies, particularly regarding the risk of kidney disease development. These discrepancies may stem from various factors. First, in the general population, the link between aldosterone and kidney disease may be weak due to most individuals having aldosterone levels within the physiological range, resulting in minimal injuring effects. Second, disparities in study locations may introduce biases as aldosterone levels are influenced by both physiological and external factors like dietary habits, potentially contributing to result variations. Third, inadequate adjustment for confounding factors could also contribute to divergent findings. Despite some studies suggesting a correlation between aldosterone and kidney damage, many did not adequately control for known confounders, potentially influencing the outcomes. Moreover, the prevalent use of cross-sectional study designs limits causal inference between aldosterone and kidney damage due to the bidirectional relationship between these variables. In conclusion, further exploration of the relationship between circulating aldoste-

rone levels and renal impairment in the general population is warranted, necessitating larger sample sizes, longitudinal study designs, and comprehensive adjustment for confounding factors.

Relationship between aldosterone and kidney disease in different disease populations

The current literature on the relationship between aldosterone and kidney disease across various patient populations is both limited and inconsistent. Evidence suggests that individuals with aldosteronism tend to have higher serum creatinine levels, increased urinary protein excretion, and reduced glomerular filtration rates compared to those with essential hypertension. Nonetheless, further research is necessary to comprehensively understand the connection between aldosterone and renal function in these patients. The JPAS study in Japan highlighted a robust association between elevated plasma aldosterone levels and kidney disease in primary aldosteronism patients [44]. Nevertheless, the cross-sectional nature of the study precluded causal determinations. Limited research has explored the link between aldosterone and kidney disease in populations with other conditions such as hypertension and diabetes, where altered circulating aldosterone levels may be present.

In summary, primary aldosteronism patients demonstrate a significant association between plasma aldosterone and kidney damage. Conversely, in hypertensive individuals with abnormal glucose metabolism lacking primary aldosteronism, plasma aldosterone levels independently correlate with kidney disease development. Therefore, targeting aldosterone may hold promise for preventing and managing kidney disease in these patients. Nonetheless, further longitudinal investigations are essential to assess the relationship between aldosterone and kidney disease progression in diverse disease populations, particularly those without aldosterone-related conditions.

Potential role of mineralocorticoid receptor antagonists on kidney disease

Aldosterone has been implicated in the progression of kidney disease, particularly in high-risk populations with conditions like hypertension and diabetes mellitus. Despite the availability of various antihypertensive and hypoglycemic medications with some protective effects, the control of kidney disease development and progression remains incomplete in these at-risk groups. Clinical trials have investigated the renal benefits of aldosterone antagonist therapy. A meta-analysis by Bolignano et al. [45] examined the impact of aldosterone antagonists in CKD patients. This analysis of 27 randomized controlled trials involving 1549 subjects revealed that adding spironolactone to ACEIs/ARBs therapy significantly reduced 24-hour urinary protein excretion without affecting glomerular filtration rate. However, aldosterone antagonist treatment increased the risk of hyperkalemia and mastocytosis. Another meta-analysis focusing on spironolactone in diabetic nephropathy patients reported similar outcomes, with a reduction in urinary protein excretion but an elevation in blood potassium levels [46].

A recent randomized placebo-controlled trial evaluating the medium- and long-term efficacy of eplerenone in CKD patients demonstrated a decrease in estimated glomerular filtration rate (eGFR) levels in both groups initially, with lower levels observed in the eplerenone group at 6 months and stable levels thereafter [47]. By the end of the 36-month study, eGFR levels were significantly higher in the eplerenone-treated group compared to the placebo group, suggesting potential long-term renal protection.

While finerenone has been extensively studied in the largest research program on non-steroidal MRA, there are other compounds that have been explored in various contexts. One such compound is esaxerenone, a non-steroidal MRA that has received approval in Japan for managing hypertension and diabetic kidney disease [48]. In the 12-week double-blind Phase III RCT ESAX-HTN, it was found that 2.5 mg esaxerenone was noninferior and 5 mg esaxerenone was superior to 50 mg eplerenone in lowering blood pressure among 1001 Japanese patients with essential hypertension, with comparable rates of adverse events observed across the study arms [49]. Furthermore, in the ESAX-DN trial, a 52-week double-blind Phase III RCT involving 455 diabetic kidney disease (DKD) patients on RAS inhibitor therapy, esaxerenone demonstrated significant

improvement in albuminuria compared to the placebo group (HR for time to first remission of albuminuria: 5.13; 95% CI 3.27, 8.04) [50]. Additionally, a Phase II dose-finding RCT with 293 DKD patients revealed that the non-steroidal MRA apararenone led to a dose-dependent reduction in albuminuria ranging from 37% to 53%, while the placebo group experienced a 14% increase [51]. There is a growing interest in targeting MR activation with enhanced safety profiles, potentially through MR modulators that do not impact renal potassium excretion. Balcinrenone (AZD9977), one such MR modulator, has demonstrated organ protection properties without affecting the urinary sodium/potassium ratio in animal models [52]. Currently, it is undergoing evaluation against a placebo in the Phase IIb RCT MIRACLE, which is enrolling 147 patients with heart failure and CKD (NCT04595370).

In summary, MRAs have shown potential in managing kidney disease, especially in high-risk populations. While they effectively reduce proteinuria and improve renal function in the short term, their long-term impact on kidney health warrants further exploration through larger studies with extended follow-up periods [53, 54]. The emergence of novel agents like finerenone offers hope for improved outcomes in patients with diabetes mellitus and CKD, emphasizing the ongoing evolution of treatment strategies for kidney damage [55].

Conclusions

Preclinical studies have demonstrated the ability of aldosterone to activate multiple pathways that lead to renal inflammation and fibrosis. Although preclinical studies have demonstrated this, the exact relationship between aldosterone and kidney disease in the general population remains unclear and requires further investigation. In populations at high risk of kidney disease, such as hypertensive patients with diabetes, plasma aldosterone levels have been found to be independently associated with the development of kidney disease. Traditional aldosterone antagonists, including spironolactone, have shown potential in the long-term renal prognosis of these patients, but larger-scale studies are needed for further evaluation. Additionally, the novel drug finerenone has shown a favorable renal and cardiovascular prognosis in patients with diabetes and CKD, and its potential for use in other populations with different diseases deserves exploration in future studies. Future research directions could focus on the efficacy of aldosterone antagonists in different patient populations and the broader application of finerenone in the treatment of kidney diseases, providing more options and possibilities for the treatment and management of kidney diseases.

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Disclosure of conflict of interest

None.

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Table S1. Pathways of action of aldosterone: genomic and non-genomic

Pathway	Mechanism	Effects
Genomic	Aldosterone binds to mineralocorticoid receptor (MR)	Regulates gene expression, activates MR, promotes nuclear translocation, binds to hormone response elements (HRE) in target genes, activates or represses gene transcription, promotes formation of proton pumps, ion channels, and transporters
	MR interacts with co-activators or repressors	Activation of epithelial sodium channels (ENaC), increases sodium-water reabsorption, regulates body fluid volume and blood pressure levels, activates glucocorticoid-regulated kinase 1 (SGK1), inhibits ENaC degradation, enhances expression of pro-fibrotic genes
	MR in cardiomyocytes activates ANP pathway	Promotes myocardial hypertrophy
Non-genomic	Aldosterone binds to MR or acts independently	Rapid increase in intracellular calcium levels, activation of tyrosine kinase c-Src, transactivation of epidermal growth factor receptor (EGFR), affects signaling pathways (ERK, PKC, PI3K), activates p38 MAP and NOX 2/4 in vascular smooth muscle cells, increases collagen synthesis and reactive oxygen species production
	Crosstalk with angiotensin II signaling pathways	Activation of G protein-coupled receptor (GPCR5), involvement of G protein-coupled receptor kinase 5 (GRK5), potential activation of estrogen receptor GPER in myocytes and non-myocytes
	MR/AT1R system activation	Linked to genomic and non-genomic effects, nuclear translocation of GPCR5, cellular hypertrophy

Table S2. Pathways of aldosterone-induced kidney damage: inflammatory and fibrosis

Pathway	Mechanism	Effects
Inflammatory Response	Induces production of pro-inflammatory factors, chemotaxis, recruitment of immune cells	Local tissue damage, active inflammation, infiltration of inflammatory cells, tissue remodeling, extracellular matrix production, collagen deposition, fibrosis
	Stimulates production of inflammatory factors	Development of inflammation and fibrosis in cardiovascular system and cardiac damage, upregulation of ICAM-1, VCAM-1, COX-2, MCP-1, OPN, coronary artery inflammation, local ischemia, necrosis
Fibrotic Response	Stimulates transcription of ICAM-1 and CTGF through SGK-1 and NF-κB activation	Renal tract fibrosis and inflammation, alleviation of glomerular injury, upregulation of NF-κB expression, increased levels of pro-inflammatory factors in kidneys, activation of NLRP3 inflammatory vesicles in podocytes
	Activates ERK1/2 signaling pathway	Vascular smooth muscle cell proliferation, expression of vascular collagen components, decreased vascular compliance, glomerular pressure elevation, renal fibrosis
	Induces expression of PAI-1 and OPN through AP-1 and NF-κB activation	Mediators of aldosterone-induced renal fibrosis, contribution to renal fibrosis development and progression