Chapter

Potential Benefit of Mineralocorticoid Receptor Antagonists in Kidney Diseases

Jonatan Barrera-Chimal, Lionel Lattenist and Frederic Jaisser

Abstract

Since the last two decades, a major paradigm shift occurred in our understanding of the physiological and pathophysiological roles of the mineralocorticoid receptor (MR). Expression of the MR in cells/tissues not involved in sodium/potassium balance and extracellular volume homeostasis, i.e., the primary role of the aldosterone/MR complex, paved the way to the discovery of unsuspected implications of MR in a variety of cellular processes and pathological consequences. It also opens the possibility for quick translation to the bedside using available MR antagonists (MRAs) such as spironolactone, canrenone, or eplerenone or using the more recently developed various nonsteroidal MRAs that are not yet marketed. Landmark clinical trials like RALES, EPHESUS, or EMPHASIS well established that MRAs provide great benefits in patients with heart failure and spironolactone or eplerenone have been recommended in these patients. The deep understanding provided by preclinical studies in various domains stimulated the possibility to extend the use of MRAs to new fields, including renal diseases even if MRAs are currently contraindicated or used with great caution in patients with renal function impairment due to the higher risk of hyperkalemia associated with MRA therapy in this at-risk population. The present review presents preclinical data supporting potential indications in renal diseases.

Keywords: aldosterone, renal, hypertension

1. Pathophysiological basis: MR activation in the kidney—where and what are the consequences?

1.1 MR expression in the kidney

Besides the well-known expression of MR in the so-called aldosterone-sensitive distal nephron (ASDN) encompassing DCT1-2, CNT, and CDD, MR is also expressed in a variety of other cell types within the kidney [1–5]. In basal condition, MR is expressed in the vasculature in both endothelium [6] and smooth muscle cells [1]. MR expression has also been reported in the mesangium [7], podocytes [8], fibroblasts [9], and immune cells (macrophages, dendritic cells, T lymphocytes) [10–13]. In **Figure 1**, we summarize the effects reported for MR antagonists in different target cells within the kidney that represent potential

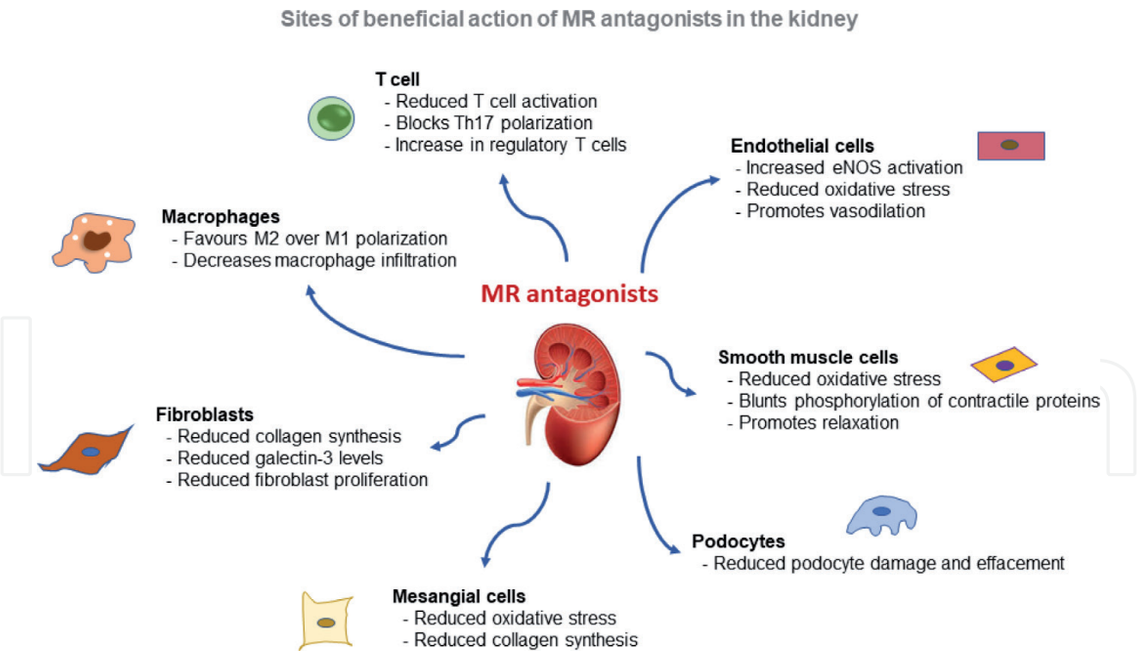

Figure 1.
MR antagonists display beneficial effects against kidney diseases by acting in several cell types and by different mechanisms.

beneficial mechanisms acting against kidney disease progression, and that will be detailed below. It is important to mention that MR expression might be upregulated in some pathological conditions such as diabetes [14], heavy proteinuria [15], vascular aging [16], and hypertension [17], leading to potential increased MR signaling. The specific physiological role of MR in the cells where its expression has been reported remains to be elucidated; however, it was recently proposed that MR in endothelial, smooth muscle, and inflammatory cells may be an evolutionary mechanism to prevent hemorrhage by promoting vasoconstriction and thrombosis and to promote wound healing by the activation of inflammation and vascular remodeling [18].

1.2 MR activation: what is the ligand?

The classical ligand of the MR is aldosterone, but glucocorticoids can bind with similar affinity with that of MR. Of note ligand-receptor dissociation is faster for glucocorticoid than aldosterone, resulting in higher transactivation potency for aldosterone as compared to glucocorticoids, especially at low concentration. However, a selectivity mechanism allows aldosterone to preferentially activate the MR in the presence of glucocorticoids, despite much higher local concentration of glucocorticoids than aldosterone. The 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts corticosterone/cortisol to compounds with low affinity for the MR [19]. The cellular aldosterone/glucocorticoid selectivity therefore depends on the expression level/activity of the HSD2. In the kidney, cells from the ASDN and endothelium express HSD2, while this is debated for the smooth muscle cells [20]. In podocytes, mesangial cells, and immune cells, for example, HSD2 is not expressed, therefore supporting the fact that glucocorticoids may be the main ligands of MR in these cells. It should be stressed, however, that there may be species differences as well as induction of HSD2 expression in some pathological conditions, allowing aldosterone to activate MR. This has not been carefully analyzed yet [1].

1.3 Major pathophysiological mechanisms involved in MR and kidney diseases

1.3.1 MR and renal hemodynamic alterations

Experimental evidence in rodent models of acute kidney injury (AKI) supports the concept that MR contributes to vascular tone regulation [1]. The benefit of MRA in renal ischemia-reperfusion injury is associated with improved renal hemodynamics and decreased renal vascular resistance [21, 22]. We recently showed that MR expressed in mouse smooth muscle cells contributes to renal injury induced by ischemia (through a mechanism involving oxidative stress and Rac1 activation) [23], as well as in acute CsA nephrotoxicity (due to increased vascular L-type calcium channel activity thereby resulting in decreased renal artery vasoconstriction and overall improvement in renal hemodynamics) [24]. Of note, the endothelial MR was not directly involved since endothelial MR gene inactivation had no effect in ischemia-reperfusion or CsA-induced renal injuries [23, 24]. Whether MR expressed in the renal vasculature contributes to renal injury in other settings like diabetes or chronic kidney diseases remains to be explored.

1.3.2 MR and oxidative stress

Multiple in vitro and in vivo studies have shown the significance of oxidative stress induced by aldosterone/MR and its detrimental consequences on kidney injury. In vivo, the DOCA-salt causes oxidative DNA damage [25], and aldosterone infusion produces an MR-dependent increase in NADPH oxidase activity and ROS generation in the kidney [26, 27]. MR expressed in the smooth muscle cell may have a major role as we recently demonstrated in ischemia-reperfusion injury using smooth muscle MR KO mice [23]. In vascular cells, aldosterone increased ROS which in turn modifies the cysteinyl thiols in the eNOS-activating region of endothelin-1 B receptor to decrease endothelin-1-stimulated eNOS activity, impairing the vasodilatory pathway. These effects have repercussions on renal hemodynamics and function in kidney ischemia/reperfusion injury in both rat and mouse [21–23]. In rat mesangial cells, aldosterone directly stimulates superoxide anion generation, which is accompanied by an increase in NADPH oxidase activity and translocation of p47phox and p67phox to the cell membrane [28]. Moreover, recent studies have shown that aldosterone induces mesangial cell apoptosis and that the administration of an antioxidant or MR antagonist attenuates the proapoptotic effects of aldosterone [29]. The increase in NADPH oxidase Nox2 plasma levels and urinary isoprostanes is also observed in patients with primary aldosteronism as compared to essential hypertensive patients [30]. Interestingly, adrenalectomy is associated with a reduction in both parameters [30]. Moreover, therapeutic MR antagonism reduced oxidative stress in diabetic [31] or kidney transplant patients [32].

1.3.3 MR and inflammation

A role for MR signaling in inflammation has been suggested since early studies showing that the treatment of rats with aldosterone and salt causes perivascular leukocyte infiltration and increased expression of inflammatory markers [1]. More recently, macrophages, dendritic cells, and T lymphocytes have been identified as MR-expressing cells [1, 11, 33]. The use of genetically modified mouse model deficient of MR in myeloid cells revealed that myeloid MR contributes to renal injury in a glomerulonephritis mouse model [8]. Moreover, our recent work showed that myeloid MR participates to CKD progression induced by AKI [34].

The deletion of MR in myeloid cells favored M2 polarization of renal macrophages leading to improved tissue repair and prevention of renal scaring, decreased function, and interstitial fibrosis. Interestingly MRA administration using the nonsteroidal MRA finerenone has similar effects, blunting CKD development after ischemia-reperfusion injury in rodents [22, 34] and in the large white pig [34]. The role of myeloid MR in the progression of CKD in other models of kidney disease has to be further studied. The role of MR expressed in T cell has not been explored in kidney disease. However, T-cell MR knockout mice prevented cardiac hypertrophy, fibrosis, and dysfunction compared with littermate control mice after abdominal aortic constriction suggesting that MR in T cells may also play a pro-inflammatory role [13]. In dendritic cells, MR stimulation with aldosterone induces the secretion of IL-6 and TGF-β, two pro-inflammatory cytokines able to polarize the adaptive immune response toward a Th17 phenotype [35]. MR antagonism with spironolactone reduced heart and kidney damage in a hypertension rat model due to blockade of Th17 polarization and the induction of regulatory T cells [36]. Pharmacological MR blockade improves the chronic inflammatory state associated with CV disease [1, 33]. Altogether, these data suggest that aldosterone/MR modulates innate and adaptive immunity, which may have a critical role in end-organ damage.

1.3.4 MR and fibrosis

Fibrosis and extracellular matrix remodeling is a well-documented effect of MR activation in various tissues, including the kidney [1]. Aldosterone induces pro-fibrotic cytokine production and accumulation of collagen and other extracellular matrix components [9, 37, 38]. Aldosterone administration is associated with an increase in renal TGF-β, collagen, and connective tissue growth factor expression and medullary and cortical fibrosis [39]. Aldosterone also influences the production of plasminogen activator inhibitor-1 leading to glomerulosclerosis [40]. MR activation in renal fibroblasts results in rapid activation of growth factor receptors and induction of PI3K/MAPK signaling, which stimulates proliferation and therefore contributes to fibrosis expansion [41]. Several molecular MR targets may be involved in the pro-fibrotic response of Aldo/MR signaling. We recently deeply explored the role of neutrophil gelatinase-associated lipocalin (NGAL) that we identified as a novel aldosterone/MR target [42]. NGAL induction by the MR might be a mechanism for MR-induced fibrosis since mice deficient in NGAL are protected from aldosterone-induced kidney fibrosis (Jaisser, unpublished data). Galectin-3 also mediates the pro-fibrotic effects of aldosterone-MR, and galectin-3 KO mice are protected against aldosterone-induced kidney fibrosis [43]. Taken together increased MR activation which may promote kidney fibrosis by inducing fibroblast proliferation and the production of several pro-fibrotic molecules.

2. Preclinical data supporting the benefit of MR antagonists (MRA) in kidney diseases

2.1 Benefit of MRA on acute kidney injury (AKI) induced by ischemia/reperfusion (IR)

A reduction of renal blood flow is occurring in several clinical settings, and this is a major cause of AKI. A number of studies in rodents and in the Large White Pig preclinical model have shown that MR antagonism with steroidal and nonsteroidal MRAs prevents and treats AKI induced by IR. In an early study, it was shown that spironolactone is a useful strategy to prevent the acute kidney dysfunction and

tubular injury induced by bilateral renal IR injury in the rat [44]. The sustained reduction in renal blood flow observed after 24 hours in the IR-untreated rats was prevented in the spironolactone-treated groups. This was reproduced using nonsteroidal MRAs in both rats and mice [21–23] leading to the discovery of a novel underlying mechanism related to the limitation of oxidative stress and impaired endothelin-B receptor signaling [21, 22]. Importantly MRA also have curative effects when administered within the first 3 hours post ischemia-reperfusion [21, 45, 46]. The benefit of MR antagonists in ischemic AKI was translated into the Large White Pig preclinical model in which MR antagonism with soludactone (potassium canrenoate, a soluble MRA used in clinics) prevented the effects of AKI including kidney dysfunction and structural injuries [23].

2.2 AKI to CKD transition

In recent years, special focus has been given to the chronic consequences of an AKI episode. Several clinical and experimental studies have shown that AKI is linked with increased risk for CKD development.

In the rat, CKD progression induced by a single event of ischemic AKI (characterized by proteinuria, kidney dysfunction, and severe structural injury including interstitial fibrosis, glomerulosclerosis, tubule dilation, and podocyte injury) is prevented by spironolactone [45] and finerenone [22, 47]. MR antagonism also prevents CKD induced by a mild ischemic period even when administered 3 hours after the ischemia episode [48]. The underlying mechanisms rely on the limitation of inflammatory events and the promotion of repair mechanisms held by M2-type macrophages and interleukin-4 receptor signaling [34]. Importantly, these benefits are also observed in the Large White Pig model: short-term soludactone administration before/after the ischemic event indeed prevents CKD progression at 3 months, with a reduction in fibrosis and proteinuria and improved renal function [34]. The data indicate that MRA treatment is an encouraging therapeutic option to prevent the AKI to CKD transition which identifies the MR expressed in inflammatory cells as a specific target in this setting.

2.3 MR antagonism in kidney fibrosis and CKD progression

Kidney fibrosis is a common endpoint of CKD from different origins. Accumulating evidences indicate that aldosterone and/or MR signaling plays a key role in CKD development in a number of animal models including nephron reduction [49, 50], hypertensive models [51, 52], unilateral ureteral obstruction [53, 54], and mineralocorticoid/salt models [55]. MR antagonism not only prevents glomerulosclerosis in the remnant kidney model but also induces regression of glomerulosclerosis as evidenced by Aldigier et al. on kidney biopsy 4 weeks after spironolactone treatment initiation in rats already presenting CKD [56]. Eplerenone also limited proteinuria in this model [50]. Renal injury observed in the Dahl-sensitive rat upon salt loading is greatly limited by eplerenone [57, 58] and the nonsteroidal MRA CS-3150 [59]. This may be related to a direct effect on podocyte, as underlined by Shibata et al., involving activation of Rac1 and possible increased Rac1-mediated transactivation of the podocyte MR [60].

2.4 Benefit of MR blockade in diabetic nephropathy

The beneficial effects of MRA in different models of type I and type II diabetic nephropathy or kidney injury related to metabolic disorders have been reported. Spironolactone administration for 3 weeks reduced renal collagen deposition in

STZ-induced diabetic rats [61]. This was thereafter reported for other MRAs such as eplerenone [62]. MRAs are also efficient in limiting progression of diabetic nephropathy in models of type 2 diabetes. Eplerenone reduced albuminuria, glomerular hypertrophy, and mesangial expansion in the db/db mouse model [62]. The novel nonsteroidal MRA AZ9977 has similar effects [63]. In the Otsuka Long-Evans Tokushima Fatty (OLETF) rats or Zucker obese rats, similar benefits have been reported after MRA treatment [64, 65].

2.5 Calcineurin inhibitor toxicity and kidney transplantation

Some studies showed a benefit of MR blockade in acute and chronic CsA nephrotoxicity, including effects on preventing structural and functional alterations [66–68]. The underlying mechanisms leading to this protection rely on hemodynamic effects (blunting the sustained vasoconstriction induced by CNI) [24, 68] or renal extracellular matrix remodeling [67]. The effect of MRA in experimental kidney transplantation has been tested in a model of chronic allograft dysfunction in the Dark-Agouti to Wistar-Furth rat with a reduced vasculopathy and glomerular macrophage influx and a trend to reduced proteinuria and glomerulosclerosis [69].

2.6 Glomerulonephritis and MR blockade

Although few studies have addressed this issue, it has been reported that spironolactone and the nonsteroidal MRA BR-4628 are beneficial in mouse models of glomerulonephritis [70–72]. The myeloid MR seems to play a key role in the kidney since genetic deletion of MR in myeloid cells, but not in podocyte, blunted glomerulonephritis development [8].

3. Conclusion

Preclinical evidences clearly support the concept of a benefit of MR antagonism to treat or delay kidney diseases from different origins including ischemic kidney disease, diabetic and hypertensive nephropathy, glomerulonephritis, and calcineurin inhibitor toxicity in the context of kidney transplant. The underlying mechanisms rely on improving local hemodynamics and reducing extracellular matrix remodeling and local inflammation (**Figure 1**). Whether this translates in clinics is already largely supported by several clinical trials, but definitive answers should be provided by well-designed, large clinical trials based on hard renal outcomes like limitation of CKD progression and/or cardiovascular outcomes. A recent study showed that in patients with heart failure with preserved ejection fraction, spironolactone treatment decreased the relative risk for cardiovascular death, heart failure hospitalization, or aborted cardiac arrest, despite an increase in the hyperkalemia risk [73]. Novel therapeutics limiting the risk of hyperkalemia upon MRA use is also warranted in these at-risk populations.

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