

*Forum Minireview***Drug Discovery for Overcoming Chronic Kidney Disease (CKD):
Pharmacological Effects of Mineralocorticoid-Receptor Blockers**Akira Nishiyama^{1,*}, Hirofumi Hitomi¹, Asadur Rahman², and Hideyasu Kiyomoto³¹*Department of Pharmacology, ³Department of CardioRenal and Cerebrovascular Medicine, Faculty of Medicine, Kagawa University, Kagawa 761-0793, Japan*²*Department of Pharmacology, Bangladesh Agricultural University, Mymensingh, Bangladesh**Received August 14, 2008; Accepted September 22, 2008*

Abstract. There is increasing evidence demonstrating that the renoprotective effects of mineralocorticoid receptor (MR) blockade are independent of the effects exerted by renin-angiotensin inhibitors. MR is expressed not only in tubular cells but also in other renal cells including glomerular mesangial cells, podocytes, and renal interstitial fibroblasts. Animal experiments have shown that MR blockers prevent aldosterone-induced proteinuria, glomerular injury, and tubulointerstitial fibrosis. In vitro studies have also demonstrated that MR blockers inhibit aldosterone-induced renal cell damage. Recent clinical studies have shown that treatment with MR blockers attenuates the development of proteinuria in patients with chronic kidney disease (CKD) and hypertension, independent of changes in blood pressure. In some cases, MR blockers elicit potent renoprotective effects in conditions where aldosterone levels are not elevated. These data suggest that treatment with MR blockers may possibly present an effective therapeutic strategy for patients with CKD.

Keywords: aldosterone, mineralocorticoid receptor (MR), eplerenone, kidney, chronic kidney disease (CKD)

Introduction

Recent studies have implicated the role of angiotensin II in mediating renal injury (1). The Seventh Report of the Joint National Committee (JNC7), the European Society of Hypertension/European Society of Cardiology (the 2003 ESH-ESC), and the Japanese Society of Hypertension (JSH2004) all recommend that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II-receptor blockers (ARBs) should be used in combination with diuretics as the first-line therapy to reduce blood pressure in hypertensive patients with chronic kidney disease (CKD) (2–5). However, it has become evident that aldosterone is a key factor in mediating renal injury through both hemodynamic-dependent and independent effects (6, 7). Patients with primary aldosteronism, who have low angiotensin II levels, show higher incidence of proteinuria or albuminuria than patients with essential

hypertension (8, 9). Plasma aldosterone levels are positively correlated with urinary protein excretion levels (10) and negatively correlated with glomerular filtration rates (11) in patients with CKD. Animal studies have shown that chronic infusion of aldosterone in combination with high salt treatment elicits severe proteinuria, glomerular mesangial injury, and tubulointerstitial fibrosis (12–14). However, these aldosterone-induced renal injuries were prevented by treatment with the selective MR antagonist eplerenone, suggesting that aldosterone induces renal injury through locally expressed MR (12). Recent in vitro studies have also demonstrated that MR is expressed not only in distal tubular cells but also in other renal cells, which mediates aldosterone-induced renal cell injury (6, 7). Along with the roles of aldosterone and MR in renal injury, studies have revealed the beneficial effects of MR blockers on renal injury. In this review, we have briefly summarized some data from both preclinical and clinical studies regarding the pharmacological effects of MR blockers on renal injury.

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Preclinical evidence for renoprotective effects of MR blockers

The renoprotective effects of MR blockers have been demonstrated in a variety of animal models. In streptozotocin-induced insulin-deficient hyperglycemic rats, treatment with the non-selective MR antagonist spironolactone had minimal effect on glucose levels, but it ameliorated the development of proteinuria and renal tissue injury (15, 16). Similar results with spironolactone or eplerenone were obtained in type 2 diabetic rats (17), mice (18), and obese spontaneously hypertensive rats (SHR) (19). Furthermore, spironolactone and eplerenone have been shown to attenuate the progression of proteinuria, glomerular injury, and tubulointerstitial fibrosis in murine lupus nephritis (20) or in rats treated with angiotensin II and an nitric oxide synthase inhibitor (21), cyclosporine A (22–24), or radiation (25). Treatment with spironolactone prevents tubulointerstitial fibrosis and tubular apoptosis in mice subjected to unilateral ureteral occlusion (26) and in rats that underwent ischemia and reperfusion (27) or 5/6 nephrectomy (28). Importantly, in these animal models, treatment with MR blockers had no effect on systemic blood pressure. Thus, these observations are consistent with the concept that aldosterone and MR-dependent renal injury is not dependent on blood pressure changes but on their local actions. This concept is supported by some recent in vitro studies that have demonstrated that MR is expressed not only in distal tubular cells but also in other renal cells, including glomerular mesangial cells (29), podocytes (30), renal interstitial fibroblasts (31), and proximal tubular cells (32), which mediates aldosterone-induced renal cell injury (6, 7).

Clinical evidence for renoprotective effects of MR blockers

Monotherapy with spironolactone elicits blood lowering effects that are similar to those of the ACE inhibitor cilazapril, but spironolactone is more effective than cilazapril in reducing proteinuria in hypertensive patients with type 2 diabetes (33). Similarly, eplerenone is more effective in reducing albuminuria than the ACE inhibitor enalapril in hypertensive patients (34). In older patients with systolic hypertension, eplerenone has blood pressure lowering effects similar to the calcium channel antagonist amlodipine, but reduces the urinary albumin/creatinine ratio more than amlodipine (35). Collectively, these observations suggest that MR blockers have strong renoprotective effects through mechanisms that cannot be simply explained by blood pressure changes.

In some patients, plasma aldosterone levels are initially decreased by treatment with ACE inhibitors or ARBs but are increased in the long term (36), a phenomenon termed “aldosterone breakthrough”. Furthermore, recent in vitro studies have reported the existence of cross-talk between aldosterone- and angiotensin II-dependent intracellular signaling pathways (37–41). Therefore, targeting aldosterone with MR blockers may amplify the beneficial effects of therapy with ACE inhibitors and ARBs (42, 43). Indeed, several clinical studies have demonstrated that the addition of spironolactone or eplerenone to ACE inhibitors or ARBs has no effects on blood pressure but markedly reduces proteinuria in patients with diabetic nephropathy (33, 44) or non-diabetic CKD (10, 45). More recently, Bombardier et al. (46) performed a systematic review of 15 clinical studies [four were parallel-group randomized controlled trials (47–50); four were crossover randomized controlled trials (33, 44, 51, 52); two were pilot studies (10, 45); and five were case studies (53–57)] that examined the effects of adding MR blockers to ACE inhibitors and/or ARBs on proteinuria and the risk of hyperkalemia in patients with CKD. In these studies, the reported decreases in proteinuria from baseline ranged from 15%–54%, whereas hyperkalemic events were significant in only one of the eight randomized controlled trials. However, MR-blocker therapy was directed exclusively at proteinuric patients, most with effective glomerular filtration rates exceeding 60 mL/min per 1.73 m² and all with pretreatment serum potassium levels less than 5.0 mmol/L. Thus, although in patients with early phase CKD, adding MR blockers to ACE inhibitors and/or ARBs yields significant decreases in proteinuria with less adverse effects on hyperkalemia, further studies are necessary to investigate the risk-benefit balance in patients with advanced CKD.

Underlying mechanisms responsible for pharmacological effects of MR blockers

During the progression of renal injury, aldosterone might be involved in injuries of glomerular podocytes, the mesangium, the tubulointerstitium, and tubules through locally expressed MR. However, the precise molecular mechanisms responsible for aldosterone and MR-induced cell injury are unclear. In the kidney, aldosterone activates multiple intracellular mechanisms including reactive oxygen species (ROS) (12, 19, 58), mitogen-activated protein kinases (MAPKs) (12, 29, 59, 60), and Rho-kinase (14), and so on by activating MR. These molecular mechanisms have been reviewed previously (6, 7), and will not be discussed in detail here.

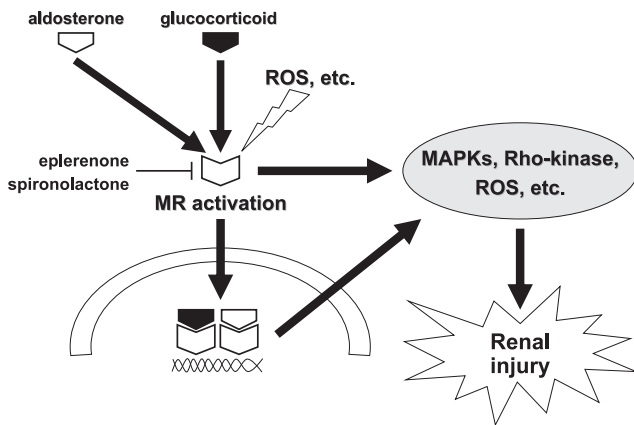


Fig. 1. Possible mechanisms of renal injury induced by mineralocorticoid receptor (MR) activation. MAPKs = mitogen-activated protein kinases. ROS = reactive oxygen species.

In high salt-treated stroke-prone SHR (61) and Dahl salt-sensitive hypertensive rats (62, 63), MR blockade with eplerenone attenuates proteinuria and renal injury, independent of blood pressure changes. However, plasma aldosterone levels were suppressed in these high salt-treated animals. Similarly, the renoprotective effects of MR blockers are often observed in patients with CKD, even when circulating aldosterone levels are normal or low. These results suggest that the renoprotective effects of MR blockers are not mediated through inhibition of aldosterone. Funder (64, 65) describes a possible role of normal-level glucocorticoids in activating MR, thus mediating tissue injury and ROS generation. Furthermore, increased renal tissue expression of 11β -hydroxysteroid dehydrogenase type 2 (11β HSD2) was observed in patients with CKD (11). Thus, it is possible that, during the progression of renal injury, a reduction in 11β HSD2 activity leads to occupancy of the MR by glucocorticoids such as cortisol. Alternatively, ROS may directly activate MR as recently suggested (66, 67). Figure 1 depicts the possible mechanisms of MR-dependent renal injury; however, it is obvious that further studies are needed to address these issues.

Adverse effects of MR blockers

Several clinical reports have indicated that treatment with MR blockers results in a dose-dependent increase in serum potassium levels (68). It has also been suggested that the frequency and the severity of hyperkalemia may be increased in certain patient populations, for example, those with diabetic nephropathy and/or severe renal failure (69). However, it should be emphasized that large clinical trials including the

Randomized Aldactone Evaluation Study (RALES) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) have demonstrated that hyperkalemia should not be a problem if subjects are carefully selected (70, 71). For example, RALES showed that the incidence of hyperkalemia did not differ between the placebo and spironolactone-treated groups (70). In this regard, Sato et al. (42) have indicated that the potassium levels are rarely problematic if subjects are picked out with the greatest possible care and followed up closely. In particular, they emphasized that adverse effects of MR blockers on serum potassium would occur if the usage recommendations based on the previous studies were not observed. Furthermore, elderly patients or those with dehydration and severe renal failure require closer monitoring or termination of MR blocker administration (42). Thus, MR blockers should be carefully prescribed by specialists for patients with CKD with a close follow-up. Other adverse effects of MR blockers including sex-hormone-related side effects of spironolactone are well summarized by a recent review (43).

Conclusions

In this review, we briefly summarized evidence of the renoprotective effects of MR blockers. From both the preclinical and clinical evidence, it seems clear that MR blockers elicit beneficial effects in patients with CKD. However, further studies are needed to investigate the risk-benefit balance in CKD patients treated with MR blockers and ACE inhibitors and/or ARBs.

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