Forum Minireview

New Approaches to Blockade of the Renin–Angiotensin–Aldosterone System:

Mineralocorticoid-Receptor Blockers Exert Antihypertensive and Renoprotective Effects Independently of the Renin–Angiotensin System

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Abstract. The role of angiotensin II in mediating hypertension and renal diseases is well documented, and inhibition of the renin–angiotensin–aldosterone system elicits antihypertensive and renoprotective effects. There is increasing evidence implicating aldosterone, in addition to angiotensin II, in the pathogenesis of hypertension and renal diseases. Beneficial effects of mineralocorticoid receptor (MR) blockers against these diseases have been reported and are independent of the effects exerted by renin–angiotensin system (RAS) inhibitors. MR blockers are increasingly being used, not only for primary aldosteronism but also for other resistant hypertensive patients whose blood pressure is insufficiently controlled by RAS inhibitors. In these settings, MR blockers have shown impressive results. In addition, anti-proteinuric effects of MR blockers have been observed in hypertensive patients treated with RAS inhibitors, but without significant effects on blood pressure. Interestingly, these effects of MR blockers are not always dependent on plasma aldosterone levels. These data suggest that MR blockers provide a potential therapeutic approach for patients with hypertension and renal impairment who are being treated with RAS inhibitors.

Keywords: aldosterone, mineralocorticoid receptor, eplerenone, angiotensin

1. Introduction

Until recently, aldosterone has been mainly recognized for its roles as an electrolyte and blood pressure regulator through the activation of mineralocorticoid receptor (MR) in tubular epithelial cells. However, there is convincing evidence for other effects of aldosterone that are mediated via the MR in the heart and vasculature. Patients with primary aldosteronism, usually with very low angiotensin II levels, have a higher incidence of cardiovascular diseases than do patients with essential hypertension (1, 2), indicating that aldosterone plays an important role in the pathogenesis of cardiovascular diseases, independent of the renin–angiotensin system (RAS). In some patients, the plasma aldosterone levels are initially decreased by treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1–receptor blockers (ARBs), but are increased in the long term (3, 4), a phenomenon known as “aldosterone breakthrough”. Aldosterone breakthrough may contribute to resistance to antihypertensive therapy by counteracting the antihypertensive effects of ACE inhibitors and ARBs. Bomback and Klemmer (4) estimated that the incidence of aldosterone breakthrough was 10% – 53% in patients treated with ACE inhibitors or ARBs.

Beneficial effects of MR blockers on cardiovascular diseases, independent of those exerted by RAS inhibitors, have been reported in several studies. The Randomized Aldactone Evaluation Study (RALES) (5) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure
Efficiency and Survival Study (EPHESUS) (6) demonstrated that adding MR blockers to standard therapies, including ACE inhibitors or ARBs, significantly reduced morbidity and mortality in patients with heart failure. Based on the results from these two multicenter clinical trials and other studies, many national guidelines now recommend MR blockers, in addition to RAS inhibitors, for the treatment of hypertension in patients with cardiovascular disease.

Potential roles of aldosterone and MR in the pathogenesis of renal injury have been indicated in recent studies. For example, the incidence of proteinuria or albuminuria is higher in patients with primary aldosteronism than in patients with essential hypertension (7, 8). Plasma aldosterone levels are positively correlated with urinary protein excretion levels and negatively correlated with glomerular filtration rate in patients with chronic kidney disease (CKD) (9, 10). The non-selective MR antagonist spironolactone elicits blood pressure-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 (11). Similarly, the selective MR blocker eplerenone is more effective in reducing albuminuria than the ACE inhibitor enalapril in hypertensive patients (12). In older patients with systolic hypertension, eplerenone has blood pressure–lowering effects similar to the calcium-channel antagonist amlodipine. Furthermore, eplerenone provides greater reductions in the urinary albumin/creatinine ratio than amlodipine (13). The addition of MR blockers to ACE inhibitors or ARBs was also reported to reduce albuminuria in patients with type 2 diabetic nephropathy (14) or CKD (15 – 18). Taken together, these observations suggest that MR blockers have strong renoprotective effects through mechanisms that cannot be explained exclusively by blood pressure changes.

In this review, we summarize the recent findings related to the effects of MR blockers on hypertension and renal impairment with particular emphasis on their RAS inhibition–independent effects.

2. Effects of MR blockers on hypertension

Aldosterone plays an important role in the development of hypertension in patients with primary aldosteronism and in patients with essential hypertension. Indeed, elevated aldosterone levels, even within the normal range, increase the risk of developing hypertension in normotensive subjects (19). It has also been shown that spironolactone elicits a dose-dependent hypotensive effect in hypertensive patients (20). However, the use of spironolactone is limited because of the high incidence of adverse effects, particularly gynecomastia in men, because of the antiandrogenic properties of this drug. These adverse effects associated with spironolactone have been overcome by the introduction of a selective MR blocker, eplerenone, which is increasingly used in patients with drug-resistant essential hypertension (21). In an observational study of Japanese patients with drug-resistant hypertension and plasma aldosterone levels and renal function within the normal range, but whose blood pressure was insufficiently controlled by treatment with
RAS inhibitors (ACE inhibitors or ARBs) monotherapy or in combination with other anti-hypertensive agents (β-blockers, calcium blockers, and/or diuretics), the patients were treated with eplerenone (50 mg per day) for 6 months. As shown in Fig. 1, 1 month after the addition of eplerenone, systolic and diastolic blood pressures decreased significantly (−23 and −10 mmHg, respectively) and these effects continued throughout the observation period (−31 and −15 mmHg, respectively, at 6 months). No obvious side effects, such as hyperkalemia, were observed in these patients. These results suggest that eplerenone is an effective anti-hypertensive therapy in Japanese patients with essential hypertension whose blood pressure is not well controlled by treatment with RAS inhibitors.

MR blockers appear to exert their antihypertensive effects through several pathways, although their effects can be largely explained by their diuretic properties. MR blockers can prevent aldosterone-induced activation of MR in the distal convoluted tubules and the collecting ducts, leading to natriuresis, potassium reabsorption, and decreases in body fluid. However, treatment with spironolactone for 2 weeks significantly decreased blood pressure in oligo-anuric hemodialysis patients (22), suggesting that the antihypertensive effect of MR blockers is partly mediated through extrarenal pathways, including their effects on sympathetic nerve activity (23 – 25) and vasculature function (26 – 29) (Fig. 2).

3. Effects of MR blockers on renal injury

Recent studies have revealed the roles of aldosterone and MR in the pathogenesis of renal injury (30, 31). Bomback et al. (16) performed a systematic review of 15 clinical studies, including four parallel-group randomized controlled trials (18, 32 – 34), four crossover randomized controlled trials (11, 35 – 37), two pilot studies (9, 38), and three case studies (15, 17, 39), 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, proteinuria was decreased by 15%–54%, and hyperkalemic events were significant in only one of the eight randomized controlled trials. Hence, in patients with early CKD, adding MR blockers to ACE inhibitors and/or ARBs significantly decreases proteinuria with few adverse effects on hyperkalemia. However, further studies are needed to investigate the risk-benefit balance in patients with advanced CKD.

The renoprotective effects of MR blockers have been demonstrated in a variety of animal models (30, 31). Importantly, these renoprotective effects of MR blockers are not dependent on blood pressure changes. In vitro studies have also shown that MR is expressed in glomerular mesangial cells (40), podocytes (41), renal interstitial fibroblasts (42), and proximal tubular cells (43), which mediates aldosterone-induced renal cell injury (6, 7) in addition to distal tubular cells. These data suggest that aldosterone mediates renal tissue injury by the activating locally expressed MR.

Podocytes extend their interdigitating foot processes that connect to neighboring cells by slit diaphragms composed of nephrin, podocin, and other molecules (44, 45). Podocytes serve as the final filtration barrier to prevent leakage of plasma proteins (44, 45). Nagase et al. (46) showed that eplerenone attenuates the loss of nephrin and podocin expression and podocyte injury in Dahl salt-sensitive hypertensive rats. They also demonstrated that cultured podocytes highly express the MR which mediates aldosterone-induced Sgk-1 expression (41). We also showed that eplerenone attenuates podocyte injury and proteinuria in type 2 diabetic rats (47). These data suggest that the beneficial effects of MR blockers on proteinuria are achieved by inhibiting local aldosterone and MR activity in podocytes. However, both Dahl salt-sensitive hypertensive rats and type 2 diabetic rats did not show an increase in plasma aldosterone levels (46, 47). Indeed, aldosterone-independent MR activation has also been reported (48, 49). That study demonstrated that constitutively activated Rac1 directly enhanced MR-dependent reporter activity, which was accompanied by increased nuclear translocation of MR (48). Despite these findings, the precise molecular mechanisms responsible for aldosterone-dependent podocyte injury are still poorly understood.

We have examined the effects of aldosterone on nephrin and podocin gene expression in cultured mouse podo-
cytes. However, we failed to show any changes in nephrin and podocin mRNA levels in response to the administration of aldosterone even at very high concentrations (0.1 – 100 nM, data not shown). On the other hand, aldosterone significantly protracted podocyte wound healing, as shown in Fig. 3. Although the pathophysiological effects of these observations are not yet clear, it is possible that aldosterone impairs podocyte function, which might be involved in the development of proteinuria. Further studies are needed to clarify the molecular mechanisms responsible for aldosterone-induced podocyte injury and proteinuria.

4. Conclusions

In this review, we briefly summarized the evidence for the RAS-independent effects of MR blockers on hypertension and renal injury. Based on the preclinical and clinical evidence, it seems clear that MR blockers offer a potential therapeutic approach for hypertensive patients with renal injury undergoing treatment with RAS inhibitors. Further studies are needed to clarify the precise pharmacological mechanisms involved in the effects of MR blockers.

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