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Mineralocorticoid Receptors in Vascular Disease: Connecting Molecular Pathways to Clinical Implications

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Abstract The mineralocorticoid receptor (MR), a steroid-hormone-activated transcription factor, plays a substantial role in cardiovascular diseases. MR antagonists (MRAs) have long been appreciated as effective treatments for heart failure and hypertension; however, recent research suggests that additional patient populations may also benefit from MRA therapy. Experimental evidence demonstrates that in addition to its classic role in the regulating sodium handling in the kidney, functional MR is expressed in the blood vessels and contributes to hypertension, vascular inflammation and remodeling, and atherogenesis. MR activation drives pathological phenotypes in smooth muscle cells, endothelial cells, and inflammatory cells, whereas MRAs inhibit these effects. Collectively, these studies demonstrate a new role for extrarenal MR in cardiovascular disease. This review summarizes these new lines of evidence and how they contribute to the mechanisms of atherosclerosis, pulmonary and systemic hypertension, and vein graft failure, and describes new patient populations that may benefit from MRA therapy.

Keywords Aldosterone · Mineralocorticoid receptor · Atherosclerosis · Vein graft failure · Essential hypertension · Pulmonary hypertension · Inflammation · Vascular remodeling

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Introduction

The mineralocorticoid receptor (MR) is a member of the steroid receptor family known for its role in blood pressure (BP) control. MR is expressed in renal epithelial cells and classically participates in BP regulation by binding the steroid hormone aldosterone to induce expression of genes involved in sodium retention, thereby increasing blood volume and BP (reviewed in [1]). MR is the terminal component of the renin–angiotensin–aldosterone system, which is activated by hypotension, leading to angiotensin II (AngII) production by renin and angiotensin-converting enzyme (ACE). AngII activates angiotensin type 1 receptors (AT1Rs) on cells of the adrenal gland to promote aldosterone release. MR antagonists (MRAs) prevent hormone from binding and activating the MR. These MRAs include spironolactone and the more MR-specific but less potent eplerenone, as well as new nonsteroidal MRAs currently in development [2]. On the basis of the role MR plays in regulating BP and blood volume, MRAs are used to treat hypertension and congestive heart failure. Clinical trials have demonstrated that treatment with renin–angiotensin–aldosterone system inhibitors affords greater cardiovascular protection than would be predicted solely on the basis of modest reductions in BP. The EPHESUS [3] and RALES [4] trials demonstrated that MRA therapy substantially reduces

morbidity and mortality in patients with severe heart failure at doses that are insufficient to exert significant renal effects and yield only small reductions in BP. Patients with milder heart failure symptoms treated with MRAs [5] and individuals at risk of coronary disease treated with ACE inhibition or AT1R blockade also have greater cardiovascular benefits than would be expected from modest improvements in hypertension alone [6, 7]. Even patients with hypertension treated with MRAs have greater protection from end-organ damage than those treated to the same target BP with other antihypertensive agents [8] (Table 1).

These clinical data implicate potential extrarenal actions of MR in the mechanism for the cardiovascular protective effects of MRAs, which has prompted substantial recent basic research on the role of aldosterone and MR in mechanisms of vascular diseases. We and others have confirmed that MR is expressed in human endothelial cells (ECs) and vascular smooth muscle cells (SMCs), where it regulates expression of genes involved in vascular cell function. This review will summarize recent experimental data demonstrating novel mechanisms by which MR in the vasculature contributes to atherosclerosis and its complications, vein graft failure, and even systemic and pulmonary hypertension. In each case, we describe how these preclinical studies have now identified new patient populations that may benefit from MRA treatment and also defined potential novel drug targets to treat or to prevent cardiovascular disease that can now be taken from the bench back to the bedside.

Aldosterone and MRs in Atherosclerosis

Epidemiological data reveal that circulating aldosterone levels are independent predictors of cardiovascular ischemia [9, 10]. Compared with individuals with the same degree of essential hypertension but normal aldosterone levels, patients with primary hyperaldosteronism have a fourfold increased risk of stroke and a sixfold increased risk of myocardial infarction (MI) [11]. In a recent study of patients with stable coronary artery disease (CAD), higher serum aldosterone levels—even within the reference range—predict a twofold to fourfold increase in subsequent MI or cardiovascular death [12••]. These studies cannot determine whether elevated serum aldosterone level is correlative or causative for ischemia; however, clinical trials evaluating the lipid-regulating drug torcetrapib in patients with dyslipidemia demonstrated an *increased* rate of MI, stroke, and progression of atherosclerosis in patients randomly assigned to receive the drug [13–16]. This outcome was later associated with an off-target increase in serum aldosterone levels in patients randomized to receive torcetrapib [16–18]. These clinical data, in addition to the earlier trials linking inhibition of aldosterone production or MR antagonism to lower mortality and a reduction in cardiovascular ischemic events [3, 4, 6, 7], suggest BP-independent effects of aldosterone that promote atherosclerosis and plaque rupture in humans. This association has led to recent investigations of the mechanisms by which aldosterone might contribute to the process of atherogenesis.

Atherosclerosis is a systemic vascular inflammatory disease initiated by cardiovascular risk factors that cause EC damage. Activated ECs express surface receptors (such as the intercellular adhesion molecules ICAM, VCAM, and selectins) that recruit leukocytes to the vascular wall [19], typically in regions of turbulent blood flow [20, 21]. Activated inflammatory cells within plaques release cytokines and chemokines that further augment protease activity and plaque inflammation, thereby promoting matrix degradation, plaque rupture, and thrombosis, the cause of most MIs and strokes [22].

Role of MR in Atherogenesis

Animal studies support a role for aldosterone in atherogenesis, with aldosterone infusion increasing vascular and macrophage oxidative stress and overall atherosclerotic plaque area [23, 24]. Conversely, MRAs [25, 26] and aldosterone synthase inhibitors [27] decrease atherosclerosis in animal models; however, the detailed molecular mechanisms are only beginning to be elucidated. Several groups have recently demonstrated that MR activation specifically enhances early atherosclerotic lesion formation in areas of nonlaminar blood flow, such as the aortic arch and great vessel bifurcations. Aldosterone also promotes the formation of lipid-rich and inflamed plaques [28–30], a phenotype associated with plaque rupture in humans. In a mouse model of atherosclerosis, infusion of aldosterone at low doses that do not affect BP resulted in recruitment of activated monocytes and T cells to atherosclerosis-prone regions of the blood vessel wall prior to promoting plaque formation [30]. This finding supports the notion that BP-independent, direct inflammatory effects of aldosterone on the blood vessel contribute to atherosclerosis. The mechanism may involve direct activation of vascular MR to modulate local vascular gene expression [31, 32] as proatherogenic genes induced by nonlaminar blood flow [33] have been shown to be preferentially regulated by aldosterone in the aortic arch in an oxidative-stress-dependent manner [34].

The proinflammatory effects of MR in the vasculature involve multiple cell types (Fig. 1). In human coronary ECs, activation of MR upregulates ICAM-1 expression, which increases leukocyte adhesion to the endothelium [32], an initiating step in vascular inflammation and subsequent plaque development. In cultured SMCs, aldosterone promotes vascular calcification, a late stage in atherosclerosis that correlates with the risk of ischemia in humans [35]. In the setting of early atherosclerosis, aldosterone triggers

Table 1 Current patient populations with proven benefit from mineralocorticoid receptor antagonist (*MRA*) therapy: summary of important MRA clinical trials

Clinical trial	Patient population	MRA treatment	Outcome
RALES [4]	NYHA class 3+ heart failure, ejection fraction ≤35 %	Spironolactone, 25–50 mg/day	30 % reduction in mortality, 35 % reduction in CHF hospitalization at 24 months
EPHESUS [3]	Recent MI (within 3–14 days), ejection fraction ≤40 %, evidence of CHF	Eplerenone, 50 mg/day	15 % reduction in mortality at 16 months
4E [61]	Cardiac hypertrophy, essential hypertension	Eplerenone, 200 mg/day	15-g reduction in left ventricular mass, 24/12 mmHg reduction in systolic/diastolic BP
Eplerenone for older patients with systolic hypertension [8]	Age ≥50 years, systolic BP ≥150 mmHg with pulse pressure ≥70 mmHg	Eplerenone, 50–200 mg/day, versus amlodipine	20-mmHg reduction in systolic BP and decrease in pulse wave velocity (same as amlodipine), 27 % reduction in urinary albumin/creatinine (versus <10 % for amlodipine)
EMPHASIS-HF [5]	NYHA class 2 heart failure, ejection fraction ≤35 %, CV hospitalization	Eplerenone, 50 mg/day	37 % reduction in CV mortality or CHF hospitalization, 24 % reduction in mortality at 21 months
ASPIRANT [62]	Resistant hypertension (systolic BP >140 mmHg when receiving 3 drugs with diuretic)	Spironolactone, 25 mg/day	10-mmHg reduction in average 24-h ambulatory BP

BP blood pressure, *CHF* congestive heart failure, *CV* cardiovascular, *MI* myocardial infarction, *NYHA* New York Heart Association

release of chemotactic factors from human coronary artery SMCs that engage the leukocyte vascular endothelial growth factor type 1 receptor (VEGFR1), thereby increasing recruitment of activated human macrophages [30]. In vivo, mice lacking the VEGFR1 ligand, placental growth factor, are protected from early aldosterone-induced vascular inflammation and atherogenesis. Moreover, human aorta specimens explanted from patients undergoing coronary artery bypass graft surgery show upregulation of the placental growth factor/VEGFR1 signaling axis when treated with aldosterone [36•]. Spironolactone inhibits this effect, indicating that these pathways are functional in human vessels and that inhibition of vascular MR-regulated genes by MRAs might contribute to the protective effects of these drugs.

Recent studies indicate that MR modulation of immune cell function may also play a role in atherogenesis. In mouse models of atherosclerosis, low-dose aldosterone infusion causes systemic inflammation with increased spleen size and circulating levels of the cytokine RANTES [30]. Deletion of MR in macrophages shifts cell populations from the classic M1 phenotype to the anti-inflammatory M2 state [37], as does systemic inhibition of MR with eplerenone in atherosclerotic mouse models [28]. Eplerenone also suppresses macrophage activation in vitro, further suggesting a direct role for leukocyte MR in inflammation [38]. In models of disease, macrophage MR deletion reduces ischemic stroke infarct size and mineralocorticoid-induced cardiac hypertrophy [37, 39, 40]. In addition to macrophages, T cells are also an integral component of atherosclerotic lesions [19] and are recruited to the vessel in response to aldosterone [30]. The potential role of MR in adaptive immune responses that contribute to atherogenesis warrants further investigation [41].

Clinical Implications

Patients with high plasma aldosterone levels exhibit higher concentrations of circulating E-, P-, and L-type selectins [42], indicating that these individuals have endothelial dysfunction and vascular inflammation and thus may be more prone to plaque rupture, the cause of most MIs and ischemic strokes. More directly, in cardiovascular disease patients, aldosterone levels correlate with the degree of atherosclerosis and plaque rupture [9, 10, 12••]. Thus, in patients at risk of CAD, circulating aldosterone levels may be a useful biomarker to identify patients who have a particularly high risk of ischemic events, which may warrant more aggressive risk factor modification to prevent adverse clinical events.

The myriad protective effects of MRAs in patients with advanced heart failure have long been appreciated [43], yet the potential for these drugs to prevent the complications of atherosclerosis have not been formally tested clinically. The ALBATROSS trial, which completed data acquisition in February 2013, is designed to evaluate MRA therapy in CAD patients without heart failure [44]. If this patient population benefits from MRA therapy, further trials will be needed to evaluate MRAs as a preventative treatment in

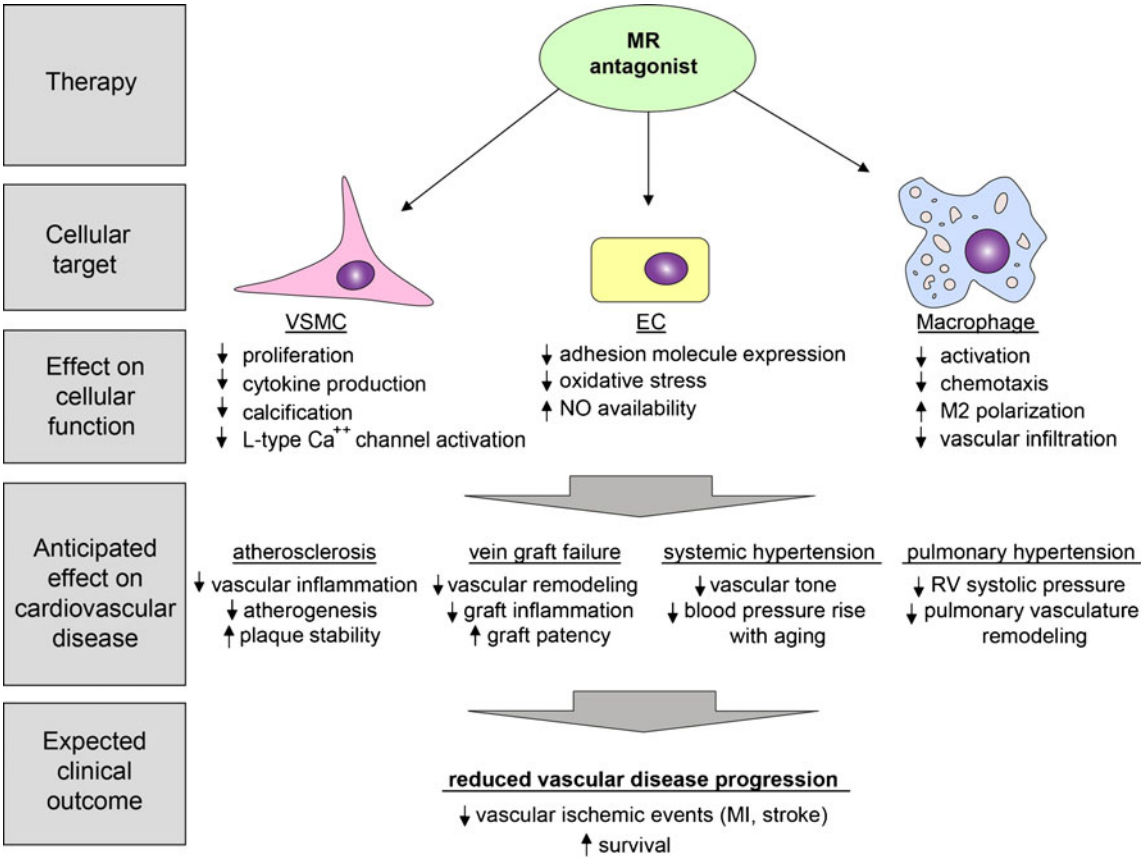

Fig. 1 Anticipated effects of mineralocorticoid receptor (*MR*) antagonist therapy in cardiovascular disease patients. Inhibition of MR signaling in vascular smooth muscle cells (*VSMC*), endothelial cells (*EC*), and macrophages induces a variety of cardioprotective actions. Collectively, these effects inhibit the progression of atherosclerosis, vein graft failure, and systemic and pulmonary hypertension, leading to fewer vascular ischemic events and improving patient survival. *MI* myocardial infarction, *RV* right ventricle

asymptomatic but high-risk individuals. On the basis of what is known about MR in atherogenesis from basic science studies, MRAs have the potential to reduce early vascular inflammation—an initiating step in atherosclerosis—to prevent inflammation-mediated rupture of existing plaques, and to modulate late stages of vascular calcification, and therefore could benefit individuals at various stages during the progression of vascular disease.

MRs in Vein Graft Failure

Bypass surgery remains an important therapeutic option for patients with diffuse or severe arterial occlusive disease, with an estimated 400,000 coronary artery bypass graft surgery cases and 75,000 peripheral arterial bypass surgical procedures performed in the USA annually [45, 46]. Because of their availability, autologous saphenous veins are the commonest conduit used during bypass procedures; however, vein graft failure rates remain high with no effective therapy. Arterialized veins undergo rapid adaptive remodeling characterized by SMC hyperplasia and vessel wall thickening, thereby reducing wall tension [47]. The mechanism involves dedifferentiation of medial SMCs from a quiescent contractile state into a synthetic phenotype that proliferates and secretes growth factors and cytokines, leading to a robust inflammatory response [48]. Proliferation of SMCs and associated inflammation promote histological changes resembling those observed with arterial atherosclerosis, including hyperplasia and the development of inflamed focal lesions that can accumulate oxidized lipids and either occlude blood flow or rupture, leading to thrombus formation and ischemic complications [49, 50].

MR and Mechanisms of Vein Graft Failure

Although the pathological aspects of failing vein grafts have been characterized [51], less is known about the molecular mechanisms that regulate the process of vein graft remodeling. As roles for MR in arterial remodeling and atherosclerosis have been elucidated, interest has recently developed in whether venous tissue might also express MR that could contribute to vein graft failure. Human saphenous vein SMCs, ECs, and whole vessels have recently been found

to express MR messenger RNA and protein, as well as 11-β-hydroxysteroid dehdyrogenase type 2, the enzyme necessary to confer aldosterone sensitivity [32, 52, 53•]. In vitro, saphenous vein SMC MR can be activated by aldosterone at physiological and pathologically relevant concentrations to modulate MR transcriptional activity [52, 53•]. In addition, aldosterone regulates expression of AT1R in human venous SMCs in an MR-dependent manner [52]. In a recent study, Bafford et al. [52] examined failed saphenous vein grafts explanted from peripheral bypass surgery patients undergoing reintervention and found that MR and 11-β-hydroxysteroid dehdyrogenase type 2 protein levels are increased compared with ungrafted veins, suggesting enhanced MR signaling in the failing vein graft. These phenomena were also observed in a rabbit vein graft model [52], supporting the potential for venous MR activation by aldosterone to play a role in the mechanism of vein graft failure.

Recent in vivo studies suggest that MR signaling may play a role in early processes that contribute to graft inflammation, fibrosis, and intimal hyperplasia. In a porcine model of carotid artery interposition grafting, low-dose treatment with the MRA spironolactone resulted in vein grafts with greater lumen cross-sectional area as early as 5 days after the procedure, with no change in neointima formation, compared with placebo-treated controls [54]. Using a mouse vena cava to aorta interposition model, we have recently demonstrated that spironolactone dramatically reduces focal vein graft remodeling and vessel fibrosis after grafting [53•]. Spironolactone treatment reduced the number of inflammatory cells in the grafted vein without changing the total SMC content, suggesting that MR signaling may contribute to graft remodeling through inflammatory processes rather than SMC hypertrophy. Additional studies also suggest that circulating inflammatory cells play an underappreciated role in vein graft stenosis [55, 56], and that inflammatory cell MRs may contribute to ischemic vascular disease [39]. Further studies are warranted to determine the molecular mechanisms for the role of MR in vein graft failure.

Clinical Implications

Despite the proven efficacy of bypass surgery for patients with advanced vascular disease, graft failure rates remain high with no effective therapy. In addition to preventing adverse vein graft remodeling, an ideal drug to preserve graft patency should inhibit subsequent clinical complications, such as progression of atherosclerosis and thrombosis. In animal models, blockade of MR signaling attenuates vein graft remodeling, fibrosis, and inflammation [53•, 54], inhibits SMC proliferation and injury-mediated vascular hypertrophy [36•], reduces atherosclerosis, plaque inflammation, and macrophage activation [28, 30], and prevents venous thrombosis (Fig. 1) [57]. Additionally, MRAs have a proven history of efficacy and safety in patients with cardiovascular disease, making these drugs attractive candidates for clinical studies to improve graft patency and long-term survival in patients undergoing vein graft surgery.

MR and Hypertension: The Vasculature as Culprit in Elevated BP

In clinical trials, MRA therapy is effective in the treatment of hypertension [8, 58–62]. Many studies in rodent models also demonstrate benefits of chronic MR antagonism in lowering BP and improving hypertension outcomes [63–68]. More recent studies have evaluated the effects of the novel nonsteroidal MRA SM-368229 on rat models of hypertension and found that this drug reduces BP and provides cardiorenal protection [69, 70]. Although renal MR regulation of BP continues to be an attractive antihypertensive target, data from animal models and human studies support the potential for extrarenal MR to also contribute to BP control. A recent meta-analysis of MRA clinical trials demonstrated that BP reduction with MR blockade does not correlate with changes in plasma potassium level, a marker of renal MR activation, thereby supporting the potential for nonrenal MR to contribute to BP modulation [71]. Moreover, mice deficient in MR in all tissues die of salt wasting in the neonatal period, which is consistent with the known role of MR in regulating vascular volume [72, 73]. However, unless challenged with low-salt conditions, mice with renal-tubule-specific MR deficiency survive [74, 75], suggesting the possibility that loss of extrarenal MR could also contribute to the hypotension and mortality associated with total MR deficiency. Over the past decade it has become clear that the vasculature is an aldosterone-responsive MR target tissue, and emerging evidence supports a direct role for the vasculature in BP regulation [76]. Studies using vascular-specific transgenic mouse models have begun to elucidate the direct role of vascular MR in BP control and may provide new insights into novel mechanisms and treatments for hypertension.

Vascular endothelial dysfunction is a hallmark of hypertension. MRA treatment improves endothelial function in animal models of hypertension and in hypertensive patients [77–81]; however, whether antagonism of MR in ECs has direct BP benefits is not yet known. Support for this possibility comes from a recent study of a mouse model with inducible overexpression of MR in ECs [82]. These EC-MR mice have elevated systolic and diastolic BP compared with controls, with no difference in renal sodium transport, heart rate, or heart weight. EC-MR mice also showed greater BP rise in response to infusion of AngII or endothelin-1 compared with controls, consistent with ex vivo vessel data supporting a role for MR in potentiating vascular responses

to contractile agonists. Further studies in endothelial-specific MR-deficient mice will help clarify the role of endogenous vascular EC MR in the regulation of BP.

A mouse model with inducible, SMC-specific deletion of MR (SMC-MR-KO) has further extended our knowledge of the role of vascular MR in BP regulation [83••]. As it does in humans, BP rises with age in SMC-MR-intact mice, yet this age-associated rise in BP is lost in SMC-MR-KO mice. The lower BP in aged SMC-MR-KO mice is independent of sodium loading, and renal MR function remains intact in these mice, supporting a renal-independent role for SMC MR in BP regulation. The vasoreactivity and tone of resistance vessels is thought to be critical in the modulation of the total vascular resistance that contributes to systemic BP. Resistance vessels from control mice develop augmented agonist-induced contraction with aging, although this effect is absent in vessels from SMC-MR-KO mice. Similarly, resistance arteries from aged SMC-MR-KO mice have structure and stiffness comparable to those from control mice, but they develop significantly less spontaneous myogenic tone. Voltage-gated calcium channels have a well-characterized role in vascular contraction and in the development of myogenic tone. The expression and activity of the $Ca_v1.2$ L-type calcium channel α_1 subunit are reduced in vessels from SMC-MR-KO mice, suggesting that MR-mediated regulation of vascular calcium channels in SMCs may participate in age-associated alterations in myogenic tone, agonist-induced contraction, and BP regulation.

Previous studies suggest that cross talk occurs between the AT1R and the MR in vascular SMCs during AngII stimulation in vitro [31, 84–87]. New evidence for in vivo cross talk between MR activation and AngII signaling comes from studies in mice deficient in aldosterone synthase. In these studies, aldosterone deficiency (or treatment with an MRA) prevented AngII-induced cardiac, renal, and vascular injury [88]. These findings do not specifically implicate SMC MR signaling; however, we have recently demonstrated that many of the detrimental effects of AngII on the vasculature require SMC MR. AngII infusion causes significant hypertension, vascular contraction, and vascular oxidative stress, all of which are attenuated in young SMC-MR-KO mice and are prevented in aged SMC-MR-KO mice [83••]. Overall, studies in this mouse model demonstrate a direct contribution of SMC MR to BP control in aged mice likely via modulation of vascular oxidative stress, AngII signaling, and calcium channel function.

MR antagonism has been beneficial in clinical trials of patients with heart disease when used in combination with standard therapies, including ACE inhibitors and AT1R blockers, and MRAs are as effective for treating hypertension as calcium channel blockers (but with better end-organ protection) [8] or AT1R inhibitors [89]. The emerging evidence for vascular MRs as regulators of BP and their link to calcium channel and AngII signaling indicates a possible benefit of combination therapy in hypertensive patients. A recent study in a rat model of salt-sensitive hypertension found that eplerenone treatment potentiated the protective effects of the L-type calcium channel blocker amlodipine against cardiovascular injury. This finding suggests that MRA/L-type calcium channel blocker combination therapy could potentially reduce the cardiovascular morbidity and mortality in hypertensive patients more effectively than either drug alone and at lower doses that might limit side effects [90]. In addition, hypertension is predominantly a disease of the elderly, affecting more than 60 % of people older than 60 years and up to 80 % of the growing population older than 80 years. Recent data in animal models suggest that SMC MR is a unique contributor to the rise in BP with aging and supports clinical studies to evaluate the efficacy of MR antagonism to treat hypertension specifically in the elderly or even to prevent the progression of hypertension with advancing age.

The Role of MR in Pulmonary Arterial Hypertension

In addition to its well-known role in regulating systemic BP, a role for MR in pulmonary hypertension has recently been identified. Pulmonary arterial hypertension (PAH) remains a progressive, fatal disease, with a mortality of up to 50 % at 5 years, even with recent advances in available therapies [91]. Pathological abnormalities of the pulmonary vasculature in this disease include medial thickening due to SMC hyperplasia and hypertrophy, muscularization of distal nonmuscular arteries, neointimal thickening composed of SMCs or myofibroblasts, and the occurrence of plexiform lesions due to EC and SMC proliferation [92].

Although several pathways, such as platelet-derived growth factor [93] and nitric oxide [94] signaling, have been previously implicated in the pathogenesis of PAH, very recently data have emerged that also support a role for MR in this disease. In three distinct experimental rodent models of pulmonary hypertension, MR antagonism attenuates the severity of the PAH phenotype [78•, 95]. MRA treatment initiated at the time of the PAH stimulus prevents the pulmonary vascular hyperplasia and the rise in right ventricular systolic pressure. More importantly, initiation of MRA therapy after establishment of PAH attenuates the progression of disease, supporting a potential for these drugs to be used therapeutically in patients. Mechanistic studies revealed that MR is functional in distal pulmonary artery SMCs and that MR inhibition prevents cell proliferation. Exposure of pulmonary artery SMCs to hypoxia or to platelet-derived growth factor promotes translocation of MR to the nucleus, whereas MR antagonism blocks the proliferative effects of these PAH activators [95]. In addition, in pulmonary artery ECs, aldosterone-induced oxidative stress impairs endothelin-B receptor signal

transduction, resulting in impaired nitric oxide synthesis [78•]. Moreover, in a cohort of PAH patients, plasma aldosterone levels were found to be elevated compared with those in controls and also to correlate with markers of disease severity [96]. Collectively, these recent results support the notion that MR contributes to the development and worsening of pulmonary vascular remodeling and elevation of pulmonary pressure in PAH. Since MRAs are available and their safety profile is well characterized—even in patients with advanced heart failure—they may be a novel therapeutic target for this devastating disease (Fig. 1).

Conclusion

It is now clear that MR signaling plays a much greater role in human physiology and disease than solely controlling electrolyte balance and BP through the kidney. Clinical studies as well as animal models demonstrate that MR activation correlates with and contributes to the pathophysiological processes involved in atherosclerosis, vascular injury, vein graft remodeling, and systemic and pulmonary hypertension (Fig. 1). Collectively, these studies show that MR activation in vascular and inflammatory cells exerts a substantial influence on the progression of these diseases and have identified new patient populations that may benefit from MRA therapy:

- Patients at high-risk of heart attack or stroke
- Vein graft surgery patients
- Patients at risk of stent failure from adverse vascular remodeling
- Patients with cardiac hypertrophy and diastolic heart failure
- Patients with age-associated hypertension
- Patients with systemic hypertension (in combination with AT1R or L-type calcium channel blocker)
- Patients with pulmonary hypertension

New clinical trials evaluating MRA efficacy outside the setting of heart failure and systemic hypertension may establish new strategies to treat or prevent a wide range of cardiovascular diseases.

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- • Of importance
- •• Of major importance

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