

Vascular Mineralocorticoid Receptors Linking Risk Factors, Hypertension, and Heart Disease

Achim Lother, Lutz Hein

Cardiovascular disease is often delineated as a continuum from risk factors leading to organ damage, remodeling, and finally dysfunction. The vasculature is ascribed a central role in that model: major cardiovascular risk factors such as the metabolic syndrome¹⁻⁶ or age^{7,8} are closely associated with chronic inflammation and oxidative stress driving impaired nitric oxide bioavailability, endothelial dysfunction, arterial stiffening, vascular remodeling, and hypertension. In the heart, this leads to fibrosis, myocyte hypertrophy, and impaired relaxation, the hallmarks of heart failure with preserved ejection fraction (HFpEF).⁹ Although in heart failure with reduced ejection fraction, primary damage mostly occurs in cardiac myocytes, in HFpEF vascular cells are seen as the predominant cell type that translates the chronic inflammatory state into cardiac injury.⁹ In line with this, patients with HFpEF are older and more often obese when compared with patients with reduced ejection fraction,¹⁰ and cardiac remodeling in HFpEF is independently associated with higher blood pressure^{11,12} and vascular stiffness.¹³

There is an increasing body of evidence that aldosterone and mineralocorticoid receptor (MR) signaling in vascular cells facilitates the transition from cardiovascular risk into hypertension and heart disease. Epidemiological data on a random population shows a significant association of elevated aldosterone levels with obesity, metabolic syndrome, hypertension, and left ventricular hypertrophy.¹⁴ Adipocytes express aldosterone synthase and may be an additional source of aldosterone in obesity.¹⁵ In a smaller population of patients with arterial hypertension, elevated aldosterone levels were related to left ventricular hypertrophy.¹⁶ Aldosterone exerts many of the detrimental cellular and molecular features of cardiovascular remodeling that are common in hypertension and heart disease, including inflammation, reactive oxygen species production and fibrosis.¹⁷ The MR is expressed in different cell types¹⁸ in the cardiovascular system that contribute to the cumulative effect of aldosterone. A series of experimental studies has recently focused on the role of MR in endothelial cells and vascular smooth muscle cells (VSMCs) in cardiovascular disease. This review summarizes the advances in the field based on articles published in *Hypertension* during the past 2 to 3 years.

Vascular Stiffness, Dysfunction, and Blood Pressure Regulation

Aldosterone and the MR, a ligand-activated transcription factor of the steroid receptor superfamily, are well-known regulators of sodium balance and blood pressure.¹⁸ In the kidney, activation of MR by aldosterone leads to an upregulation of the epithelial sodium channel (ENaC) located in the apical membrane of collecting duct principal cells. In collaboration with the Na⁺-K⁺-ATPase in the basolateral membrane, this leads to increased sodium reabsorption and potassium loss.¹⁸

There are a long-lasting debate and controversial findings on the effect of aldosterone on vascular constriction or relaxation.¹⁹ MR deletion from VSMCs (VSMC-MRKO) improves coronary flow reserve and left ventricular compliance after experimental myocardial infarction.²⁰ In line with this, cardiomyocyte-restricted aldosterone synthase overexpression decreased expression of Ca²⁺-activated potassium channels and impaired Ca²⁺-activated potassium channel-dependent relaxation in coronary VSMC, suggesting an aldosterone-dependent effect.²¹ In previous studies, MR deletion improved arterial relaxation²² and distensibility²³ and dampened the age-associated or angiotensin II-induced increase in blood pressure.²² Interestingly, this blood pressure-lowering effect was not present after aldosterone/salt treatment,^{22,23} and Ca²⁺-activated potassium channel activity was not altered in mesenteric arteries from VSMC-MRKO mice.²² Preserved coronary relaxation was associated with an improved nitric oxide availability in VSMC-MRKO,²⁰ potentially because of less reactive oxygen species production in VSMC.^{20,22}

Endothelial cell-restricted overexpression of the MR in mice enhanced the contractile response of mesenteric arteries and increased blood pressure at baseline and in response to angiotensin II or endothelin-1.²⁴ In contrast, MR deletion from endothelial cells (EC-MRKO) did not alter blood pressure at baseline or in response to mineralocorticoid, mineralocorticoid/salt, or angiotensin II stimulation.^{25,26} Vascular relaxation at baseline or after aldosterone treatment was unaltered in mesenteric arteries from MR-deficient mice^{25,27} but improved in coronary²⁵ or aortic^{6,27} sections. Obesity and enhanced leptin signaling increased plasma aldosterone levels by 2- to 3-fold in mice.²⁸ This was associated with elevated blood pressure

From the Institute of Experimental and Clinical Pharmacology and Toxicology, Faculty of Medicine, (A.L., L.H.), Heart Center, Department of Cardiology and Angiology I, (A.L.), and BIOS Centre for Biological Signaling Studies (L.H.), University of Freiburg, Germany.

Correspondence to Achim Lother, Institute of Experimental and Clinical Pharmacology and Toxicology, University of Freiburg, Albertstr. 25, 79104 Freiburg, Germany. E-mail achim.lother@universitaets-herzzentrum.de

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and impaired endothelium-dependent vascular relaxation which was both prevented by spironolactone.²⁸ Similar results were obtained in wild-type mice that received high-fat diet.⁵ In line with this, high-fat diet-induced endothelial dysfunction and impaired vascular relaxation was restored by endothelial MR deletion.^{1,6} This was accompanied by reduced oxidative stress and improved nitric oxide production in EC-MRKO mice^{1,6} or after spironolactone treatment.⁵

It has been demonstrated that ENaC is also expressed outside of the kidney in endothelial cells and contributes to endothelial cell and vascular stiffness.^{29,30} ENaC expression increases with age or in response to high-fat diet.^{1,29} EC-MRKO¹ as well as treatment with spironolactone²⁹ or the ENaC inhibitor amiloride²⁹ prevented high-fat diet-induced or salt-induced endothelial cell stiffening. In a mouse model of Liddle syndrome, an inherited form of hypertension, aldosterone MR dependently increased endothelial ENaC expression and stiffness.³¹

In summary, aldosterone via MR in vascular cells alters activity of ion channels, increases reactive oxygen species production, and impairs nitric oxide availability which might contribute to vascular stiffness and dysfunction (Figure). After endothelial injury or in the presence of risk factors, aldosterone predominantly exerts a contractile response, but this effect depends on the vascular bed and might involve different mechanisms. MR in endothelial cells contributes to arterial hypertension at pathological expression level, but it is dispensable at physiological expression level. MR in VSMC is essential for age-related or angiotensin II-related but not

mineralocorticoid/salt-related hypertension. Interestingly, MR deletion from macrophages prevented the mineralocorticoid/salt-induced increase in blood pressure,³² suggesting that MR in different cell types are decisive for the response to different hypertensive stimuli.

Inflammation and Novel MR Targets in Cardiovascular Remodeling

Aldosterone induces leukocyte infiltration, vascular inflammation, and fibrosis.³³ In part, this effect is mediated via MR in monocytes and macrophages,³² but endothelial cells are a key regulator of leukocyte adhesion and transmigration. Accordingly, EC-MRKO prevented adverse cardiac remodeling in response to mineralocorticoid/salt-induced hypertension in mice.^{26,27} This was associated with a downregulation of intercellular cell adhesion molecule or vascular cell adhesion molecule in MR-deficient endothelial cells and less macrophage infiltration of the heart.^{26,27} EC-MRKO⁴ or treatment with spironolactone³⁴ protected from high-fat diet-induced macrophage accumulation, oxidative stress, cardiac fibrosis, and diastolic dysfunction. Together, these data show that the proinflammatory effect of aldosterone strongly depends on MR in endothelial cells. However, it has been shown earlier that aldosterone can rapidly induce vascular permeability by rearrangement of the actin cytoskeleton, suggesting that nontranscriptional signaling might as well be involved in the process.³⁵ Interestingly, the protective effect of endothelial MR deletion did not apply to mineralocorticoid/salt-induced kidney injury, suggesting that MR-dependent regulation of

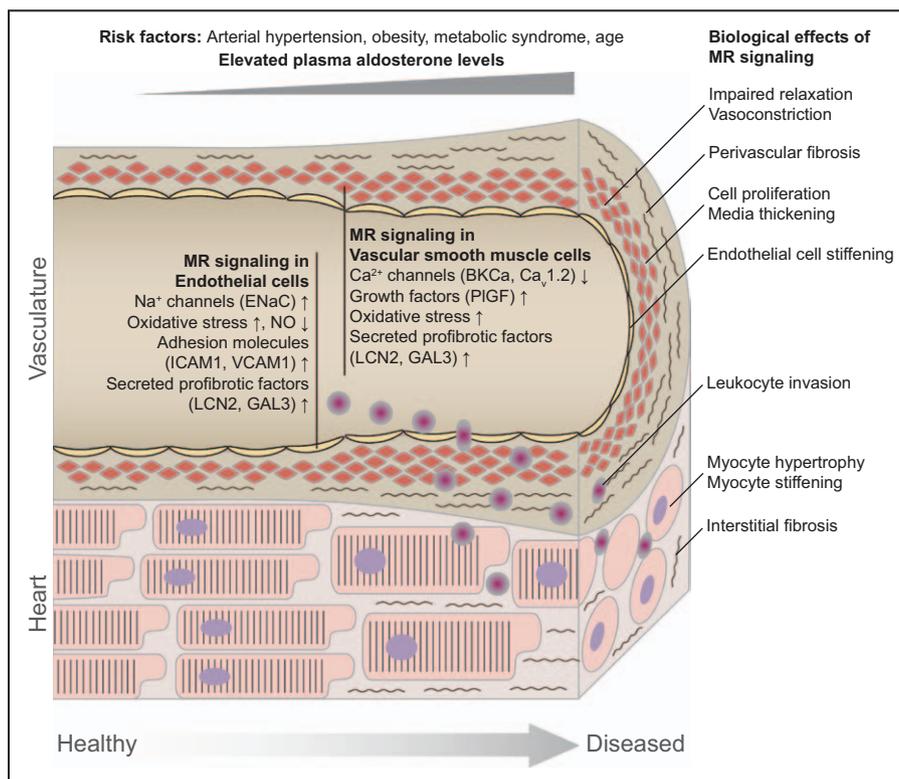


Figure. Schematic representation summarizing the biological effects in cardiovascular disease and proposed molecular mediators induced by mineralocorticoid receptors in endothelial cells and vascular smooth muscle cells. BKCa indicates Ca²⁺-activated potassium channels; Ca_v1.2, L-type Ca²⁺ channel subunit Ca_v1.2; ENaC, epithelial sodium channel; GAL3, galectin-3; ICAM-1, intercellular adhesion molecule 1; LCN2, lipocalin-2; NO, nitric oxide; PIGF, placental growth factor; and VCAM-1, vascular cell adhesion molecule 1.

adhesion molecules in endothelial cells is context sensitive and might require tissue-specific cofactors.²⁶

VSMC contribute to cardiac remodeling as well because VSMC-MRKO reduced oxidative stress and cardiac fibrosis after experimental myocardial infarction.²⁰ Earlier studies have shown that aldosterone aggravates VSMC proliferation and perivascular fibrosis after experimental vessel injury via placental growth factor signaling which was prevented by MR deletion.³⁶

Lipocalin-2 is a secreted protein that is expressed in endothelial and VSMC and becomes upregulated by aldosterone.³⁷ In humans, lipocalin-2 binds to and stabilizes matrix metalloproteinase 9, an important regulator of cardiac fibrosis.³⁸ Deletion of lipocalin-2 prevented the development of perivascular fibrosis in response to mineralocorticoid/salt in the heart and aorta of mice and reduces blood pressure.³⁸ In vitro stimulation of human fibroblasts with lipocalin-2 leads to an upregulation of different profibrotic genes, among others, galectin-3.³⁸

Galectin-3 is a secreted protein that is involved in fibrosis, inflammation, and cell–cell interaction. Galectin-3 expression has been found to positively correlate with aortic pulse wave velocity in humans,³⁹ and it is upregulated in obese patients with left ventricular diastolic dysfunction.⁴⁰ In experimental models, galectin-3 is upregulated by high-fat diet,⁴⁰ isoproterenol,⁴¹ or aldosterone treatment.⁴² Treatment with the galectin-3 inhibitor–modified citrus pectin^{40,41} or spironolactone^{41,42} similarly prevented cardiac and aortic inflammation and fibrosis. Galectin-3–deficient mice were protected from aldosterone-induced cardiac remodeling.⁴²

In conclusion, inflammation is a key mechanism mediating the detrimental effects of aldosterone in the cardiovascular system. MR in endothelial cells determines leukocyte adhesion and transmigration throughout diverse experimental models of cardiovascular injury. Different proinflammatory molecules from endothelial or VSMC source have been proposed as mediators of mineralocorticoid-induced remodeling (Figure).

Clinical Trials: Arterial Hypertension

Although the antihypertensive properties of spironolactone are well described, until some years ago only a minority of patients with resistant hypertension received a MR antagonist.^{43,44} In a prospective single-arm study, adequate blood pressure control could be achieved in 48% of the patients treated with spironolactone.⁴⁵ Recently, the remarkable blood pressure–lowering effect of spironolactone in patients with resistant hypertension has been confirmed in the randomized, controlled Prevention and Treatment of Hypertension With Algorithm-Based Therapy (PATHWAY)-2 clinical trial.⁴⁶ In that trial, spironolactone reduced blood pressure by 8.7 mmHg when compared with placebo and was superior to treatment with an α_1 - or β_1 -adrenoceptor antagonist.⁴⁶ In the PRAGUE-15 trial, spironolactone treatment reduced blood pressure more effectively than catheter-based renal denervation in patients with resistant hypertension on optimized background pharmacotherapy.⁴⁷ Although further trials are required to confirm these promising results in a larger population, a renaissance of MR antagonists for the treatment of arterial hypertension can be expected.

Clinical Trials: Heart Failure With Preserved Ejection Fraction

MR antagonists such as spironolactone or eplerenone are a cornerstone in the therapy of chronic heart failure with reduced ejection fraction (HF_rEF).^{17,18} In the recent phase III trial Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT), spironolactone reduced the rate of hospitalization for heart failure in patients with HF_rEF but not the primary composite hospitalization and mortality end point.⁴⁸ Of note, subgroup analysis revealed substantial regional differences.^{48,49} Patients enrolled in the United States, Canada, Argentina, and Brazil versus Russia and Georgia experienced a >3-fold higher rate of primary outcome events in the respective placebo groups which was significantly improved by spironolactone.⁴⁹ Other pharmacological responses to spironolactone such as blood pressure lowering or hyperkalemia were greater in patients from the Americas. The latter were older and had a higher prevalence of diabetes mellitus, dyslipidemia, and chronic kidney disease.⁴⁹ The proportion of patients enrolled on the basis of elevated natriuretic peptide levels versus previous hospitalization for heart failure was higher in the American collective.⁴⁸ On the one hand, this illustrates the mess with making the diagnosis HF_rEF and the need for robust inclusion criteria. On the other hand, it supports the hypothesis derived from experimental studies that aggravated risk is associated with increased MR signaling. This gives reason to hope that MR antagonists could turn out to be effective in the now following studies on that high-risk patient collective.

Summary and Perspective

Taken together, the experimental evidence discussed above strongly supports the hypothesis that MR in endothelial cells and VSMCs are decisive mediators of cardiovascular remodeling. They are involved in blood pressure regulation and closely link cardiovascular risk factors and disease. The underlying cellular and molecular mechanisms include inflammation, reactive oxygen species production, and altered ion channel activity. These findings provide the mechanistic rationale for MR antagonist use in the treatment of hypertension and heart failure. Further understanding of the molecular basis is needed toward the development of novel pharmacological approaches selectively targeting MR signaling in the cardiovascular system.

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Achim Lother and Lutz Hein

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