Effects of aldosterone on blood pressure control have classically been attributed to sodium retention through its action on the kidney. However, increasingly it has been appreciated that aldosterone exerts effects directly on the vasculature. Here, we comment on novel data published recently that sheds light on new mechanisms, whereby aldosterone acting through the mineralocorticoid receptor on blood vessels, in interaction with angiotensin II and via oxidative stress and calcium channels, may affect age-associated changes in myogenic tone and exert effects on blood pressure regulation.

Aldosterone is produced by the adrenal glomerulosa in response to angiotensin (Ang) II, elevated serum potassium, and corticotropin. It acts on the kidney to increase sodium reabsorption in the distal nephron interacting with the mineralocorticoid receptor (MR) and by activation of the apical epithelial sodium channel. In humans, primary hyperaldosteronism clearly establishes the role that aldosterone has on blood pressure (BP) and hypertension. However, in both normotensive subjects and in essential hypertension, contribution of aldosterone to BP has been more difficult to establish. In the Framingham study, quartiles of plasma levels of aldosterone were directly associated with BP. A fraction of patients with essential hypertension shows mild elevation of aldosterone plasma concentrations. On the contrary, treatment with MR antagonists lowers BP in human patients with essential hypertension, and particularly drug-resistant hypertension. Because aldosterone synthase inhibitors have similar effects as MR blockade in humans with hypertension, it is likely that the effects reported for MR antagonism are mediated by blockade of the action of aldosterone.

On which organs does aldosterone act to raise BP? The initial answer is that it may in large measure do so by increasing sodium and water retention through its action on sodium reabsorption in the distal nephron of the kidney, a classical action of aldosterone. However, aldosterone also exerts effects directly on blood vessels as demonstrated in experimental models and in vitro on isolated vessels and vascular smooth muscle cells. It produces inflammation, oxidative stress, endothelial stiffness and dysfunction, and fibrosis and hypertrophic vascular remodeling, particularly when experimental animals are exposed to a high-salt intake. The MR blocker spironolactone prevented vascular fibrosis independently of BP reduction in spontaneously hypertensive rats, and in humans with stage 1 essential hypertension, the more selective but less potent MR blocker eplerenone achieved similar results.

Cardiovascular remodeling usually attributed to Ang II can be significantly reduced by the use of MR blockers. In Sprague-Dawley rats infused with Ang II, spironolactone reduced systolic BP and blunted the hypertrophic remodeling of small resistance arteries. Numerous publications have since supported the idea of an interaction between signaling of Ang II and aldosterone, which indicates that both agents together result in greater responses. The mechanism for this effect, still unclear, could implicate a role for MR-stimulated transglutaminase-mediated Ang AT1 receptor dimerization and enhanced responses. Aldosterone infusion into uninephrectomized Sprague-Dawley rats receiving a high-salt diet increased large artery stiffness with resulting increase in pulse pressure and carotid elastic modulus, as a consequence of increased aortic fibronectin expression, interestingly with no change in collagen density, a phenotype that was prevented by the selective MR antagonist eplerenone. In hypertensive patients, an inverse correlation was found between plasma aldosterone concentration and large vessel compliance, independently of age and BP. In addition, a polymorphism of CYP11B2 (aldosterone synthase) was associated with higher aortic stiffness in hypertensive patients.

A recent study by McCurley et al in Nature Medicine has now extended our knowledge on the role of MR in BP regulation. These investigators have shown with a very elegant molecular approach that mice with smooth muscle cell (SMC)-specific deficiency of MR (SMC-MR) have decreased BP with aging in the absence of defects in renal sodium handling or altered vascular structure. Aged SMC-MR-deficient mice had reduced vascular myogenic tone, agonist-dependent contraction and expression, and activity of L-type calcium (Ca) channels. Their study confirmed that SMC-MR contributes to Ang II–induced vascular oxidative stress, contraction, and elevated BP and suggested that vascular MR-mediated vascular tone is involved in BP control and vascular aging.
McCurley et al. studied mice lacking MR specifically in SMCs by generating mice with a loxP-flanked MR (MRf/f) allele and breeding these with mice containing the SMA-Cre-ERT2 transgene, in which the SMC actin promoter drives the expression of tamoxifen-inducible Cre-ERT2 recombinase. BP was lower in male SMC-MR–deficient (Cre+) mice compared with Cre– littermates that increased with age, a difference that achieved significance only at 7 months of age. Vessels from Cre+ adult mice showed some increase in contraction to phenylephrine and endothelin-dependent vasodilatation, whereas in aged Cre– mice contraction was significantly augmented in response to KCl or the thromboxane receptor agonist U46619, suggesting a direct role for SMC-MR in BP regulation with aging. These effects could neither be attributed to enhanced BP salt sensitivity or difference in serum or urine electrolytes or aldosterone, nor responsiveness to aldosterone infusion. MR function in the kidney was unaffected, as demonstrated by total and fractional urinary sodium excretion, in agreement with an extrarenal, SMC-MR–dependent mechanism for effects on BP.

Aortic structure and collagen, and cardiac hypertrophy were blunted in the Cre+ mice compared with Cre– mice, potentially as a result of lower BP. Resistance arteries from aged Cre+ had similar structure and stiffness as those from Cre– mice, but mesenteric resistance arteries from the aged Cre+ mice developed significantly less spontaneous myogenic tone than the Cre– mice, supporting the notion that SMC-MR contributes to vascular tone and BP regulation in aged mice. However, the L-type Ca channel Cav1.2 was less abundant in vessels from Cre+ mice, and response of vessels to the L-type Ca channel agonist BayK8644 was attenuated, suggesting that these changes participate in age-associated alterations in myogenic tone, agonist-induced contraction, and BP.

Previous data have suggested that AT1 receptors cross talk with MR during Ang II stimulation of SMCs. In the study by McCurley et al., Ang II infusion failed to raise BP in aged Cre+ mice, and contraction of mesenteric resistance arteries by Ang II were abrogated. Ang II–stimulated reactive oxygen species production in the vascular wall measured with dihydroethidium staining was reduced in Cre+ mice. Thus, SMC-MR contribute to Ang II–induced vascular oxidative stress, vascular constriction, and BP elevation, particularly in the aging vasculature, demonstrating the in vivo relevance of cross talk between MR and AT1 receptor. Reduced Ang II–induced reactive oxygen species may also underlie the attenuated Cav1.2 expression Cre+ mice that could be responsible for the decreased myogenic tone associated with SMC-MR deficiency.

Systolic BP rises in humans older than 50 years, and systolic hypertension occurs in 80% or more of subjects older than 80 years. SMC-MR inactivation prevented manifestations of cardiovascular aging in mice lacking SMC-MR. This finding suggests that the development of MR antagonists with selectivity for SMC-MR might have beneficial effects on BP and cardiovascular morbidity and mortality in elderly hypertensive subjects. Likewise, such agents might be devoid of the limitations in clinical use of MR blockers, such as hyperkalemia mediated by renal MR inhibition that occurs predominantly in patients with impaired renal function and eGFR below 40 mL/min.

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References
of signaling pathways requires activity of angiotensin type 1a receptors. 


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