Endothelial Cell Mineralocorticoid Receptors
Turning Cardiovascular Risk Factors Into Cardiovascular Dysfunction

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Clinically, mineralocorticoid receptor (MR) antagonists are widely prescribed for the treatment of hypertension and heart failure because of their diuretic action in aldosterone-sensitive distal nephron. Clinical trials of MR antagonism in patients with various degrees of heart failure severity have also demonstrated a pronounced reduction of cardiovascular mortality in MR--treated patients.1 The underlying mechanisms of these cardiovascular benefits are still debated and are probably diverse. Potential beneficial effects of MR antagonism on extracellular matrix remodeling, arrhythmia susceptibility, coronary flow reserve, cardiovascular inflammation, and vascular function have all been suggested. Indeed, the vasculature has been recently highlighted as a primary target of aldosterone and MR antagonists. MR is expressed in human vascular endothelial cells (ECs) and smooth muscle cells as is the 11β-HSD2 enzyme that allows for selective aldosterone versus cortisol activation of MR. The effects of MR activation on vascular reactivity in healthy humans remains controversial because of conflicting results from clinical studies with many demonstrating a constrictive response and some showing vascular relaxation.2 Discrepancies may be due to differences in the vascular health of study participants as well as differences in study design. However, when patients with underlying cardiovascular diseases are studied, the data are consistent with MR activation promoting increased systemic vascular resistance and reduced forearm blood flow and MR antagonism improving endothelium-dependent vasodilatation, independent of changes in blood pressure. The aggregate of data supports that, in healthy vessels, acute MR activation may evoke endothelium-dependent, NO-mediated vasodilatation, whereas, in the presence of endothelial dysfunction, vascular injury, or high vascular oxidative stress (as in patients with cardiovascular risk factors or heart failure), MR activation promotes vasoconstriction.2

Recently, 2 experimental studies, using a mouse model with targeted inactivation of MR in the endothelium, have attempted to address this controversy more directly.3,4 Both studies demonstrate that, in a healthy animal, EC-specific deletion of the MR has no effect on systemic blood pressure or contractile or relaxation function of mesenteric resistance vessel, indicating that endothelial MR does not contribute substantially to these parameters in the absence of disease stimuli. However, both studies reveal that, in the setting of cardiovascular risk factors, vascular function is negatively affected by the presence of MR in ECs. Diet-induced obesity or aldosterone infusion was used in the Schäfer et al study,5 whereas mineralocorticoid/salt-induced hypertension was used to induce cardiovascular dysfunction in the Rickard et al study.6 A decline in endothelium-dependent relaxation to acetylcholine caused by the induction of obesity or aldosterone infusion was blunted in the aortae of obese mice lacking EC MR, mimicking the beneficial effect of chronic treatment with eplerenone, a specific MR antagonist.1 This was independent from proinflammatory changes in aortic ECs. EC MR was also mandatory for mineralocorticoid/salt-induced hypertension to induce endothelial dysfunction.4 Conversely, a chronic increase of MR expression specifically in the endothelium has been shown to increase the vasoactive response to angiotensin II and endothelin 1, as well as basal blood pressure and angiotensin II/endothelin 1–induced hypertension.3 The mechanisms remain to be determined, but EC MR likely contributes to vascular oxidative stress and NO production as 1 mechanism that regulates vascular contraction and relaxation in the setting of cardiovascular risk factors. Indeed, EC deletion of MR prevented aldosterone induction of NADPH oxidase subunit p22phox and COX1 in ECs.3 This suggests that EC MR is necessary for aldosterone to induce oxidative stress and associated vascular dysfunction, at least in the setting of obesity-induced vascular disease.

In the present issue, Rickard et al4 provide compelling evidence that MR expression in the endothelium is required for mineralocorticoid/salt hypertension to induce cardiac fibrosis. This study, therefore, provides new insights into the crucial role of MR activation in the endothelium to sustain the inflammatory process induced by mineralocorticoid/salt challenge leading to the stimulation of extracellular matrix remodeling in the heart. The underlying mechanisms remain to be completely elucidated, but it is suggested that protection could be because of the absence of macrophage invasion into the cardiac tissue in EC MR--deficient mice. EC MR has been found to regulate endothelial intercellular adhesion molecule-1 expression to promote leukocyte EC adhesion, a necessary step for cardiovascular inflammation.4 Indeed, EC MR deletion attenuated the increase in cardiac intercellular adhesion molecule-1 expression induced by DOCA-salt and prevented cardiac inflammation and cardiac fibrosis. Of note, 1 limitation of these models...
is the use of the Tie2/Tek promoter to drive the expression of Cre recombinase. Indeed, the Tie2/Tek promoter sequence has been previously found to target not only ECs but also myeloid cells, resulting in decreased macrophage MR expression when used with MR recombinant mice. Thus, it cannot be excluded that the prevention of cardiac remodeling also relies on the deletion of macrophage MR in the DOCA-salt model because macrophage MR has already been found to contribute to proinflammatory macrophage phenotype that is necessary for cardiac and vascular fibrosis. It is possible that both blunted macrophage infiltration and decreased macrophage MR activation may participate to decrease cardiac remodeling induced by mineralocorticoid/salt challenge in this EC MR knockout model.

In addition to the contribution to cardiovascular inflammation by the regulation of adhesion molecules or impaired relaxation related to oxidative stress, EC MR might contribute to vascular function by other mechanisms that remain to be explored. Local aldosterone infusion into the eye induced a major vasodilatation of retinal choroid vascular bed, mimicking a vision-threatening disease called central serous chorioretinitis, providing the rationale for a spectacular benefit of eplerenone in these patients. The underlying mechanism relied on the increased activity of endothelial KCa2.3 potassium ion channel involved in endothelium-dependent vasodilation. Endothelial MR also participates to endothelium stiffening via the modulation of epithelial sodium channel subunits expression/activity in the endothelium. Recent work revealed that aldosterone unexpectedly induced the downregulation of thrombin generation by the endothelium, an effect caused by an enhancement of thrombomodulin-mediated protein C activation. This was blunted by dospirenone, a contraceptive with potent MR antagonist property associated with increased thrombosis in healthy women, highlighting a novel role of endothelial MR with potential therapeutic issues.

In conclusion, the data presented by Rickard et al in the current issue of Hypertension support a model in which EC MR may be beneficial or neutral (Figure) in healthy vasculature (no effect on blood pressure and neutral or beneficial effects in terms of endothelial function or endothelial-dependent vasodilation) while playing a crucial role in the setting of cardiovascular risk factors, including obesity, hypertension, and other likely risk factors that remain to be tested. EC MR activation by aldosterone (or other activators such as corticosteroids in the eye) seems to mediate at least some of the detrimental effects of these risk factors on vascular function and cardiovascular fibrosis. These findings might help explain the substantial benefits of MR inhibition in patients with heart failure. Whether endothelial MR also participates to the pathophysiology of other diseases such as atherosclerosis, sepsis, tissue ischemia including myocardial infarction, stroke, or renal ischemia remains to be explored. Because the use of MR antagonists could be limited by their side effects (hyperkalemia, gynecomastia), further exploration of molecular mechanisms by which EC MR mediates the detrimental effects of known cardiovascular risk factors could identify novel treatment strategies that retain the substantial cardiovascular benefits of MR antagonists without the limiting side effects.

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None.

References


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