Mineralocorticoid Receptor, the Main Player in Aldosterone-Induced Large Artery Stiffness

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Whether aldosterone acts only through MR-dependent signaling pathways or involves other receptors is still matter of debate. Aldosterone exerts some effects on the vasculature with a time course that is likely incompatible with transcriptional mechanisms and involves nongenomic mechanisms. Some of these are likely to be MR independent. Indeed, the rapid constrictor effect of aldosterone on mesenteric vessels remains unaffected by MR blockers but blunted by angiotensin II receptor blocker, candesartan, and by transglutaminase inhibitor cystamine and monodansyl cadaverine. It has also been suggested that the epithelial receptor GPR30 was involved in the rapid action of aldosterone. Data from type 1 pseudohypoaldosteronism, a rare disease affecting MR function leading to mineralocorticoid resistance, provide interesting findings on this debate. Two different forms of this disease have been identified. The autosomal recessive one, caused by loss-of-function mutations in genes encoding subunits of the amiloride-sensitive epithelial sodium channel, is characterized by severe symptoms persisting during the whole life of the patients. The autosomal dominant one, or sporadic type 1 pseudohypoaldosteronism, is caused by inactivating mutations in NR3C2 gene, which codes for the MR. Despite high aldosterone levels, cardiac and vascular remodeling, evaluated by gold standard approaches (cardiac MRI, ultrasound, and aortic pulse wave velocity) were not significantly different between MR mutation carriers and noncarriers. These observations support the hypothesis that, in humans, MR is the main receptor involved in aldosterone effect. However, the renal loss of sodium associated with this disease could, per se, explain the observed defect in cardiovascular remodeling. The absence of arterial remodeling, despite high levels of aldosterone and the presence of functional MR in patients with Bartter and Gitelman syndromes, which are characterized by a renal loss of sodium, is an argument favoring this observation.

Lessons from transgenic mice could help disentangling the renal and vascular effects of aldosterone and the role of MR in vascular remodeling. Cre/loxP recombination system allowed inactivating MR gene expression in specific cell/tissues. For example, specific deletion of MR in mice macrophages showed normal inflammatory cell recruitment in response to deoxycorticosterone/salt treatment but a cardiovascular protection in terms of fibrosis, inflammation, and oxidative stress. Specific deletion of MR in cardiomyocytes improved infarct healing and adverse remodeling after myocardial infarction.

In the present issue of Hypertension, Galmiche et al have demonstrated the major implication of MR in large artery remodeling in response to aldosterone. These investigators tested the effect of uninephrectomy associated with aldosterone
and salt administration (NAS) on large artery remodeling in an elegant model of mice with conditional inactivation of the MR in vascular smooth muscle cells (MRSMKO). Renal adaptation to sodium handling and restriction was not affected in MRSMKO mice. Despite lower baseline systolic blood pressure in MRSMKO mice compared with control, NAS treatment was associated with a similar increase in systolic blood pressure in MRSMKO and control mice. NAS treatment induced a similar increase in media cross-sectional area of large vessels in MRSMKO and control mice. Conversely, the increased arterial stiffness in response to NAS treatment was blunted completely in MRSMKO mice. This result suggests that MR-dependent signaling pathways in vascular smooth muscle cells are the only pathways involved in arterial stiffness increase in response to aldosterone. The absence of arterial stiffness increase in NAS-treated MRSMKO mice is impressive because blood pressure response to NAS was maintained. Blood pressure response to NAS, in MRSMKO mice, suggests that aldosterone renal effect is the key determinant of blood pressure increase. Another possibility would be that small artery response to aldosterone is preserved in this model because (1) MR deletion may not be efficient in resistant arteries in this model; (2) aldosterone may act through MR-independent pathways in resistant arteries; and (3) the presence of MR in other cell types could be sufficient enough to induce small artery remodeling. As a consequence, peripheral resistances would participate to the preserved blood pressure response to NAS in MR SMKO mice. Further characterization of resistant artery reactivity and remodeling in response to aldosterone in this model could help to complete the description.

Galmine et al explored the possibility that extracellular matrix composition could be involved in aldosterone-induced increased arterial stiffness. Fibronectin expression, previously shown to be involved in aldosterone-induced stiffening, was not differentially affected by aldosterone in MRSMKO and control mice. Same observations were made with collagen and elastin contents. These results suggest that the effect of aldosterone on fibronectin/collagen/elastin content described in other experimental models could be the result of MR activity in other cell types, such as macrophages for instance. In the present study, the increase in α5-integrin expression, in control mice, in response to aldosterone is blunted in NAS-treated MRSMKO mice. Integrins are implicated in the attachment between vascular smooth muscle cells and extracellular matrix. Alteration of the relation between vascular smooth muscle cells and the extracellular matrix is more likely to increase arterial stiffness than fibronectin/elastin/collagen content does in this model. As stated by the authors, the ratio fibronectin/α5 is crucial for arterial stiffness increase in response to aldosterone and could be a new pharmacological target for destiffening drugs.

The hypertrophic response of carotid artery is maintained in response to aldosterone, despite lacking MR in vascular smooth muscle cells. Two hypotheses could be proposed from this observation: (1) non-MR receptors are involved in the hypertrophic response to aldosterone and (2) pressure stimulus is sufficient per se to induce large vessel hypertension. This result is in line with previous studies of Coffman’s group showing that, in mice with selective deletion of type 1 angiotensin II receptor in vascular smooth muscle cells, the blood pressure increase in response to angiotensin II was maintained as well as the hypertrophic remodeling of the aorta. Elevated blood pressure is the major mechanism driving medial expansion in large vessels.

In conclusion, MR is the main player in aldosterone-induced large artery stiffness through its action on integrin α5, in mice. MR-specific response to aldosterone is limited to arterial stiffness because the hypertrophic response in response to blood pressure increase is maintained. Further characterization of small artery remodeling and reactivity, inflammation, and oxidative stress in this elegant model would improve our comprehension of the MR-dependent effects of aldosterone on vascular system.

Disclosures

None.

References

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Hypertension. 2014;63:442-443; originally published online December 2, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.02581

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