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

Marie Briet

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.5 It has also been suggested that the epithelial receptor GPR30 was involved in the rapid action of aldosterone.5 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.6 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.7 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.8 Specific deletion of MR in cardiomyocytes improved infarct healing and adverse remodeling after myocardial infarction.9

In the present issue of Hypertension, Galmiche et al10 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

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Pharmacology, INSERM U1083, CNRS UMR 6214, Centre Hospitalier et Universitaire d’Angers, Angers, France.

Correspondence to Marie Briet, Department of Pharmacology, Centre Hospitalier et Universitaire d’Angers, 4 Rue Larrey, 49100 Angers, France. E-mail marie.briet@chu-angers.fr

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.113.02581

DOI: 10.1161/HYPERTENSIONAHA.113.02581
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 (MR\textsuperscript{SMKO}). Renal adaptation to sodium handling and restriction was not affected in MR\textsuperscript{SMKO} mice. Despite lower baseline systolic blood pressure in MR\textsuperscript{SMKO} mice compared with control, NAS treatment was associated with a similar increase in systolic blood pressure in MR\textsuperscript{SMKO} and control mice. NAS treatment induced a similar increase in media cross-sectional area of large vessels in MR\textsuperscript{SMKO} and control mice. Conversely, the increased arterial stiffness in response to NAS treatment was blunted completely in MR\textsuperscript{SMKO} 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 MR\textsuperscript{SMKO} mice is impressive because blood pressure response to NAS was maintained. Blood pressure response to NAS, in MR\textsuperscript{SMKO} 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\textsuperscript{SMKO} mice. Further characterization of resistant artery reactivity and remodeling in response to aldosterone in this model could help to complete the description.

Galmiche 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 MR\textsuperscript{SMKO} 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.\textsuperscript{9} In the present study, the increase in α5-integrin expression, in control mice, in response to aldosterone is blunted in NAS-treated MR\textsuperscript{SMKO} 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 hypertrophy. This result is in line with previous studies of Coffman’s group showing that, in mice with selective deletion of type I 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.\textsuperscript{11} 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

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

Hypertension. published online December 2, 2013;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2013/12/02/HYPERTENSIONAHA.113.02581.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/