Networking Between Systemic Angiotensin II and Cardiac Mineralocorticoid Receptors

Augusto C. Montezano, Rhian M. Touyz

The traditional view of the renin-angiotensin-aldosterone system as a circulating system with a linear organization, where angiotensin (Ang) II, the final effector peptide of the renin angiotensin system, mediates effects through Ang II type 1 receptor (AT1R) to induce aldosterone production (renin→angiotensinogen→Ang I→Ang II→aldosterone), has been challenged recently. It is becoming increasingly evident that, in addition to circulating Ang II, there is a rich and dynamic local (tissue) renin-angiotensin-aldosterone system, that the system is circuitous in that Ang II and its peptide derivatives feed back to influence upstream and downstream components of the renin-angiotensin-aldosterone system, that Ang II signals through multiple receptor subtypes, and that an intracellular (intracrine) renin-angiotensin-aldosterone system may contribute to extracrine Ang II actions.1 The paradigm appears to be even more complex with the recent observations that not only does Ang II/AT1R mediate effects in part through transactivation of receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR) in a cell-specific manner, but that Ang II may induce some of its actions through aldosterone and its mineralocorticoid receptor (MR).2

This interaction was first identified in the 1980s, where it was shown that, in rats, aldosterone administration increases expression of vascular Ang II receptors3 and, more recently, that aldosterone upregulates angiotensin I–converting enzyme (ACE), resulting in increased generation of Ang II.4 Moreover, there is intracellular networking between aldosterone and Ang II, resulting in modulation of mitogen-activated protein kinase activity, c-Src phosphorylation, NADPH oxidase–driven generation of reactive oxygen species, Rho kinase activation, EGFR transactivation, cytokine production, and matrix metalloproteinase (MMP) activation.2,5

Exact mechanisms whereby Ang II, a peptide hormone signaling through membrane-associated G protein–coupled receptors, mediates cellular effects via aldosterone, a mineralocorticoid hormone that signals through an intracellular steroid receptor, remain elusive. Additionally, the functional significance of tissue specificity and implications of interactions between the systemic and local renin-angiotensin-aldosterone system are unclear. Recent data from molecular studies, transgenic mice, and clinical observations have shed some light on these issues, and it is now apparent that there is important cross-talk between Ang II/AT1R and aldosterone/MR resulting in activation of signaling pathways involved in cell growth, contraction, inflammation, collagen deposition, and migration.4–6 These processes may be particularly important in the heart, where aldosterone and Ang II may induce clinically significant cardiac fibrosis and remodeling, important in cardiac disease.7 Although there is evidence that aldosterone could have a direct effect on the heart independent of hemodynamic changes, it is still unknown whether this process involves Ang II through AT1R/MR cross-talk, whether the effect is cardiac cell specific, and whether aldosterone-sensitive cardiac remodeling involves oxidative/inflammatory responses.

In the present issue of Hypertension, using an elegant transgenic mouse model with conditional and cardiomyocyte-restricted overexpression of the human MR, Zhang et al7 show that Ang II infusion promotes left ventricular hypertrophy (LVH) and diastolic, but not systolic, dysfunction through redox-dependent, blood pressure–independent effects. These events are mediated, at least in part, through MR, because pharmacological MR antagonism with canrenoate inhibited molecular, structural, and functional cardiac actions of Ang II.

Although previous investigations demonstrated an interdependency between Ang II/AT1R and aldosterone/MR in the cardiovascular system, this study provides novel insights on the interactions between systemic Ang II and local cardiac increase in MR activation and highlights the critical role of cardiomyocyte-specific MR in Ang II–induced cardiac hypertrophy and diastolic dysfunction, a process that involves activation of gp91phox-containing NADPH oxidase, generation of reactive oxygen species, activation of MMPs (MMP2 and MMP9), and increased collagen deposition, without overt inflammation. Interest these phenomena may not depend on increased cardiac aldosterone production, because transgenic mice that overexpress the terminal enzyme of aldosterone biosynthesis, aldosterone synthase, have demonstrated endothelium-independent dysfunction with no detectable alterations in cardiac structure and function.8

There are, however, some limitations relating to the study of Zhang et al7 that warrant further consideration. First, the MR antagonist used was canrenoate, which is a nonspecific MR antagonist. As such, not only are actions of aldosterone inhibited, but also those of androgens and glucocorticoids. This is of interest because cortisol, through cardiac MR, can induce cardiac hypertrophy, possibly through redox changes.9 Second, not all studies have documented redox-sensitive mitogenic actions of aldosterone/MR. Hayashi et al10 dem-
onstrated that, in cultured neonatal cardiomyocytes, aldosterone nongenomically induces NADPH oxidase–dependent reactive oxygen species generation, activation of apoptosis signal-regulating kinase 1, and cardiomyocyte apoptosis, which could contribute to progression of heart failure. Reasons for the conflicting data may relate to the fact that the study of Zhang et al7 was performed in whole animals and not in cultured cells; that MR-mediated, redox-sensitive cardiac hypertrophy and diastolic dysfunction were dependent on systemic Ang II, which was absent in isolated cells; and that studies were performed in adult mice and not in neonatal models. Third, the study does not provide any information on whether cardiac Ang II receptors are upregulated or downregulated in the presence of cardiomyocyte MR overexpression. Considering that aldosterone influences components of the renin-angiotensin system and AT1R and Ang II type 2 receptor expression/activity and that Ang II modulates MR status, it is possible that cardiac Ang II receptor expression may be altered by MR overexpression and increased aldosterone signaling.10 In fact, recent data indicate that aldosterone, but not Ang II, reduced ACE2 mRNA levels and increased ACE mRNA levels in rat cardiomyocytes via MR, suggesting that aldosterone might play an important role in cardiac remodeling by upregulating ACE and downregulating ACE2 levels.4

Because canrenoate prevented Ang II–induced LVH, cardiac fibrosis, and oxidative stress in transgenic mice overexpressing cardiomyocyte MR, it is concluded that cardiac remodeling involves cross-talk between mineralocorticoid and Ang II signaling. However, Zhang et al7 shed little light on the molecular mechanisms of cross-talk, although this probably involves interactions at the level of AT1R and MRs.2 Such processes may necessitate physical associations, possibly in cholesterol-rich domains (caveolae/lipid rafts); transactivation through common receptor tyrosine kinases, such as EGFR; subcellular redistribution and shuffling between compartments; and MR posttranslational modification by phosphorylation, sumoylation, and ubiquitylation2,6 (Figure). Molecular cross-talk may also occur at the postreceptor level through converging signaling pathways. Signaling molecules implicated in such interactions include extracellular signal–regulated kinase 1/2, RhoA/Rho kinase, Ki-ras2A, and NADPH oxidase, among others.2,4,6

Despite the shortcomings of the study, Zhang et al7 present important data highlighting the role of an integrated system involving systemic Ang II and local cardiac MR/aldosterone through reactive oxygen species in the regulation of cardiac function and structure. Although there is still much to be learned regarding the molecular processes and networks linking Ang II and mineralocorticoid signaling, this study provides further evidence for potential therapeutic clinical benefits of combination MR blockers and renin-angiotensin system inhibitors, particularly in the context of LVH and diastolic dysfunction.

**Sources of Funding**

Studies from the authors’ laboratory were supported by grants 57786 and 44018 from the Canadian Institutes of Health Research and from the Heart and Stroke Foundation of Canada. R.M.T. is supported through a Canada Research Chair/Canadian Foundation for Innovation award.

**Disclosures**

None.

**References**


---

**Figure.** Scheme demonstrating putative mechanisms whereby systemic Ang II interacts with cardiomyocyte MR to induce cardiac fibrosis, LVH, and diastolic dysfunction. Molecular mechanisms linking AT1R and MR are unclear as indicated by the question mark (?) but may occur at the level of cholesterol-rich domains (caveolae/lipid rafts). It is also possible that AT1R/MR interactions involve transactivation of EGFR as indicated by the dashed line. Cross-talk between Ang II and cardiomyocyte MR induces activation of gp91phox-containing NADPH oxidase and generation of reactive oxygen species, as well as activation of MMP2, MMP9, and increased collagen deposition. These processes may contribute to cardiac remodeling.


Networking Between Systemic Angiotensin II and Cardiac Mineralocorticoid Receptors
Augusto C. Montezano and Rhian M. Touyz

Hypertension. 2008;52:1016-1018; originally published online November 3, 2008;
doi: 10.1161/HYPERTENSIONAHA.108.121269
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/52/6/1016

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/