Angiotensin II: A Devious Activator of Mineralocorticoid Receptor-Dependent Gene Expression

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In this issue of Circulation Research Jaffe and Mendelsohn1 show that angiotensin II (Ang II) directly activates the mineralocorticoid receptor (MR). Using cultured human coronary and aortic vascular smooth muscle cells (VSMC) they show strong evidence for expression of both the MR and the cortisol inactivating enzyme 11-β-hydroxysteroid-dehydrogenase-2 necessary for mineralocorticoid action. Importantly they show that Ang II activation of MR is independent of aldosterone generation by VSMC, suggesting a direct effect. Finally they used microarray analysis to define genes induced by aldosterone-dependent MR transcription. The microarray results yielded an “All Star” parade of candidates for vascular aging as they included genes involved in vascular fibrosis, inflammation and calcification. These data provide further support for the evolving role of the MR as a signal effector for Ang II and provide a new MR-dependent mechanism by which Ang II promotes cardiovascular disease.

The links between Ang II and aldosterone have become increasingly numerous over the past 10 years. Because Ang II stimulates the synthesis and release of aldosterone, it has been suggested that vascular effects of Ang II are mediated in part by aldosterone. Support for this concept includes findings that Ang II receptors are up-regulated by aldosterone,2 data that spironolactone decreased cardiac hypertrophy, inflammation and fibrosis induced by Ang II,3 and evidence that Ang II-mediated oxidative stress, endothelial dysfunction, and resistance artery structural remodeling were blocked by spironolactone.4 However, it was believed that these effects were mediated by MR activation via either aldosterone produced in the adrenal cortex or locally in endothelial cells and VSMC.5 The novel contribution of Jaffe and Mendelsohn is to show that there is a direct effect of Ang II via Ang II type 1 receptor (AT1R) signaling to activate the MR independent of VSMC production of aldosterone.

The ability of Ang II to activate the MR also represents a new example of receptor transactivation by the AT1R. Our group6,7 and others8 have shown that transactivation of epidermal growth factor and platelet-derived growth factor receptors is a critical aspect of Ang II-mediated vascular signaling. Ang II-mediated transactivation requires generation of reactive oxygen species, which fits perfectly with the current article that demonstrates MR-dependent gene expression because the MR has been shown to stimulate NAD(P)H oxidases in response to aldosterone.9 Previously, it has been shown that nuclear hormone receptors can modulate Ang II signaling. For example, in rats infused with Ang II, thiazolidinedione peroxisome proliferator-activated receptor (PPAR)-γ activators limited hypertension and vascular remodeling, improved endothelial dysfunction and prevented increases in AT1R and proinflammatory mediators.10

Nuclear receptors like PPAR-γ have been the subject of intense investigation in vascular biology because many have been linked to inhibition of vascular disease processes.11 The retinoid receptors and their ligands (eg, retinoic acids) have been linked to the promotion of VSMC differentiation and inhibition of vascular narrowing related to atherosclerosis and injury-induced neointimal formation.12 Retinoic acid receptor-related orphan receptor-α appears to impede atherosclerosis susceptibility by activating apolipoprotein-AI transcription.13 Moreover, ligands to the estrogen receptors,14 liver X receptors,15 and farnesoid X receptors16 all have yielded promising results with respect to vascular pathology. A common theme among these nuclear receptors is their antagonism of processes (most notably inflammation) associated with vascular disease. In sharp contrast to the above nuclear receptors, the present study demonstrates a pathologic role for the MR.

The genes regulated by Ang II via MR suggest an important role for this signaling pathway in vascular aging. To determine alterations in VSMC gene expression resulting from aldosterone treatment, the authors utilized a microarray and quantitative RT-PCR validation approach. Aldosterone synthase was undetected in VSMC, bolstering evidence for Ang II transactivation of MR in VSMC lacking autocrine aldosterone production. Increased expression of genes involved in fibrosis, calcification and inflammation were found following 1 or 24 hours of aldosterone treatment. Chronic Ang II exposure is known to cause vascular and cardiac pathology, however it has also previously been shown to induce the expression of genes involved in proliferation, growth, hypertrophy and contractility. While the gene expression data in the current manuscript were obtained following aldosterone treatment, the general findings of the manuscript raise the possibility of a novel subset of genes induced by Ang II via MR transactivation (in the absence of local aldosterone production) that mediate the pathophysiological vascular consequences of aging.

The sample size and data analysis of the microarray experiments were substantially underpowered, leading the authors to report only fold change from a minimum of 2...
“quality replicates per time point” and statistical validity only on the quantitative RT-PCR data. As a result, the expression of a very limited number of genes were found to be altered, particularly considering the ability of the arrays utilized to detect over 30,000 gene products. Subsequent experiments with a larger sample size and robust statistical methods should provide substantial insight into MR-mediated gene expression in VSMC. Furthermore, robust investigation of gene expression alterations following MR activation either directly (aldosterone) or indirectly (Ang II) may elucidate important similarities and differences in these signaling pathways and their pathophysiological consequences in VSMC. To highlight the differences in the acute MR and Ang II signaling pathways, Campos et al recently reported changes in gene expression in rat VSMC following 6 hours of Ang II treatment. While their study was also somewhat limited in sample size, there was little overlap in gene expression alterations between Ang II treatment in rat VSMC and aldosterone treatment in human VSMC.

Finally, it should be noted that the present study suggests additional roles for a local renin-angiotensin aldosterone system in the vasculature. There has been evolving evidence for pathologic roles for Ang II in both endothelial cells and macrophages in the pathogenesis of atherosclerosis. All components of the system are present locally, since endothelial cells have been shown to produce aldosterone and macrophages to produce Ang II. Several studies also show important roles for MR in endothelium including generation of ROS, and production of endothelin-1. Furthermore, aldosterone administration to apolipoprotein E-/- mice increased macrophage oxidative stress and atherosclerosis, while MR blockade or an AT1R blocker reduced the proatherogenic effects of aldosterone. In summary, the study by Jaffe and Mendelsohn highlights the importance of defining the specific roles of the MR independent from aldosterone, as we evaluate the clinical trials of drugs that inhibit the MR or the synthesis of aldosterone.

References

Key Words: angiotensin II ▪ mineralocorticoid receptor ▪ aldosterone ▪ spironolactone
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Circ Res. 2005;96:610-611
doi: 10.1161/01.RES.0000162163.75564.8b

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