Growth Factor Receptor Transactivation in Mediating End Organ Damage by Angiotensin II

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Angiotensin II (Ang II) and its major heterotrimeric G protein-coupled receptor (GPCR) AT₁, have long been believed to mediate end organ damage associated with cardiovascular and metabolic diseases. In the past decade, efforts have been made to dissect intracellular signal transduction mechanisms by which Ang II exerts its pathophysiological effects on target cells and tissues. Recent accumulating evidence suggests the critical role of the “transactivation” of the growth factor receptors with intrinsic tyrosine kinase activity in this context. Transactivation of the platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR) could be mediated by numbers of GPCRs, including the AT₁ receptor that appears to activate important downstream signal transductions and functions such as extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (ERK/MAPK), cell growth, and migration.¹ However, there is still a void in our knowledge regarding the relative contribution of PDGFR and EGFR in end organ damage together with cardiovascular remodeling induced by Ang II as well as detailed molecular mechanisms by which AT₁ mediates the growth factor receptor transactivation.

The article by Schellings et al in this issue of Hypertension² provides significant insights into the pathophysiological roles of the growth factor receptor transactivation in hypertensive end organ damage induced by Ang II. The study demonstrates that despite continuous hypertension and left ventricular hypertrophy, the cardiac dysfunction induced in the transgenic Ren2 rat (a model of Ang II–driven hypertension and end organ damage) was attenuated by a tyrosine kinase inhibitor, imatinib mesylate, which preferentially blocks the PDGFR. The tissue protective effects were associated with decreased transactivation of PDGFR-β, activation of ERK, cardiac fibrosis, renal microvascular hypertrophy, and perivascular fibrosis. Imatinib also attenuated collagen and DNA synthesis in cultured cardiac fibroblasts. Imatinib, which also blocks tyrosine kinase activity of the Bcr/Abl and c-KIT, has been used as an anti-cancer agent and proven to be well tolerated. Imatinib targets ATP binding sites of tyrosine kinases and effectively inhibits activation of both isoforms of PDGFRs, PDGFRα and PDGFRβ.

Overactivation of the PDGF/PDGFR system has long been implicated in atherosclerosis as well as restenosis after vascular injury. PDGF is one of the strongest agonists to stimulate proliferation and migration of vascular smooth muscle cells (VSMCs). The enhancement of PDGFR activation in cardiovascular disease may not be solely due to enhanced PDGF induction but likely involves its transactivation by a number of risk factors including Ang II. Although PDGFR transactivation has been demonstrated in several Ang II–target cells such as in VSMCs,³ little is known regarding the mechanism of the transactivation. Ang II–induced PDGFR transactivation in VSMCs is ligand-independent but requires a reactive oxygen species (ROS)-sensitive tyrosine kinase distinct from Src or JAK2.³ However, H₂O₂–induced PDGFR transactivation appears to require PYK2, Src, as well as protein kinase C-δ.⁴

In the study by Schellings et al, imatinib attenuated glomerular expansion and interstitial lesions of the kidney.² PDGFR transactivation has been reported to mediate an Ang II–induced mitogenic signal, ERK, in mesangial cells.⁵ Therefore, in addition to its effect on fibrosis, imatinib may reduce glomerular lesions by inhibiting mesangial proliferation. In this regard, decreased collagen deposition and proliferation by imatinib was demonstrated in an experimental model of diabetic nephropathy.⁶ Acute Ang II infusion also leads to activation of the PDGFR as well as EGFR in the vasculature.⁷ Kelly et al recently found that imatinib treatment inhibits Ang II–induced PDGFR transactivation as well as mesenteric arterial hypertrophy and matrix expansion in rats regardless of sustained hypertension,⁸ suggesting its role in mediating vascular remodeling. The mechanism and contribution of PDGFR transactivation by Ang II in mediating cardiovascular end organ damage are illustrated in the Figure.

Ang II also transactivates EGFR in many target cells, including VSMCs and cardiac myocytes.¹ In contrast to PDGFR transactivation, EGFR transactivation by Ang II via the AT₁ receptor appears to be ligand-dependent, requiring production of EGFR ligand such as heparin-binding EGF-like growth factor (HB-EGF) from its precursor (ectodomain shedding) mediated by the ADAM (A Disintegrin And Metalloprotease) family metalloproteases⁹ (Figure). The upstream mechanism of transactivation further involves ROS, Gq, caveolin/lipid raft, and/or AT₁ Tyr319 phosphorylation. In turn, EGFR mediates Ang II–induced ERK activation, hypertrophy, and migration.¹

Evidence also suggests the critical involvement of EGFR transactivation in the cardiovascular pathophysiology of Ang II. EGFR transactivation appears to mediate cardiac hypertrophy in response to Ang II infusion. It may partially mediate the hypertension as well.¹⁰ Asakura et al further provided evidence for a functional role of EGFR transactivation in mediating cardiac hypertrophy. ADAM12 likely mediates growth HB-EGF shedding and subsequent EGFR transactivation in the heart.

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

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Hypertension is available at http://www.hypertensionaha.org
DOI: 10.1161/01.HYP.0000202497.83294.50

following AT1 and other GPCR stimulation. Lautrette et al recently reported that transgenic mice overexpressing a dominant negative form of the EGFR were protected from renal lesions induced by Ang II infusion. Moreover, a pharmacological inhibitor of ADAM17 known also as tumor necrosis factor-α-converting enzyme (TACE) prevented EGFR transactivation as well as renal lesions induced by Ang II. Therefore, it is likely that end organ damage induced by enhanced Ang II systems is mediated through collaboration between EGFR and PDGFR, and each contribution may be tissue/lesion and disease specific.

Inhibition of enhanced Ang II action has been recognized as one of the major treatment strategies against the progression of cardiovascular diseases. As it becomes clearer by this article in the current issue of Hypertension, Ang II–induced growth factor receptor transactivation seems to be a key player in driving multiple dysfunctions associated with end organ damage in cardiovascular diseases. However, the detailed contributions of PDGFR and EGFR in Ang II–dependent tissue dysfunction such as in atherosclerosis, diabetes/metabolic syndrome, or endothelial dysfunction remain unclear. The precise molecular mechanisms of each receptor transactivation by Ang II also remain to be characterized. Further studies on the growth factor receptor transactivation by Ang II should help us to understand molecular mechanisms of these diseases and to provide additional opportunities to develop unique strategies against cardiovascular diseases.

Acknowledgments
We thank Kunie Eguchi for her assistance and Dr Gerald D. Frank for his critical reading of this comment. This article was supported by the National Institutes of Health Grant HL076770 (S.E.) and funds from Tonohata Co. LTD (S.E.), and Kisyu Hosokawa Co. LTD (S.E.).

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Hypertension. 2006;47:339-340; originally published online January 23, 2006;
doi: 10.1161/01.HYP.0000202497.83294.50
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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