Cross-Talk Between Angiotensin II Receptor Types 1 and 2
Potential Role in Vascular Remodeling in Humans

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Angiotensin (Ang) II exerts its important physiological functions through 2 distinct receptor subtypes, the type 1 (AT1) and type 2 (AT2) receptors. The AT1 receptor is expressed in diverse adult tissues, and its distribution is indicative of the fundamental role of Ang II on the regulation of cardiovascular and renal homeostasis. The predominant actions of Ang II, such as vasoconstriction, cellular proliferation and growth, renal sodium retention, and release of aldosterone, are linked to the activation of various signal-transduction pathways modulated by the AT1 receptor. Although the AT2 receptor is highly expressed in the fetus, its expression in adult tissues is low but increases in response to injury.  

It has been demonstrated that AT1 and AT2 receptors have counterregulatory interactions in the cardiovascular system. The AT2 receptor has been shown to exert an inhibitory effect on the growth-promoting action of the AT1 receptor. The cross-talk between AT1 and AT2 receptors has also been suggested to participate in the regulation of blood pressure. Ang II binding to the AT1 receptor activates G protein–coupled phospholipase C and inositol-1,4,5-triphosphate, which increases intracellular Ca2+ levels resulting in vasoconstriction. On the other hand, Ang II binding to the AT2 receptor activates a counter-regulatory pathway to induce vasorelaxation via activation of the kinin/NO/cGMP system. Indeed, it has been demonstrated that stimulation of the AT2 receptor induces vasorelaxation in mesenteric, uterine, renal, coronary, and cerebral resistance vessels, as well as in large conduit vessels. AT2 receptor null mice manifest slightly higher blood pressures at baseline than wild-type mice and enhanced acute blood pressure responses to low-dose Ang II infusion. In mice overexpressing AT2 receptors, the pressor response to Ang II infusion is significantly attenuated but is restored after blockade of AT2 receptors and/or blockade of NO synthase. Based on these studies, it has been proposed that AT2 receptor–mediated vasorelaxation may partly counteract AT1 receptor–mediated vasoconstriction and thereby contribute to the antihypertensive and/or vasoprotective effects of AT1 receptor blockers.

Recent studies suggest that the upregulation of AT2 receptor expression and associated vasorelaxation may play an important role in vascular remodeling. Consistent with this notion, the study by Savoia et al in this issue of Hypertension provides exciting data demonstrating that small peripheral resistance arteries from hypertensive diabetic patients receiving long-term treatment with the AT1 receptor blocker valsartan exhibited enhanced AT2 receptor expression. This effect may be independent of blood pressure reduction, because AT2 receptor expression was not changed in the atenolol-treated patients with similar blood pressure control.

Savoia et al demonstrated that, in human resistance vessels, AT2 receptors are not only present but functional. Indeed, AT2 receptor activation was unmasked in resistance vessels of valsartan-treated patients in which, when AT1 receptors were blocked, exogenous Ang II–induced vasorelaxation was blunted by the AT2 receptor blocker PD123319. However, in the resistance vessels from these AT1 receptor blocker–treated patients, the Ang II–mediated vasorelaxation was only 7.5%. This modest vasodilatory effect suggests that the role of the AT2 receptor in reducing blood pressure may be minimal, if at all. In the patients studied by Savoia et al, upregulation of AT2 receptors in the setting of AT1 receptor blockade was associated with an improvement in resistance artery remodeling that was independent of blood pressure effects. Thus, these results suggest that the AT2 receptor may play a significant role in vascular remodeling.

AT2 receptors have been shown to be upregulated under conditions associated with cardiovascular tissue injury, such as common carotid balloon injury, myocardial infarction, heart failure, and hypertension. In the model of carotid balloon injury, treatment with valsartan significantly reduced intimal hyperplasia and concomitantly increased intimal, and to a lesser extent medial, AT2 receptor expression in the injured vessel but not in the contralateral normal vessel. These studies suggest that injury, as well as increased levels of Ang II associated with AT1 receptor blockade, is required for the upregulation of AT2 receptors in adult animals (Figure). Despite normalization of blood pressure and reasonable, although not perfect, control of glycemia, the diabetic patients studied by Savoia et al exhibited upregulation of the AT2 receptor in resistance vessels after 1 year of treatment with valsartan. What could have been the ongoing injury maintaining increased AT2 receptor expression: genetic predisposition to vascular injury or phenotypic changes in the vasculature that occurred during the time that the patients were hypertensive and/or hyperglycemic and that could not be reversed by the antihypertensive therapy over a period of
Cross-talk between AT1 receptor (AT1R) and AT2 receptor (AT2R) in vascular remodeling and the role of vascular injury, Ang II, and AT1R blockers (ARBs).

a year? These are questions, among others, that need to be addressed by future research.

Ang II, via the AT1 receptor, has been demonstrated to increase reactive oxygen species production in the vessel wall through activation of reduced nicotinamide-adenine dinucleotide-reduced nicotinamide-adenine dinucleotide phosphate oxidase. AT1 receptor activation by Ang II stimulates inflammatory, fibrotic, and thrombotic processes, which contribute to Ang II–mediated inflammation and atherogenesis. Experimental and clinical studies using angiotensin-converting enzyme inhibitors and AT1 receptor blockers have provided indirect evidence supporting the role of oxidative stress in the pathogenesis of endothelial dysfunction and atherogenesis. These latter studies also suggested that the role of oxidative stress in hypertensive vascular injury is in addition to, but independent of, the hemodynamic stress of blood pressure.

The AT1 receptor–mediated increase in vascular reactive oxygen species production leads to a decrease in the bioavailability of NO. Stimulation of AT2 receptor increases NO production. An intriguing emerging notion is that the cross-talk between AT1 and AT2 receptors may play an important role in the maintenance of cardiovascular homeostasis in humans. The study by Savoia et al implies that further elucidation of the interactions between the AT1 and AT2 receptors may provide us with a better understanding of the global role of Ang II in cardiovascular diseases.

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References