Role of Angiotensin Type 2 Receptors in Vasodilation of Resistance and Capacitance Vessels

Robert M. Carey, Jennifer Park

Angiotensin II (Ang II), the major effector component of the renin–angiotensin system, has an important regulatory role in cardiovascular and renal function. Ang II exerts its actions by binding with equal affinity to angiotensin type 1 (AT$_1$) and type 2 (AT$_2$) receptors. The predominant receptor subtype found in the vasculature of adults is the AT$_1$ receptor. Ang II activation of AT$_1$ receptors induces vasoconstriction, cellular proliferation, tissue growth, renal sodium retention, sympathetic nervous system stimulation, and aldosterone secretion, the integrated response of which leads to increased blood pressure. The AT$_2$ receptor is expressed in large quantities in the fetus and decreases markedly after birth but is still present in low amounts in adult tissues. AT$_2$ receptors are upregulated under conditions associated with cardiovascular tissue damage, such as myocardial infarction, heart failure, and hypertension. The relatively low expression level of AT$_2$ receptors compared with that of AT$_1$ receptors is a major reason why the actions and cell signaling mechanisms of AT$_1$ receptors are well characterized compared with those of AT$_2$ receptors.

Ang II binding to AT$_2$ receptors activates a counterregulatory pathway whereby vasoconstriction mediated by AT$_1$ receptors is opposed by AT$_2$ receptor–induced vasodilation. AT$_2$ receptor–mediated vasodilation has now been demonstrated in a large variety of resistance vessels including the mesenteric, uterine, renal, coronary, and cerebral vascular beds. The integrated counterregulatory response to AT$_2$ receptor activation can be unmasked in normal and hypertensive animals in which, when AT$_1$ receptors are blocked, exogenous Ang II induces hypotension that is abolished by the specific AT$_2$ receptor antagonist PD-123319 (PD). Through a multitude of studies, it is now generally accepted that AT$_2$ receptor–mediated vasodilation is mediated by activation of a bradykinin B$_2$ receptor, NO, and cGMP cell signaling cascade.

During the past 3 years, evidence has accumulated that not only documents the vasodilatory role of AT$_2$ receptors in the microcirculation but also in large capacitance vessels. Yayama et al demonstrated in the thoracic aorta that AT$_2$ receptors are upregulated with overload hypertrophy in response to suprarenal abdominal aortic banding and that Ang II–induced aortic constrictor responses were abolished under these conditions but that these responses were restored with AT$_2$ receptor antagonist PD. The observed differences in Ang II responsiveness were abolished by denuding the endothelium, strongly suggesting that the increase in AT$_2$ receptor expression with aortic banding limits Ang II–induced aortic constriction. Of importance, Ang II activation of AT$_1$ receptors was required for the upregulation of AT$_2$ receptors in the pressure-overloaded aorta, suggesting the possibility of a counterregulatory positive feedback loop in which AT$_1$ receptor–mediated vasoconstriction is opposed by AT$_2$ receptor–induced AT$_2$ receptor upregulation, engendering counterregulatory vasodilation. Interestingly, van Esch et al demonstrated recently that AT$_1A$ receptor activation is also required for AT$_2$ receptor-mediated vasodilation in the mouse coronary circulation.

The general mechanism of AT$_2$ receptor–mediated vasodilation in the pressure-overloaded aorta was identified by Hiyoshi et al as bradykinin/NO-dependent cGMP production, because aortic cGMP levels were markedly increased after aortic banding but were restored by either PD or bradykinin B$_2$ receptor antagonist icatibant. These findings may be applicable to the pathophysiology of renovascular hypertension, because aortic cGMP production was increased in 2-kidney, 1-clip Goldblatt hypertensive rats via activation of AT$_2$ receptors that stimulated endothelial NO synthase (eNOS) phosphorylation and NO production through a bradykinin B$_2$ receptor–dependent pathway.

In the vasculature, NO is produced by the enzyme eNOS, the activity of which is regulated by Ca$^{2+}$/calmodulin but recently a host of posttranscriptional and posttranslational modifications have been described. In particular, several posttranslational phosphorylation sites have been identified that activate eNOS, including Ser$^{1172}$ and Ser$^{633}$ (both human sequence). Phosphorylation at these sites increases the sensitivity of eNOS to Ca$^{2+}$/calmodulin and stimulates NO production.

The study of Yayama et al in this issue of Hypertension provides exciting information regarding the interplay of Ang II, AT$_2$ receptors, and eNOS phosphorylation in rat capacitance vessels. After suprarenal aortic banding, Ang II binding to upregulated AT$_2$ receptors stimulated eNOS phosphorylation at both Ser$^{453}$ and Ser$^{1177}$, and phosphorylation was abolished by either AT$_1$ receptor blockade with PD or B$_2$ receptor blockade with icatibant. The elevations in phosphorylated eNOS were also inhibited by protein kinase A inhibitors H89 and KT5720. These findings suggest that increased pressure in the thoracic aorta activates Ang II–AT$_2$ receptor binding, which stimulates eNOS phosphorylation via a bradykinin B$_2$ receptor and protein kinase A–dependent pathway.

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(Figure). Because AT₁ and AT₂ receptors generally oppose each other physiologically, this study would have been strengthened if vasodilator and cell signaling responses to the AT₁ receptor antagonist alone and combined with the AT₂ receptor antagonist had been provided. Nevertheless, this important study not only furnishes a cellular mechanism for AT₂ receptor-mediated vasodilation in the mouse heart but also may be applicable to cell signaling mechanisms of AT₂ receptors in other cardiovascular tissues, such as resistance microvessels and the renal proximal tubule. These questions should be addressed by future research.

**Disclosures**

None.

**References**


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