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

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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 (AT1) and type 2 (AT2) receptors. The predominant receptor subtype found in the vasculature of adults is the AT1 receptor. Ang II activation of AT1 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 AT2 receptor is expressed in large quantities in the fetus and decreases markedly after birth but is still present in low amounts in adult tissues. AT2 receptors are upregulated under conditions associated with cardiovascular tissue damage, such as myocardial infarction, heart failure, and hypertension. The relatively low expression level of AT2 receptors compared with that of AT1 receptors is a major reason why the actions and cell signaling mechanisms of AT1 receptors are well characterized compared with those of AT2 receptors.

Ang II binding to AT1 receptors activates a counterregulatory pathway whereby vasoconstriction mediated by AT1 receptors is opposed by AT2 receptor–induced vasodilation. AT2 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 AT2 receptor activation can be unmasked in normal and hypertensive animals in which, when AT1 receptors are blocked, exogenous Ang II induces hypotension that is abolished by specific AT2 receptor antagonists H89 and KT5720. These findings suggest that increased responsiveness were abolished by denuding the endothelium, strongly suggesting that the increase in AT2 receptor expression with aortic banding limits Ang II–induced aortic constriction. Of importance, Ang II activation of AT1 receptors was required for the upregulation of AT2 receptors in the pressure-overloaded aorta, suggesting the possibility of a counterregulatory positive feedback loop in which AT1 receptor–mediated vasoconstriction is opposed by AT1 receptor–induced AT2 receptor upregulation, engendering counterregulatory vasodilation. Interestingly, van Esch et al demonstrated recently that AT2 receptor activation is also required for AT2 receptor-mediated vasodilation in the mouse coronary circulation.

The general mechanism of AT2 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 B2 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 AT2 receptors that stimulated endothelial NO synthase (eNOS) phosphorylation and NO production through a bradykinin B2 receptor–dependent pathway.

In the vasculature, NO is produced by the enzyme eNOS, the activity of which is regulated by Ca2+/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 Ser417 and Ser633 (both human sequence). Phosphorylation at these sites increases the sensitivity of eNOS to Ca2+/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, AT2 receptors, and eNOS phosphorylation in rat capacitance vessels. After suprarenal aortic banding, Ang II binding to upregulated AT2 receptors stimulated eNOS phosphorylation at both Ser417 and Ser1177, and phosphorylation was abolished by either AT2 receptor blockade with PD or B2 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–AT2 receptor binding, which stimulates eNOS phosphorylation via a bradykinin B2 receptor and protein kinase A–dependent pathway.
Schematic diagram depicting the cell signaling process in the endothelium of the rat thoracic aorta whereby Ang II induces vasodilation. Ang II binds to AT1 receptors in the plasma membrane. AT1 activation stimulates the bradykinin (BK) B2 receptor (B2), which stimulates serine phosphorylation of eNOS at Ser1177 and Ser83 by a protein kinase A (PKA)-dependent pathway. Phosphorylation of eNOS increases NO production, activating soluble guanylyl cyclase (sGC), which converts GTP to cGMP. cGMP mediates vasodilation.

(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 AT1 receptor action in the thoracic aorta, 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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