The major biological actions of the renin–angiotensin system are mediated by angiotensin (Ang) II, which binds with equal affinity to Ang type 1 (AT1) and type 2 (AT2) receptors. The majority of Ang II actions, however, are mediated by the AT1 receptor, including vasoconstriction, cellular proliferation, tissue growth, direct renal tubular sodium reabsorption, sympathetic nervous stimulation, and aldosterone secretion, which, in aggregate, lead to a rise in blood pressure.1 Because the AT1 receptor is expressed ubiquitously in relatively high levels at renal and cardiovascular sites, an increase in blood pressure represents the net response to increased circulating Ang II.

By contrast, AT2 receptors carry a relatively low level of tissue expression in the adult compared with that of AT1 receptors.1 AT2 receptors are expressed in large quantities in fetal tissues, but their expression decreases in the neonatal period and reaches a comparatively low level in the adult animal. However, the capacity for AT2 receptor re-expression is retained in the adult, because upregulation is a common response to circumstances of cardiovascular tissue damage, such as myocardial infarction, heart failure, and hypertension.

Activation of AT2 receptors by the binding of Ang II stimulates a hormonal cascade consisting of bradykinin (BK), NO, and cGMP, leading to vasodilation that is counterregulatory to the vasoconstriction induced by Ang II via AT1 receptors.2 AT2 receptor–induced vasodilation has been unequivocally demonstrated in both resistance and capacitance vessels.3,4 In capacitance vessels, Ang II binding to the AT2 receptor activates the BK B2 receptor, stimulating the phosphorylation of endothelial NO synthase at its serine633 and serine1177 residues by a protein kinase A–dependent mechanism, inducing NO generation.4 In mesenteric, uterine, and coronary small resistance arteries, Ang II–induced vasodilation is mediated by the BK/NO/cGMP pathway and is not subject to desensitization, as is AT1 receptor–mediated vasoconstriction. In whole-animal studies, in the presence of AT1 receptor blockade, Ang II induces sustained vasodilation and hypotension that is abolished by AT1 receptor antagonist PD-123319 and is mediated by the BK/NO/cGMP pathway.5,6 Thus, it is now generally accepted that the AT2 receptor induces counterregulatory vasodilation that opposes AT1 receptor–mediated vasoconstriction.

Because AT2 receptor expression is developmentally regulated, and its activation has been described as inhibitory to flow–mediated dilation in hypertensive animals, Pinaud et al,7 in this issue, hypothesized that AT2 receptor function might behave differently in the resistance arteries of aged rats compared with nonaged control adult rats. As expected, their results show that resistance arteries from old rats had lower flow– and NO–mediated vasodilation and lower endothelial NO synthase expression than that of young control rats. However, a surprising finding was that, in old rats, AT2 receptor blockade improved flow–mediated dilation, suggesting an unusual vasoconstrictor action mediated by the AT2 receptor. Interestingly, the aging process was associated with increased AT2 receptor expression, mainly in vascular smooth muscle cells rather than endothelial cells. Activation of the receptor induced direct vasoconstriction that was independent of the presence of the endothelium accompanied by increased reactive oxygen species. Both the increase in reactive oxygen species and the vasoconstriction were reversed by the antioxidant Tempol. In old rats, treatment with the vasodilator hydralazine also reduced AT2 receptor induction of reactive oxygen species and direct vasoconstriction, enhancing flow–mediated vasodilation. This observation is consistent with earlier work showing that hydralazine is an antioxidant. Differences in AT2 receptor expression and function between young and aged rats, as demonstrated in this and other studies, are summarized in the Table.

The findings described in this article raise a number of important questions, the answers to which await future investigation. First, because this is the first description, is the vasoconstrictor action mediated by AT2 receptors in old rats a replicable finding? Second, because AT2 receptors clearly induce vasodilation in younger animals, what is the molecular switch that converts agonist activation of AT2 receptors from vasodilator to vasoconstrictor during the aging process? Is this related simply to changes in cellular expression (vascular smooth muscle versus endothelium)? In particular, as rats age, does the BK/NO/cGMP vasodilator cascade become less sensitive or responsive to AT2 receptor activation? Alternatively, is there a cell signaling switch that converts AT2 receptor inhibition of mitogen–activated protein kinase (extracellular signal–related kinase 1/2) phosphorylation into stimulation? Third, at what juncture in vascular maturation does the transformation of AT2 receptors from vasodilator to vasoconstrictor occur? Fourth, by what mechanism does hydralazine correct AT2 receptor–mediated vasoconstriction and accumulation of reactive oxygen species, restoring flow–mediated dilation? Is this simply related to hydralazine’s previously described direct antioxidant action? Fifth, are the results of this study in rats applicable to humans? A vanishingly small number of studies indeed are available on the expression and function of AT2 receptors in humans. The only

Editorial Commentary

Angiotensin Receptors and Aging

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

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available study on microvascular AT2 receptor expression and action in humans demonstrates that the receptor can be induced chronically in hypertensive diabetic subjects by AT1 receptor blockade and, under these circumstances, mediates vasodilation. AT1 receptor blockade increases vascular AT2 receptor expression and interrupts Ang II negative feedback on renin secretion stimulating the production of Ang II, which is available to act at unblocked AT2 receptors. If the upregulated AT2 receptors induce direct vasoconstriction in aging humans, as described for the rat in this article, AT1 receptor blockers would be potentially dangerous drugs in the elderly. However, AT1 receptor blockers in elderly humans are clearly efficacious in controlling blood pressure, preventing stroke, and reducing vascular elasticity. There is no suggestion of a vasoconstrictor action of AT1 receptor blockade in elderly hypertensive subjects, with large numbers of elderly patients included in the many clinical trials reported to date. Therefore, the findings reported in this article in the rat are not necessarily applicable to humans.

**Disclosures**

R.M.C. serves as a consultant and advisory board member for Novartis.

**References**
