Editorial

Influence of Changes of Blood Pressure on Vascular Angiotensin II Receptor Subtype Expression

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The evolving complexity associated with the renin-angiotensin cascade has been the focus of increasingly sophisticated pharmacological experimentation. The identification of at least 2 angiotensin II (Ang II) receptor subtypes led to functional subclassification of their activity. Activation of the type 1 (AT\(_1\)) receptor is associated with the vasoconstrictive and aldosterone-secreting effects of Ang II. Mice that lack the gene that encodes the AT\(_2\) receptor demonstrate normal development but an impaired drinking response to water deprivation and a reduction in spontaneous movements. Basal blood pressure is higher, and sensitivity to the pressor actions of exogenously delivered Ang II is increased. Differences in diastolic blood pressure persist even when AT\(_1\) receptors are blocked by losartan, indicating that this effect is independent of AT\(_1\). The greater pressor response to Ang II requires AT\(_2\) receptor activation and therefore, normally, AT\(_2\) receptors may serve to limit this. As a consequence, the concept of a vasodilator role for this receptor was introduced.

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Subsequently, a variety of reports have emerged linking the stimulation of AT\(_2\) with vasodilation in small resistance arteries in normotensive rats. The mechanism invoked usually is associated with nitric oxide (NO) production by endothelial cells and cGMP production by vascular smooth muscle cells. In addition, some studies have demonstrated bradykinin B\(_2\) receptor activation may be involved. What is not in question is the ubiquity of the AT\(_2\) receptor in vascular tissues, with studies localizing them to the endothelium, smooth muscle, and adventitia. A dilator function in circulatory homeostasis seems intriguing, given that the primary role ascribed to Ang II is one of vasoconstriction, particularly in times of volume depletion. Nevertheless, there is the enduring concept of a delicate balance between overstimulation of AT\(_1\) receptors’ doing harm and activating AT\(_2\) receptors to restore a beneficial equilibrium.

Beyond the circulatory effects of Ang II, a further concept has emerged—that of the association between stimulating the AT\(_1\) receptor and the generation of reactive oxygen species, with resulting endothelial function and atherosclerosis. An interaction with AT\(_2\) receptors in modulating this phenomenon also has been postulated.

Therefore, the elegant study reported by You et al in this issue of Circulation is of particular interest. The authors have used in vitro pressure myography to examine the functional characteristics of resistance-sized mesenteric arteries from normotensive Wistar Kyoto (WKY) rats and their spontaneously hypertensive (SHR) counterparts. By the time the rats reached 12 weeks of age, a difference in mean arterial blood pressure had been established. Preconstricted arterial segments from WKY rats incubated with the AT\(_1\) antagonist candesartan dilated when exposed to Ang II in a dose-dependent manner. Conversely, vessels from SHR rats demonstrated a possible small vasoconstriction, with Western blot analyses showing a significant reduction in AT\(_2\) receptors and an absence of them in the endothelium.

How a vasoconstrictor response is brought about against a background of reduced dilating AT\(_2\) receptors is difficult to understand. If it is genuine, then it is possible that issues of methodology may contribute. The in vitro rate of perfusion through the vessels is somewhat high. Alternatively, the pressure under which the arterial segments have been studied is similar for both strains, but it might be regarded as low for SHR and might alter sensitivity to Ang II, or less tenacious binding of candesartan to AT\(_1\) receptors might permit Ang II to effect contraction. You et al suggest that the AT\(_2\) receptor changes function, inevitably implying the switching of its intracellular signaling cascade, which seems unlikely. It should be noted that the change in lumen diameter is \(\approx4\%\), which must be regarded as the limit of detection.

What is not in dispute is that the accepted Ang II–induced vasodilation observed at normal pressures disappears when hypertension supervenes. Removal of the endothelium in vessels from WKY rats abolishes this response, but in the SHR rats, the lack of dilation remains. The impression is that the level of blood pressure genomically influences AT\(_2\) receptor distribution throughout the vascular wall.

In addition, You et al proceeded to treat animals with a variety of drugs to ameliorate the hypertension. Irrespective of whether agents specifically targeting the renin-angiotensin system were used, partial lowering of blood pressure caused less vasoconstriction when Ang II was applied, and normalizing it was associated with a restoration of the AT\(_2\) receptor population in both the endothelium and media and with vasodilation.

These responses have been elicited in vitro and revealed only when the predominantly AT\(_1\)-induced response is blocked. Whether they are associated with hemodynamically important consequences in vivo has not been established;
however, these studies suggest that hypertension causes a downregulation of AT\textsubscript{2} receptor activity, which may result in reduced NO bioavailability. Whether or not this is responsible, recent evidence suggests that AT\textsubscript{2} receptor activation is associated with compensatory structural changes in the circulation. The AT\textsubscript{2} receptor–knockout mouse does not develop left ventricular hypertrophy or cardiac fibrosis when exposed to Ang II by infusion.\textsuperscript{6} The developing wealth of evidence linking AT\textsubscript{1} receptor activation to increased vascular oxidative stress endothelial dysfunction and atherosclerotic lesion formation means that loss of AT\textsubscript{2} receptor activity induced by a rise in blood pressure could increase the risk of target-organ damage by diminishing any protective effects operating in the endothelium. Most recently it has been shown that disrupting the AT\textsubscript{1} receptor in the apolipoprotein E–deficient mouse leads to reduced atherosclerosis.\textsuperscript{3} The presence of hypertension exacerbates atheroma formation, and it is tempting to implicate the endothelial loss of AT\textsubscript{2} receptor–mediated activation of protective mechanisms as being responsible.

Also encouraging is the restoration of endothelial AT\textsubscript{2} receptors by good blood pressure control, irrespective of the class of drug used. Restoration was accompanied by a functional improvement in dilation, which reinforces the clinical need to lower blood pressure as much as possible to protect the circulation from the effects of hypertension-associated target-organ damage. Suddenly, the AT\textsubscript{2} receptor has moved to center stage in providing one mechanism by which this protection occurs.

References

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Circulation. 2005;111:956-957
doi: 10.1161/01.CIR.0000157898.06133.5B
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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