The Role of the AT₂ Receptor in Hypertension
Helmy M. Siragy

The renin-angiotensin system (RAS) is integrally involved in maintaining the healthy body’s hemodynamic status. It is also involved in many pathogenic situations. Angiotensin II (Ang II) is the major effector hormone of this system. Ang II subtype 1 receptor blockers (ARB), like angiotensin-converting enzyme (ACE) inhibitors, modulate the potent vasoconstricting and growth-promoting effects of Ang II. Thus, it is reasonable to assume that ACE inhibitors and ARB provide similar benefits in patients with hypertension and other diseases. There are salient differences, however, in that ARB antagonize Ang II at its AT₁ receptor subtype but spare its AT₂ receptor subtype, which has unique—and largely oppositional—effects on the blood vessels, kidneys, and adrenals. ACE inhibitors decrease the amount of Ang II available to its AT₁ and AT₂ receptors alike without totally suppressing its formation. This article reviews recent findings about the role of the AT₂ receptor in both health and disease and the actions of ARB mediated by this receptor. Am J Hypertens 2000;13:62S–67S © 2000 American Journal of Hypertension, Ltd.

KEY WORDS: Angiotensin II, angiotensin II subtype 1 receptor blockers, angiotensin-converting enzyme inhibitor, bradykinin.
**c-fos protooncogene of vascular smooth muscle cells, which may sequentially activate other genes, and result in growth and proliferation of these cells.**

**Heart** Because Ang II causes cellular proliferation, persistently high levels of Ang II can lead to pathologic myocardial hypertrophy. Experimental studies in rats have demonstrated that infusion of Ang II can promote synthesis and accumulation of collagen in the nonmyocytic (ie, interstitial) compartments of the myocardium, resulting in fibrosis and ventricular remodeling.

**Kidneys** Ang II causes vasoconstriction of the afferent arterioles and has an even greater effect on the efferent arterioles. This preferential constriction maintains intraglomerular filtration pressure and increases the filtration fraction when the renal perfusion pressure is low. However, sustained elevation of Ang II, as often occurs in the early stages of hypertension, results in hyperfiltration and may contribute to nephropathy over time. Stimulation of AT₁ receptors on the juxtaglomerular or macula densa cells leads to decreased release of renin, and inhibition of those receptors leads to feedback secretion of renin and angiotensin-converting enzyme (ACE)-catalyzed production of Ang II.

**Adrenals** Aldosterone is released in response to Ang II stimulation of AT₁ receptors in the adrenal cortex. This action contributes to sodium and fluid regulation and maintenance of blood pressure (BP).

**Brain and Pituitary** Ang II further modulates fluid and electrolyte homeostasis by triggering the release of arginine vasopressin (antidiuretic hormone) from the posterior pituitary via stimulation of the supraoptic nucleus of the hypothalamus and by stimulating the brain regions that mediate thirst. This results in increased BP and increased drinking behavior.

### Table 1. Tissue Sites and Effects of Ang II Stimulation

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Receptor Subtype</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Vasculature</td>
<td>AT₁</td>
<td>Smooth muscle contraction</td>
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<td></td>
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<td>Intimal hyperplasia</td>
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<td>Angiogenesis</td>
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<td>AT₂</td>
<td>Inhibition of hyperplasia and angiogenesis</td>
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<td></td>
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<td>Vasodilation via bradykinin and NO</td>
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<tr>
<td>Myocardium</td>
<td>AT₁</td>
<td>↑ Contractility</td>
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<tr>
<td></td>
<td></td>
<td>Hypertrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Collagen synthesis and myocardial fibrosis</td>
</tr>
<tr>
<td></td>
<td>AT₂</td>
<td>↓ Collagen synthesis via production of collagenase</td>
</tr>
<tr>
<td>Kidneys</td>
<td>AT₁</td>
<td>↑ Efferent arteriolar constriction and glomerular filtration</td>
</tr>
<tr>
<td>Adrenals</td>
<td>AT₁</td>
<td>↑ Aldosterone release from cortex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Catecholamine release from medulla</td>
</tr>
<tr>
<td>Brain and pituitary</td>
<td>AT₁</td>
<td>↑ ADH release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Thirst and drinking</td>
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</tbody>
</table>

NO, nitric oxide; ADH, antidiuretic hormone.

**Heterogeneity of Angiotensin II Receptor Subtypes**

The AT₁ receptor subtype participates in a complex signaling system that involves coupled G protein–dependent secondary messengers. It is linked to various phosphorylation pathways in addition to phospholipases, adenylate cyclase, and calcium ion channels. Two closely related isoforms of the AT₁ receptor (of which the AT₁a isoform predominates over the AT₁b in virtually all tissues) have been found in rodents and cloned. However, in humans there is only one form of AT₁ receptor that can be blocked by the Ang II subtype 1 receptor blockers (ARB).

The AT₂ receptor subtype, which was identified approximately 10 years ago with radioligand binding studies, has not, until recently, been investigated as intensively as the AT₁ receptor subtype. Although both subtypes are members of the seven-transmembrane–domain G protein–coupled receptor superfamily and have similar affinities for the peptides Ang II and saralasin, their amino acid sequences have only 34% homology. Emerging data indicate a mutual antagonism of actions mediated by these two receptor subtypes.

The ARB (ie, losartan, valsartan, candesartan, eprosartan, irbesartan, and telmisartan) are nonpeptide inhibitors of AT₁ receptors. They have a high affinity for the AT₁ receptor subtype without exerting agonistic effects and do not bind to the AT₂ receptor when given at the recommended doses. Likewise, specific inhibitors of the AT₂ receptor do not bind to the AT₁ receptor. These inhibitors have been used experimentally to elucidate further the actions mediated via the AT₂ receptor. Unlike the AT₁ receptor, the AT₂ receptor is coupled to various phosphatases and mediates protein dephosphorylation. A representation of the signaling pathway for the AT₂ receptor is shown in Figure 1.
dulla, where it predominates. It should also be noted that the distribution of AT2 receptors varies largely among species. The adrenal zona glomerulosa is supplied with both AT1 and AT2 receptors. In vitro studies in human adrenal tissues suggest that both receptors may be involved in the regulation of aldosterone secretion.9 AT2 receptors have also been shown to predominate in the adventitia of the human renal vasculature.23 In the rat skeletal muscle vasculature, AT2 receptors are present on vascular endothelial cells and on vascular smooth muscle cells, allowing these receptors to antagonize the actions mediated by the AT1 receptors.24 In humans, however, they appear to be virtually absent from vascular smooth muscle cells. AT2 in the human heart is localized to fibrous tissue and endothelial cells.25

During stressful situations, such as vascular injury, myocardial infarction, heart failure, wound healing, or sodium depletion, AT2 receptors are reexpressed.26–30 This upregulation of AT2 receptors may oppose the pathologic effect mediated by the AT1 receptors.

Selective alteration of the genes that encode for AT2 receptors in mice has provided an ingenious experimental tool for exploring the role of AT2 receptors.31 When cells that express only AT1 receptors are incubated with Ang II, protein phosphorylation increases with the concentration of Ang II. The opposite, increased protein dephosphorylation, takes place in cells that express only AT2 receptors. Moreover, monitoring of DNA fragmentation as a marker for stimulation of programmed cell death in smooth muscle cells of rats that have been transfected with AT2 receptor cDNA shows that apoptosis correlates with Ang II concentration. This suggests that AT2 receptor stimulation facilitates apoptosis and AT1 receptor stimulation inhibits it.32

**Renal AT2 Receptors**

The kidney is equipped with all of the components of the RAS. Intrarenally confined doses of Ang II decrease renal excretory and hemodynamic functions. The role of the AT2 receptor in renal hemodynamics is being extensively investigated at the University of Virginia Health Sciences Center in Charlottesville. The results and connotations of some key experiments are summarized here.

In one study, the renal interstitial fluid of rats fed a normal-sodium diet and infused with Ang II showed significant increases in cyclic guanosine 3',5'-monophosphate (cGMP) and prostaglandin PGE2.33 A combination of Ang II and the ARB losartan decreased the PGE2 response to Ang II but had no further effect on the increase in cGMP. Conversely, a combination of Ang II and the AT2 receptor blocker PD 123319 significantly increased PGE2 and blocked the cGMP response. This demonstrates that the AT2 receptor mediates renal production of cGMP during sodium depletion and modulates AT1 receptor-mediated production of PGE2.

This experiment did not identify the mechanism by which stimulation of AT2 receptors increases cGMP. Among substances that release cGMP during sodium depletion, nitric oxide (NO) was the most likely candidate.33,34 The ability of nitro-l-arginine-methyl-ester (l-NAME), 7-nitroindazole, and other nitric oxide synthase (NOS) inhibitors to depress the cGMP response to Ang II bolstered the hypothesis. Accordingly, another experiment was designed in which Ang II, PD 123319, and NOS inhibitors were infused in rats.35 During normal sodium intake, both PD 123319 and NOS inhibitors attenuated the Ang II-induced increase in renal cGMP; there was no additive suppression of cGMP when these agents were given concurrently.

The data suggested that activation of the RAS increases renal production of NO by stimulating AT2 receptors, in turn leading to increased production of cGMP.

In the search for another factor that might serve as an intermediary between the AT2 receptor and NO, tissue-generated bradykinin, which acts locally on B2 subtype receptors of the vascular endothelium to form and release NO, was an obvious candidate. When Ang II was infused with an ARB, it bound to AT2 receptors, triggering a cascade of release of tissue bradykinin, increased synthesis of NO, and release of cGMP, ultimately leading to vasodilatation and reduction of the increased BP associated with Ang II.36,37

These results led to the investigation of the protective role of the renal AT2 receptor in an experimental model of renal vascular hypertension in rats (two kidney, one figure-8 wrap).37 The products associated
with AT₂ receptor stimulation—bradykinin, NO end-products, and cGMP—were all higher in the renal interstitial fluid of the intact kidneys than in the wrapped kidneys. AT₁ receptor blockade normalized SBP and produced a further increase in bradykinin, NO end-products, and cGMP in the intact kidneys. In contrast, AT₂ receptor blockade with PD 123319 significantly increased SBP and decreased those products in both kidneys. This led to the conclusion that Ang II triggers production of bradykinin in the kidney via stimulation of AT₂ receptors, which then releases NO and cGMP to produce counterregulatory vasodilatation in this experimental model. In addition, it is possible that the AT₂ receptor directly influences NO and cGMP, as bradykinin-B₂ receptor blockade did not completely inhibit NO and cGMP release. This study also suggests that the hypotensive response associated with AT₁ receptor blockade is partially mediated by the AT₂ receptor.

Finally, the question of what the effect of total absence of the AT₂ receptor on vascular and renal responses to Ang II would be was asked. Data showed that a 7-day infusion of a subpressor dose of Ang II into mice lacking the gene for the AT₂ receptor (ie, AT₂-null mice) produced a marked and sustained increase in SBP and a reduction in urinary sodium excretion but had no effect on wild-type mice. Moreover, dietary restriction of sodium or infusion of Ang II increased renal interstitial fluid bradykinin and cGMP levels in the wild-type mice but not in the AT₂-null mice. These results demonstrated that the AT₂ receptor is necessary for the normal physiologic responses of bradykinin and NO to stimulation of Ang II. Deletion of AT₂ receptors in genetically altered mice leaves AT₁ receptors unopposed, an imbalance that results in renal and vascular hypersensitivity to Ang II, sustained antinatriuresis, and severe hypertension. Thus, it is highly likely that the AT₂ receptor subtype plays a counterregulatory protective role, mediated by bradykinin and NO, against the antinatriuretic and pressor actions of Ang II in humans.

These results are consistent with research on other mammalian species. In one in vitro study in rabbit tissue, Ang II activation of the AT₂ receptor in renal arterioles produced dilation, whereas blockade of this receptor augmented constriction.

**STIMULATION OF AT₂ RECEPTORS IN OTHER TISSUES**

Recently, it was found that stimulating serosal AT₂ receptors in the rat jejunum induces a net absorption of fluid through generating NO and cGMP production via activation of soluble guanyl cyclase. Previously, it had been shown that stimulation of AT₁ receptors has the contrary effect of inhibiting jejunal absorption of sodium and water by decreasing levels of cAMP and increasing those of PGE₂.¹⁰

**SOME IMPORTANT ISSUES TO PONDER**

Should we be concerned that pharmacologic blockade of the AT₁ receptors in patients with hypertension causes a feedback increase in Ang II production by triggering the release of renin? Based on what has been discussed here and reviewed in the literature, we should not be as long as there is adequate blockade of the AT₁ receptor. We believe that the Ang II diverted from the AT₁ receptors by ARB will bind to and stimulate AT₂ receptors, initiating a counterregulatory response that in fact will add to the protective actions of ARB.

Another issue is that although ACE inhibitors limit the conversion of Ang I to Ang II, they do not entirely suppress it. Plasma levels of Ang II and aldosterone initially decrease in patients undergoing long-term antihypertensive therapy with ACE inhibitors, but levels of Ang II and aldosterone eventually may rebound to baseline or higher levels and thus, Ang II will have a direct access to the AT₁ receptor. Moreover, ACE inhibitors do not inhibit an alternative pathway for the formation of Ang II that is catalyzed by chymase, a serine proteinase found in the heart, vasculature, and kidneys.

On the other hand, ACE inhibitors tend to preserve bradykinin, which provides potentially beneficial as well as detrimental effects. Recent data have indicated that bradykinin contributes to at least the acute effects of ACE inhibitors on BP. The magnitude of the contribution of bradykinin to the overall effect of ACE inhibitors is still under evaluation. Additionally, this increase in bradykinin is believed to be at least partly responsible for the 5% to 20% incidence of cough that is associated with ACE inhibitors.

Theoretically, the combination of an ACE inhibitor with an ARB should more effectively block Ang II, allow for stimulation of the AT₂ receptor, and increase bradykinin levels through reduced degradation and through stimulation of the AT₂ receptor. The benefits of this combination therapy remain to be proven in clinical use. Long-term trials are currently ongoing to evaluate this combination in various clinical situations.

**CONCLUSIONS**

Although the AT₁ receptor subtype is the major and predominant site of activity of Ang II, certain events that it sets in motion may be opposed by stimulation of the AT₂ receptor. The AT₁ receptor is associated with vasoconstriction, growth and proliferation of vascular smooth muscle, myocardial contractility, mechanical stress-induced cardiac hypertrophy, inhibition of renin release, secretion of aldosterone, and
thirst, whereas the AT$_2$ receptor is associated with vasodilatation, antiproliferation, and relaxation of heart muscle. Conversely, blockade of the AT$_2$ receptor potentiates the Ang II actions mediated by the AT$_1$ receptor. ARB do not antagonize the AT$_2$ receptor, leaving the recuperative processes it mediates unaffected while attenuating the pathologic processes mediated by the AT$_1$ receptor in hypertensive patients. Ongoing research will further clarify the role of AT$_2$ receptors in modulating the effects of the RAS on hypertension.

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