Angiotensin II and the Endothelium
Diverse Signals and Effects

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Abstract—The initial view of the renin-angiotensin system focused on the role of angiotensin II as a hormone involved in blood pressure control, based on its role in renal salt and water regulation, as well as central nervous system (thirst) and vascular smooth muscle tone. Subsequent data showed a role for angiotensin II in long-term effects on cardiovascular structure, including cardiac hypertrophy and vascular remodeling. Importantly, recent human studies with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have demonstrated exciting clinical benefits including decreases in incidence of stroke, diabetes, and end-stage renal disease that suggest important new mechanisms of action. In this review, we focus on new roles for the renin-angiotensin system in the endothelium based on the concepts of diverse signals and effects mediated by multiple angiotensin I- and angiotensin II-derived peptides, multiple angiotensin metabolizing enzymes, multiple receptors, and vascular bed-specific intracellular signals. (Hypertension. 2005; 45:163-169.)

Key Words: angiotensin II ■ endothelium ■ signal transduction

In this review, we discuss the evolving role of angiotensin II (Ang II) as a regulator of endothelial cell (EC) function. In particular, recent clinical trials of angiotensin-converting enzyme (ACE) inhibitors and Ang II receptor blockers (ARBs) suggest that several of the beneficial effects of these drugs are mediated by inhibiting Ang II effects at the endothelium. Initially, Ang II was identified as a hormone that controlled blood pressure based on regulation of renal salt and water metabolism, central nervous system mechanisms (thirst and sympathetic outflow), and vascular smooth muscle cell (VSMC) tone. Later, Ang II was found to exert long-term effects on tissue structure, including cardiac hypertrophy, vascular remodeling, and renal fibrosis. Importantly, recent human studies with ACE inhibitors and ARBs have yielded exciting clinical benefits such as decreased incidence of stroke, diabetes mellitus, and end-stage renal disease. This article discusses the endothelium-specific effects of these drugs and Ang II, based on the concept of diverse signals and effects mediated by multiple angiotensin receptors (AT1R, AT2R, and AT4R), multiple angiotensin I- and Ang II-derived peptides [Ang III, Ang IV, and Ang (1–7)], and vascular bed-specific events (Figure 1). The enzymes that control generation of these peptides, including ACE, ACE2, endopeptidases, and aminopeptidases, interact with each other. In addition, drugs such as ACE inhibitors and ARBs that inhibit formation of Ang II and binding to its receptor also modify the expression of receptors for Ang II and of other vasoactive hormones, including bradykinin and adrenomedullin. This complex interplay of pathways helps to explain the findings that Ang II can have both beneficial and detrimental effects on vascular function.

Effects of Angiotensin Type-1 Receptor
The AT1R has been shown to mediate most of the physiological actions of Ang II. However, as discussed, important regulatory roles for the AT2R and AT4R, have been defined, especially in EC. Recent data show several pathways by which the AT1R and AT2R modulate EC function.4

Apoptosis
Ang II has been shown both to increase and decrease EC apoptosis, suggesting that other factors influence the actions of Ang II (eg, presence of oxidized low-density lipoprotein [oxLDL]). In fact, both the AT1R and the AT2R have been suggested to mediate EC apoptosis.5,6 As discussed further, we speculate that the relative AT1R and AT2R expression levels are important determinants of the effects of Ang II in EC (Figure 2). Ang II-mediated EC apoptosis is in part mediated by generation of reactive oxygen species (ROS), because antioxidants suppress EC apoptosis. Ang II increases NADPH oxidase activity in EC, enhancing superoxide production via AT1R and AT2R.5 Ang II and ROS also promote EC apoptosis by inhibiting the function of the anti-apoptotic protein Bcl-2.6 For example, ROS generated by Ang II cause transcriptional downregulation of Bcl-2 and upregulation of pro-apoptotic Bax. In addition, Ang II was shown to inactivate extracellular signal-regulated kinase (ERK) (ERK1/2) by upregulating mitogen-activated protein kinase (MAPK) phos-
phatase 3, thereby decreasing Bcl-2. Ang II may indirectly cause EC apoptosis via induction of Fas and LOX-1. Finally, the AT1R directly alters endothelial nitric oxide synthase (eNOS) function by binding to membrane-localized eNOS. Marrero et al showed that eNOS was bound and its activity was inhibited by the bradykinin B2 receptor (B2R), the AT1R and the endothelin-1 ETB receptor. The interaction is controlled in part by phosphorylation of serines and tyrosines that interact with eNOS, although the physiological importance and kinases involved remain to be clarified. In summary, Ang II promotes apoptosis in EC via direct and indirect mechanisms.

Recently, Ang II was shown to inhibit microvascular EC apoptosis via AT1R by activating PI3-kinase and Akt, which stimulated expression of an anti-apoptotic protein named survivin. The findings that Ang II has both pro-apoptotic and anti-apoptotic effects may be a consequence of the growth state of EC, vascular bed-specific phenotype, and the nature of their interaction with extracellular matrix. For example, the initial phase of Ang II-mediated angiogenesis may require microvascular EC growth and migration, whereas subsequent maturation and pruning of the neovasculature may require EC differentiation and apoptosis.

**Lectin-Like OxLDL Receptor-1**

There is increasing evidence that Ang II modulates the effects of oxLDL on EC function, thereby promoting atherosclerosis. Uptake of oxLDL by EC impairs nitric oxide (NO) production, induces expression of white blood cell adhesion molecules, and promotes EC apoptosis. Lectin-like oxLDL receptor-1 (LOX-1) is a novel endothelial receptor for oxLDL that has been shown to mediate oxLDL-induced responses and uptake of oxLDL in EC. Activation of this pathway stimulates ROS production, MAPKs, and NF-κB. In EC,
Ang II via the AT\textsubscript{1}R upregulates LOX-1, stimulates oxLDL uptake, and enhances oxLDL-mediated EC ROS generation and apoptosis.\textsuperscript{6} As part of a positive feedback mechanism, oxLDL also upregulates AT\textsubscript{1}R (but not AT\textsubscript{2}R) expression. As expected, ARBs and ACE inhibitors decrease LOX-1 expression in aortas from hypercholesterolemic rabbits\textsuperscript{10} and arteries from patients with coronary artery disease.\textsuperscript{11} These data suggest important roles for LOX-1 and oxLDL in the effects of Ang II on EC function, especially EC apoptosis.

**Plasminogen Activator Inhibitor Type 1**

Plasminogen activator inhibitor type 1 (PAI-1) is the major physiological inhibitor of tissue-type plasminogen activator and urokinase-type plasminogen activator, and plays a key role in the regulation of thrombosis. Elevated PAI-1 is associated with myocardial infarction and atherosclerosis. Several experimental and clinical studies have shown that Ang II is a potent regulator of PAI-1 expression.\textsuperscript{12} Ang II has been reported to increase PAI-1 mRNA and protein expression in EC.\textsuperscript{13} Some studies have reported that Ang II-induced PAI-1 expression is mediated by AT\textsubscript{1}R via a pathway involving Rho/Rho kinase, cAMP, and ROS.\textsuperscript{15} AT\textsubscript{1}R blockade with ARBs decreases PAI-1 antigen and PAI-1 activity in patients with chronic hypertension and heart failure, suggesting a key role for the AT\textsubscript{1}R.\textsuperscript{16} However, as noted, the AT\textsubscript{1}R may also be an important mediator of PAI-1 expression.\textsuperscript{13} Taken together, the evidence suggests that Ang II inhibits the fibrinolytic system via AT\textsubscript{1}R by inducing PAI-1 expression in EC.

**Cyclooxygenase-2 and Vascular Endothelial Growth Factor**

Cyclooxygenase-2 (COX-2) is induced by many stimuli, including Ang II, and catalyzes the formation of prostaglandins and thromboxane A\textsubscript{2}.\textsuperscript{17} COX-2 expression in EC appears to be important in both atherosclerosis\textsuperscript{18} and angiogenesis.\textsuperscript{19} Mukai et al reported that ACE inhibitors and ARBs ameliorated endothelial dysfunction associated with aging through the inhibition of COX-2–derived eicosanoids.\textsuperscript{20} In mouse models, overexpression of renin or angiotensinogen, as well as treatment with Ang II, induced COX-2 through the AT\textsubscript{1}R, which led to EC dysfunction.\textsuperscript{21} Thus, COX-2 is an important mediator of Ang II effects on EC.

Ang II increases vascular endothelial growth factor (VEGF) via the AT\textsubscript{1}R in EC and induces angiogenesis through both a COX-2 mediated inflammatory process and VEGF-related pathways.\textsuperscript{21} In addition, recent reports suggest that Ang II-induced VEGF expression is mediated by hypoxia-inducible factor-1 and causes vascular remodeling.\textsuperscript{22} Ang II-mediated increases in VEGF may be detrimental by increasing vascular permeability and edema formation. In summary, Ang II has powerful inflammatory effects on EC mediated by COX-2 and VEGF. These effects may be pathogenic by promoting accumulation of inflammatory cells and edema.

**Angiotensin Type-2 Receptor**

There is growing evidence that the AT\textsubscript{2}R plays an important role in cardiovascular physiology. Whereas the AT\textsubscript{1}R is widely distributed throughout the body, the AT\textsubscript{2}R is highly expressed only in the fetus, including early EC.\textsuperscript{23} AT\textsubscript{2}R expression decreases soon after birth to low levels, so that the predominant EC Ang II receptor is the AT\textsubscript{1}R. However, in adult humans, low levels of AT\textsubscript{2}R expression occur in aorta and coronary arteries.\textsuperscript{24} It has become clear that the AT\textsubscript{2}R participates in both normal physiology and cardiovascular disease. For example, AT\textsubscript{2}R knockout mice have an exaggerated vasopressor response to Ang II.\textsuperscript{25} AT\textsubscript{2}R upregulation occurs in pathologic conditions such as in failing cardiomyopathic hearts\textsuperscript{26} or after myocardial infarction.\textsuperscript{27} Substantial evidence with the AT\textsubscript{2}R knockout mouse indicates that the AT\textsubscript{2}R protects both heart and brain tissue from ischemia. Specifically, the size of cerebral and myocardial infarction is significantly greater in the AT\textsubscript{2}R knockout mouse.\textsuperscript{28} In addition, the beneficial effects of ARBs on cardioprotection are mediated in part by an AT\textsubscript{2}R-dependent pathway.

The AT\textsubscript{2}R-pathway appears to protect tissues from ischemia via an AT\textsubscript{2}R-bradykinin-NO-cyclic guanosine monophosphate (cGMP) pathway as shown in Figure 3.\textsuperscript{29} As diagrammed, Ang II binding to the AT\textsubscript{2}R inhibits the Na–H exchanger and promotes intracellular acidification. This activates a kinogenase that increases production of bradykinin, which now binds to the B\textsubscript{2}R on both VSMC and EC. In EC, the B\textsubscript{2}R increases eNOS activity, and NO stimulates cGMP and VSMC relaxation, a mechanism for AT\textsubscript{2}R-dependent vasorelaxation. Although this pathway was ini-

![Figure 3. Proposed mechanism by which the AT\textsubscript{1}R and AT\textsubscript{2}R interact with the kinin system in the vessel wall to control vascular tone.]
tially described in VSMC and cardiomyocytes, similar pathways may occur in EC. Of interest, ARBs increase AT1R expression in EC, which may be an important mechanism by which these drugs produce their effects. As shown in Figure 3, the increase in BK generated by the AT1R stimulates eNOS and also increases the expression of extracellular superoxide dismutase. Extracellular superoxide dismutase decreases superoxide formation and thereby increases bioavailable NO. Finally, we have proposed that Ang II regulates the expression of eNOS and NO production, whereas NO downregulates AT1R. NO also regulates Ang II receptors in vitro. Treatment of rat VSMC with NO donors inhibited Ang II binding to cells, without altering receptor affinity. However, treatment of the cells with cGMP analogs had no significant effect on Ang II binding, suggesting that NO regulates Ang II receptors through a cGMP-independent mechanism. In VSMC, inhibition of Ang II binding by NO is caused by decreased AT1R mRNA expression and occurs at the transcriptional level. In addition, downstream effectors of Ang II and NO signaling pathways also interact with each other. In particular, cyclic nucleotide phosphodiesterases play critical roles in controlling intracellular cGMP levels by converting cGMP to 5′-GMP. Ang II exhibits inhibitory effects on cGMP accumulation elicited by NO donor or atrial natriuretic peptide in VSMC and vessels, which is likely to be mediated by activation of Ca2+/CaM-stimulated phosphodiesterases. To date, very little is known regarding the roles of phosphodiesterase isoforms in Ang II–mediated effects on EC function.

The mechanisms for AT1R signaling remain poorly described, especially in EC. A recent study by Gendron et al showed in the neuronal cell line NG108 that Ang II–AT1R–mediated neurite outgrowth involved activation of Rap1 and B-Raf, with stimulation of MAPK kinase-1 (MEK1) and ERK1/2. Exciting new data from Feng et al showed that the AT1R coupled to the G protein αs (Gαs) independent of Gβγ and Gγ. The authors found that SH2 domain-containing phosphatase 1 (SHP-1) constitutively associated with the AT1R, and SHP-1 was activated on AT1R stimulation by Ang II. These recent publications regarding the AT1R demonstrate tissue specific pathways and involve protein tyrosine phosphatases, MAPK and Gαs.

A simple generalization is that AT1R and AT2R signaling produce effects that are antagonistic. One mechanism that partially accounts for this is that the 2 receptors heterodimerize inhibiting AT1R signaling. This may have significance in Ang II effects on angiogenesis. AT1R knockout mice exhibit impaired angiogenic potential, but other studies have shown that AT1R inhibits EC migration and is antiangiogenic. We propose an explanation for these contradictory results based on the relative levels of AT1R and AT2R expression (Figure 2). Normally, AT1R expression is significantly greater than AT2R expression and Ang II mediates angiogenesis. However, in response to tissue injury or drug treatment with ARBs, AT1R expression increases and now heterodimerizes with AT2R. Because this heterodimerization inhibits AT1R signaling, AT1R expression now is antiangiogenic (Figure 2).

Similarly, we propose that the relative expression of these receptors may determine the effect of Ang II on EC apoptosis. The AT1R has the ability to promote apoptosis independent of ligand binding in fibroblasts, supporting the concept that receptor expression is important for its physiological outcome. The effects of this receptor on apoptosis are cell type-specific in that it has been shown to be anti-apoptotic in cardiomyocytes but pro-apoptotic in VSMC. There is less evidence for its role in EC, with the limited available data suggesting AT1R signaling also promotes apoptosis. As the evidence grows, it may become apparent that heterodimerization plays an important role in this process (Figure 2).

**Effects of AT1R**

Ang IV [Ang (3–8)] is an important angiotensin degradation peptide (Figure 1) that binds to the AT2R, which is expressed primarily in EC. Upregulation of AT2R was detected in the re-endothelialized cell layer after balloon injury. Ang IV has been shown to increase PAI-1 expression via the AT1R, an AT1R blocker, but not AT2R or AT3R blockers, inhibited Ang IV–induced PAI-1 expression. In addition, an aminopeptidase inhibitor suppressed Ang II-induced PAI-1 expression, suggesting a key role for metabolism of Ang II to generate Ang IV. Ang IV has been reported to mediate cerebral and pulmonary artery vasorelaxation via NO release and pulmonary microvascular EC proliferation. Ruiz-Ortega et al suggested that Ang IV is proinflammatory because Ang IV activates NF-κB. To define the role of Ang IV in vascular disease, identification of the AT2R will be necessary.

**ACE and Bradykinin in the Endothelium**

Studies using transgenic mice have defined the role of ACE in cardiovascular physiology. ACE knockout mice are hypotensive, and arterial blood pressure closely follows ACE expression in partial knockouts. Recently, endothelial ACE was specifically knocked-out in the ACE 1/3 mice. Although these mice are normotensive under basal conditions, when the mice were stressed by a low-salt diet they became hypertensive compared with wild-type controls. These studies show that endothelial ACE is important, but not essential, for normal blood pressure regulation.

ACE is a major link between the renin-angiotensin system and the kinin systems, because it not only converts Ang I to Ang II but also degrades kinins (Figure 1). ECs are an important site for the effects of BK and have been shown to express both B1R and B2R. ACE inhibitors potentiate the actions of BK by reducing its degradation, which causes an increase in BK binding to EC receptors. In addition, ACE inhibitors alter B2R binding site affinities and targeting to caveolin-rich areas of the membrane, illustrating another regulatory link between the renin-angiotensin system and the kinin system.

**ACE-Related Carboxypeptidase**

Recently, a homologue of ACE, termed ACE-related carboxypeptidase (ACE2) has been identified. ACE2 is a membrane-associated, zinc metalloprotease expressed predominantly on endothelium in heart, kidney, and testis. ACE2 has been shown to convert Ang I and Ang II into Ang
(1–9) and Ang (1–7), respectively (Figure 1).\(^\text{50}\) Ang (1–7) is an active peptide that has been shown to be a potent vasodilator. Ang (1–7) potentiates BK actions through the release of prostaglandins, NO, or endothelium-derived hyperpolarizing factor.\(^\text{51}\) Ang (1–7) also possesses antithrombotic and anti-inflammatory effects. Although Ang II is a potent stimulus for PAI-1, Ang (1–7) decreases PAI-1 expression in EC.\(^\text{52}\) Deletion of ACE2 results in a severe cardiac contractility defect that may be associated with changes in the cardiac renin-angiotensin system.\(^\text{53}\) In addition, ACE2 hydrolyzes apelin 13 and dynorphin A with comparable catalytic efficiency to the conversion of Ang II to Ang (1–7). Apelin has been identified as an endogenous ligand for APJ (a protein-coupled receptor) that is a G protein-coupled receptor.\(^\text{54}\) Although APJ has 31% amino acid sequence homology with the AT, it does not exhibit specific binding of Ang II. Recently, it was shown that binding of apelin to APJ has vasodilative effects in vivo and may play a counter-regulatory role to Ang II.\(^\text{55}\) These results suggest that ACE2 interacts with Ang II and bradykinin pathways and may modulate the renin-angiotensin system by multiple mechanisms.

**ACE Inhibitors**

There is strong evidence that inhibiting ACE activity has clinical benefits to limit cardiovascular events including myocardial infarction, congestive heart failure, and stroke.\(^\text{2,56,57}\) ACE inhibitors work in part by improving endothelial dysfunction.\(^\text{58}\) ACE inhibitors have been shown to increase arterial dilation via B,NO-pathways.\(^\text{59}\) ACE inhibitors also improve EC survival after hypoxic injury via B,NO–dependent pathways.\(^\text{60}\) In addition, these drugs induce B,R in the renal vasculature and increase NO production from EC expressing these receptors.\(^\text{61}\) Recently, a novel mechanism for ACE inhibitors has been discovered that involves signal transduction by ACE itself (Figure 4). Specifically, the protein kinase, CK2, was found to phosphorylate the cytoplasmic tail of ACE, thereby activating intracellular signaling via JNK. ACE inhibitors potentiate this signaling, which may be another mechanism by which these drugs produce their beneficial effects.\(^\text{62}\)

**ARB Effects**

Recently, 3 randomized studies compared the clinical benefits of ARBs in patients with hypertension to other types of antihypertensive therapy: the Losartan Intervention For Endpoint reduction in hypertension (LIFE),\(^\text{3}\) Study on COgnition and Prognosis in the Elderly (SCOPE),\(^\text{61}\) and Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trials.\(^\text{64}\) In the LIFE trial, 9193 hypertensive patients with left ventricular hypertrophy were randomized to the ARB losartan or the \(\beta\)-blocker atenolol plus conventional therapy. The results showed a significant beneficial effect of losartan on total mortality as well as stroke, despite similar reductions of blood pressure in the 2 groups. Similarly, there was a significant 28% reduction of nonfatal stroke in the SCOPE trial, which compared candesartan to placebo in 4964 elderly patients with hypertension.\(^\text{63}\) In VALUE, 15 245 hypertensive patients were randomized to the ARB valsartan or the calcium antagonist amlodipine. The results of the VALUE trial showed that valsartan was associated with a slightly higher incidence of stroke and myocardial infarction, particularly during the first 6 months of the study, which was apparently associated with a slower reduction in blood pressure.\(^\text{64}\) However, at study end (mean, 4.2 years), there was no difference in the primary composite end point of cardiac morbidity and mortality.

Likely explanations for blood pressure-independent effects of ARBs in LIFE trial are improved endothelial function caused by decreased coagulation and inflammation and altered vessel structure. For example, Schiffrin et al demonstrated that endothelium-dependent relaxation and the media/lumen ratio of resistance arteries from hypertensive patients were normalized after 1 year by losartan but not by atenolol.\(^\text{65}\) Recently, several articles have shown that some ARBs have AT,R-independent anticoagulant and anti-inflammatory effects.\(^\text{17,66}\) Kraimer et al demonstrated that the losartan metabolite EXP3179, which has no AT,R -blocking properties, inhibited expression of COX-2 and suppressed thromboxane A2-induced platelet aggregation. We found that losartan and EXP3179 activated Akt, increased eNOS phosphorylation, and prevented EC apoptosis.\(^\text{67}\) These AT,R-independent actions may be related to the individual chemical characteristics of losartan and irbesartan rather than to an ARB class effect.\(^\text{17,66}\) AT,R-independent effects of other ARBs remain to be investigated.

Recently, 2 groups suggested that PPAR\(\gamma\) activation represents a novel mechanism for the beneficial effects of ARBs.\(^\text{68,69}\) Irbesartan and telmisartan potently enhanced PPAR\(\gamma\)-dependent adipocyte differentiation associated with
increases in mRNA expression of PPAR-γ-responsive genes. The PPAR-γ-activating properties differed, with EC₅₀ values ranging from low (telmisartan), to medium (irbesartan), to very high (losartan). These differences among ARBs are likely caused by their physicochemical properties, because high lipophilicity (telmisartan is highest) is required to obtain sufficiently high penetration rates to bind to intracellular PPAR-γ. When PPAR-γ-activating ARBs were compared with the PPAR-γ ligand pioglitazone, the ARBs behaved like partial PPAR-γ agonists, suggesting tissue and concentration-specific effects. To date, little is known regarding the effects of ARBs on PPAR-γ function in EC.

Summary and Conclusions

Exciting new findings suggest novel roles for angiotensin peptides and the angiotensin receptors (AT₁R, AT₂R, and AT₃R) present on EC. An important concept highlighted in this review is the extensive cross-talk between bradykinin (generated in increased levels in the presence of ACE inhibition) and the AT₁R (Figure 4). It appears well-established that many beneficial effects of ACE inhibition require AT₁R-dependent increases in NO. In addition, we discussed several novel mechanisms by which the AT₁R may directly regulate the AT₁R, including signal transduction by phosphatases and heterodimerization. Equally exciting are recent discoveries for ACE inhibitors and ARBs that suggest actions independent of their primary mechanism of action: ACE signaling to JNK and activation of multiple AT₁R-independent pathways for ARBs (Figure 4). The novel ARB pathways include binding of metabolites to the thromboxane A₂ receptor, activation of eNOS by stimulation of a PI₃-kinase/Akt pathway, and activation of PPAR-γ. These new mechanisms may account for some of the unique clinical benefits of ARBs to decrease stroke, diabetes, and end-stage renal disease. It is now clear that the endothelium is an important target for the renin-angiotensin system and for the action of ACE inhibitors and ARBs.

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