Role of the Renin-Angiotensin System in Vascular Diseases

Expanding the Field


Abstract—The renin-angiotensin system (RAS) has emerged as one of the essential links in the pathophysiology of vascular disease. Angiotensin (Ang) II, the main peptide of the RAS, was considered as a vasoactive hormone, but in the past years, this view has been modified to a growth factor that regulates cell proliferation/apoptosis and fibrosis. Recently, this view has been enlarged with a novel concept: Ang II participates in the inflammatory response, acting as a proinflammatory mediator. In resident vascular cells, Ang II produces chemokines, cytokines, and adhesion molecules, which contribute to the migration of inflammatory cells into the tissue injury. Ang II is also a chemotactic and mitogenic factor for mononuclear cells. The molecular mechanisms of Ang II–induced vascular damage are mediated by the activation of transcription factors, redox signaling systems, and production of endogenous growth factors. In addition, other components of the RAS could also be involved in the pathogenesis of cardiovascular diseases. The Ang II degradation product Ang III shares some of its properties with Ang II, including chemotaxis and production of growth factors and chemokines. All these data clearly demonstrate that Ang II is a true cytokine, show the complexity of the RAS in pathological processes, and provide some mechanistic responses of the beneficial effects of the treatment with RAS blockers in cardiovascular diseases. (Hypertension. 2001;38:1382-1387.)

Key Words: angiotensin II • inflammation • fibrosis • vascular damage • renal damage

Numerous clinical and laboratory data are now available supporting the hypothesis that the renin-angiotensin system (RAS) is relevant in the pathogenesis of cardiovascular diseases and have changed the traditional view on the role of angiotensin (Ang) II. Historically, Ang II was only seen as a regulatory hormone that regulates blood pressure, aldosterone release, and sodium reabsorption. Now it is generally accepted that locally formed Ang II could activate the cells regulating the expression of many substances, including growth factors, cytokines, chemokines, and adhesion molecules, which are involved in cell growth/apoptosis, fibrosis, and inflammation.1–5 The production of Ang II within the arterial wall is important in the normal regulation of arterial tone and is clearly involved in the pathogenesis of atherosclerosis. In human atherosclerotic lesions, local RAS is activated, presenting high levels of ACE, Ang II and angiotensin type 1 receptor (AT1).6 Another important observation is that monocytes/macrophages present in vascular lesions express high ACE activity,7 and during the differentiation of monocytes to macrophages, there is an activation of the RAS and reexpression of AT1.8 Ang II regulates many processes implicated in vascular pathophysiology, including cell growth/apoptosis of vascular cells, migration of vascular smooth muscle cells, inflammatory responses, and extracellular matrix (ECM) remodeling.2,4,5,9 Drugs that block Ang II actions, such as ACE inhibitors or angiotensin receptor antagonists, are currently employed in the treatment of hypertension, heart failure, atherosclerosis, and other cardiovascular diseases.2,4,5,9 The (Heart Outcomes Prevention Evaluation (HOPE) trial showed that chronic ACE inhibition can reduce cardiovascular events in patients with multiple risk of atherosclerosis.10 In animal models, these drugs have been demonstrated to ameliorate organ damage, diminishing the inflammatory response, cell proliferation, and fibrosis.2,4,5,9 Despite the widespread use of these agents in clinical practice, it is not completely defined by which of them Ang II exerts its effects on the vasculature.

Ang II and the Vascular Inflammatory Response

Recent studies have demonstrated that Ang II is a potent proinflammatory agent.5 Ang II may modulate some responses of immune and inflammatory cells, such as chemotaxis, proliferation, and the differentiation of monocytes into...
macrophages (Figure 1). Also, ACE inhibitors present immunomodulatory properties. The presence of an inflammatory response in the arterial wall has been described in vascular diseases, including atherosclerosis and hypertension. Ang II is involved in this response through the release of several proinflammatory mediators, including adhesion molecules, chemokines, and cytokines. Ang II induces the adhesion of monocytes and neutrophils to endothelial cells, through the production of P-selectin, intercellular adhesion molecule type 1, and vascular cell adhesion molecule type 1 (VCAM-1) on vascular endothelial cells and smooth muscle cells in vivo and in vitro. Hypertensive patients present elevated serum levels of adhesion molecules, and patients with coronary artery disease have high levels of L-selectin on leukocytes. Endothelial dysfunction is characterized by increasing adhesiveness of circulating monocytes and the expression of the same adhesion molecules as observed in response to Ang II. In animal models, Ang II causes endothelial dysfunction, measured by impaired vasorelaxation in response to acetylcholine, and ACE inhibitors improve endothelial dysfunction in patients with coronary artery disease, suggesting that endothelial dysfunction is an important mechanism by which Ang II promotes atherosclerosis.

In experimental models of atherosclerosis and hypertension, ACE inhibition and AT1 antagonists diminished inflammatory cells, adhesion molecules, and cytokine and chemokine expression. In vivo, infusion of Ang II into rats caused hypertension characterized by marked monocyte infiltration, as well as VCAM-1 and MCP-1 expression in the aorta, although levels of cytokines have not been evaluated. Monocytes from hypertensive patients are preactivated, producing more cytokines and adhesion to endothelial cells than do normal ones. Biochemical strain regulates macrophage phenotype and induces the expression of the class A scavenger receptor, an important lipoprotein receptor in atherogenesis, suggesting a potential mechanism favoring the development of atherosclerosis in hypertensive patients.

apoprotein E (apoE) knockout mice, Ang II infusion causes vascular pathology, characterized by atherosclerosis and aneurysm. In this model, the effect of Ang II is not dependent on the hyperlipidemic state, showing that the effect of Ang II must be direct and independent of changes in blood pressure. The potential explanation could be that Ang II promotes an inflammatory reaction in the vessel wall by activation of multiple cell types. In vascular smooth muscle, endothelial, and mononuclear cells, Ang II increased monocyte chemotactic protein type 1 (MCP-1), the main chemokine for monocytes/macrophages, and interleukin (IL)-8 and IP-10, which are potent chemoattractants and activators of neutrophils. In vascular cells, Ang II increases IL-6 production, and in macrophages, Ang II upregulates tumor necrosis factor-α and IL-6 gene expression. Deficiency of the major receptor for MCP-1 (CCR2) reduces atherosclerosis in apoE knockout mice. A recent study using this CCR2 mouse has demonstrated the important contribution of macrophage recruitment for Ang II–induced vascular hypertrophy. These data show that Ang II activates vascular and inflammatory cells to secrete proinflammatory mediators that help to recruit new mononuclear cells and could result in additional inflammatory response, contributing to the progression of vascular damage (Figure 1).

Molecular Mechanism of Ang II–Induced Vascular Injury

The role of oxidative stress in the pathogenesis of vascular diseases has been well recognized. Ang II stimulates the production of reactive oxygen species (ROS) by inducing vascular NADH oxidase. Recent studies suggest that the enzymatically active flavoprotein subunit gp91phox of NADPH oxidase present on endothelial and adventitial fibroblasts is chiefly responsible for Ang II–stimulated vascular oxidative stress and smooth muscle cells growth in vivo. In contrast, in vascular smooth muscle cells, Ang II–stimulated ROS generation and activation of growth-promoting signaling
proteins Akt and p38 MAPK is mediated by nox1, a NADPH oxidase that is functionally analogous. Ang II promotes atherosclerosis by two redox mechanisms: (1) by increasing the levels of lipid-oxidizing ROS, which promotes the loading of lipid into foam cells and (2) by inducing the expression of redox-sensitive gene products, such as VCAM-1 and MCP-1. In vascular smooth muscle cells, the induction of MCP-1 and IL-6 by Ang II is dependent on the activation of NADPH oxidase. Both Ang II and IL-6 are colocalized in the macrophages present in the shoulder region of the atherosclerotic plaques, the place suggested to be prone to plaque rupture in acute coronary syndromes. Ang II is also associated with other sources of oxidative stress, as oxidized LDL and NO that can participate in inflammation and apoptosis.

Emerging data suggest a potential role of nuclear factor-κB (NF-κB) as a mediator of Ang II–induced inflammatory process. In vivo, systemic infusion of Ang II into normal rats increases NF-κB activity in vessels (Figure 2) and kidney, both in resident and infiltrating cells. Ang II activates NF-κB in several cell types, including vascular smooth muscle, endothelial, renal, and mononuclear cells. Ang II acts through its binding to two main specific receptors, AT1 and AT2. Although their intracellular signals are different, both receptors share a common molecular pathway, the activation of NF-κB. In vascular smooth muscle cells, using specific Ang receptor antagonists and agonists, we have demonstrated that both AT1 and AT2 mediate Ang II–induced NF-κB DNA binding, IkB degradation, and transcription of a NF-κB reporter gene. Ang II increases NF-κB activity in vascular smooth muscle cells from AT1 knockout mice. In glomerular endothelial cells, Ang II also activates NF-κB through AT1 and AT2. In cultured cells, Ang II via the AT1/NF-κB pathway upregulates some proinflammatory genes, such as IL-6, VCAM-1, and MCP-1, whereas the AT2/NF-κB pathway could regulate RANTES expression. In vivo, Ang II infusion increased renal NF-κB activity, which was partially diminished by treatment with AT1 and AT2 antagonists. In rats with unilateral ureteral obstruction, both antagonists also decreased NF-κB activation in the obstructed kidney. In addition, we have observed that AT1 knockout mice presented less NF-κB activity in the obstructed kidney than that of wild-type mice. This model, only ACE inhibition, but not the AT1 blockade, reduced monocyte/macrophage infiltration. Interestingly, only AT2 antagonists diminished Ang II–induced renal inflammatory cell infiltration. The Ang II/NF-κB pathway plays a critical role in the hypertrophic growth of terminally differentiated cardiomyocytes. In addition, some differences exist in the Ang II/NF-κB signaling pathway depending on the cell type involved, suggesting a tissue-selective modulation of Ang II effects. These data show that Ang II participates in the inflammatory response by a direct activation of inflammatory cells or by the regulation of adhesion molecules and chemokines expression, via redox mechanisms and NF-κB pathway, contributing to the recruitment of inflammatory cells into the lesion (Figure 1).

**Ang II, Cell Growth, and Fibrosis**

Early studies have demonstrated that Ang II is a growth factor, inducing hyperplasia/hypertrophy depending on the cell type and the balance between growth factors. Transforming growth factor-β (TGFβ) could induce cell growth or inhibition depending on the cell culture conditions. Interestingly, in endothelial cells Ang II induces apoptosis, which could have effects on binding to platelets and inflammatory cells and suggest a potential mechanisms of promoting atherosclerosis. In vivo, Ang II infusion could cause cell proliferation or apoptosis and ECM accumulation. We have recently observed that parathyroid hormone–related protein
(PTHrP), a mitogenic and vasodilator agent, is induced in Ang II–infused rats in aorta and in the kidney and is associated with cell proliferation and fibrosis. Ang II modulates ECM synthesis and degradation (Figure 3). Ang II–induced ECM production is mainly mediated by TGFβ. 

We have recently described a novel mediator of Ang II–induced fibrosis: the connective tissue growth factor (CTGF), a profibrogenic cytokine, which acts as a downstream mediator of TGFβ profibrotic activities. It is overexpressed in atherosclerotic lesions in humans. We have observed that Ang II–induced hypertension increases CTGF production in the aorta. In addition, in cultured VSMC, Ang II, via AT1, increased mRNA and synthesis of CTGF, suggesting that CTGF could be a mediator of profibrogenic effects of Ang II. The excessive ECM accumulation is due to the increase of ECM production and downregulation of its degradation, a process caused by protease inhibitors. Metalloproteinases (MMP) can degrade a variety of ECM proteins. Ang II increases ECM and MMP production. On the other hand, degradation of ECM by upregulation of MMP production is a critical event leading to weakening of the vessel wall. The RAS is also linked to the induction of plasminogen activator inhibitor type 1 (PAI-1) possibly via AT1 receptors, and therefore facilitating both thrombosis and fibrosis.

**Other Aspects of the RAS: Potential Role of Ang II Degradation Products in Vascular Diseases**

Although Ang II has been considered the effector peptide of the RAS, some of the degradation metabolites, such as Ang III, Ang IV, and Ang-(1-7) also possess biological properties. Ang-(1-7) presents some opposite effects to Ang II, acting as a vasodilator agent and inhibiting cell growth. Among these peptides, Ang III seems to be very important because it shares many physiological functions with Ang II in the cardiovascular and central nervous system, including pressor response, vasopressin release, and water consumption. Some recent data suggest that Ang III could also be involved in some pathological processes. Ang III also presents proinflammatory properties. In mononuclear cells, Ang III regulates MCP-1 chemokine production and activates the transcription factors NF-κB and AP-1. In pathological situations, such as hypertension, diabetes mellitus, and nephritis, renal aminopeptidase A (APA), the enzyme that degrades Ang II to Ang III, is increased. Ang II overexpressed growth-related, profibrotic, and proinflammatory genes. All these data suggest that Ang III could regulate cell growth, ECM accumulation, and inflammatory cell responses and therefore contribute to the progression of kidney damage (Figure 4). Some intracellular signaling systems elicited by Ang III—such as calcium mobilization, induction of c-fos gene expression, and activation of several transcription factors—are similar to those of Ang II. We have found that although both Ang II and Ang III activate the transcription factor NF-κB, the receptor subtype stimulated by each peptide is different. Ang II/NF-κB pathway is mediated by both AT1 and AT2, whereas Ang III/NF-κB is mainly by AT2 (data not shown). Although more studies are necessary, these data could explain the differences observed between ACE inhibitors and AT1 antagonists in the inflammatory response in various experimental models of kidney diseases. Ang IV is another important angiotensin degradation peptide with a potential role in vascular pathophysiology. In atherosclerotic plaques, there is an upregulation of AT4 receptors, and Ang IV increases cell proliferation. We have recently observed that in vascular smooth muscle cells, Ang IV activates NF-κB. Although future studies are necessary, these data suggest that Ang IV could be involved in some proinflammatory processes. All these data further support a novel view of the RAS, in the sense that other peptides besides Ang II could participate in the initiation and progression of vascular diseases.

**Acknowledgments**

The papers from our group that are cited in this text have been supported by research grants from Comunidad Autónoma de Madrid (08.4/0017/2000 and 08.9/0002.1/2000), EU Concerted Action Grant BMH 4-CT98 to 3631 (DG 12-SSM1) by Fondo de Investigaciones Sanitarias (00/0126) and Fundación Renal Iñigo Alvarez de Toledo, Fundación Maphre Medicina, and Fundación Ramón Areces.

**References**


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Hypertension. 2001;38:1382-1387
doi: 10.1161/hy1201.100589

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/38/6/1382

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