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 AT2.8 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.

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 NADPH oxidase. Recent studies suggest that the enzymatically active flavoprotein subunit gp91(phox) 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, AT<sub>1</sub> and AT<sub>2</sub>. 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 AT<sub>1</sub> and AT<sub>2</sub> mediate Ang II–induced NF-κB DNA binding, IκB degradation, and transcription of a NF-κB reporter gene. Ang II increases NF-κB activity in vascular smooth muscle cells from AT<sub>1</sub> knockout mice. In glomerular endothelial cells, Ang II also activates NF-κB through AT<sub>1</sub> and AT<sub>2</sub>. In cultured cells, Ang II via the AT<sub>1</sub>/NF-κB pathway upregulates some proinflammatory genes, such as IL-6, VCAM-1, and MCP-1, whereas the AT<sub>2</sub>/NF-κB pathway could regulate RANTES expression.

In vivo, Ang II infusion increased renal NF-κB activity, which was partially diminished by treatment with AT<sub>1</sub> and AT<sub>2</sub> antagonists. In rats with unilateral ureteral obstruction, both antagonists also decreased NF-κB activation in the obstructed kidney. In addition, we have observed that AT<sub>1</sub> 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 AT<sub>1</sub> blockade, reduced monocyte/macrophage infiltration. Interestingly, only AT<sub>2</sub> 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

![Figure 2. Ang II activates NF-κB in rat aorta. By Southwestern histochemistry, we observed that control animals did not present staining for NF-κB. In Ang II-infused rats (50ng · kg · 1min<sup>1</sup>) for 72 hours, a clear nuclear staining for NF-κB was located in vascular smooth muscle and endothelial cells. From Ruiz-Ortega et al<sup>42</sup> with permission.](Image 305x532 to 539x718)

![Figure 3. Ang II regulates cell growth and fibrosis through the production of several mediators. The activation of vascular cells by Ang II increases the production of many agents, including growth factors, cytokines, chemokines, that participates in cell proliferation and ECM accumulation. Ang II also increases metalloproteinase production involved in matrix degradation.](Image 47x508 to 283x718)
by each peptide is different. Ang II/NF-κB pathway is mediated by both AT\(_1\) and AT\(_2\), whereas Ang III/NF-κB is mainly by AT\(_1\) (data not shown). Although more studies are necessary, these data could explain the differences observed between ACE inhibitors and AT\(_1\) antagonists in the inflammatory response in various experimental models of kidney diseases.\(^{61}\) Ang IV is another important angiotensin degradation peptide with a potential role in vascular pathophysiology. In atherosclerotic plaques, there is an upregulation of AT\(_4\) receptors.\(^{63}\) and Ang IV increases cell proliferation.\(^{64}\) We have recently observed that in vascular smooth muscle cells, Ang IV activates NF-κB.\(^{65}\) 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**


Role of the Renin-Angiotensin System in Vascular Diseases: Expanding the Field

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

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/