

# The Renin-Angiotensin System as a Risk Factor and Therapeutic Target for Cardiovascular and Renal Disease

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**Abstract.** The renin-angiotensin system (RAS) plays an important homeostatic role in BP regulation, water and salt balance, and tissue growth control under physiologic conditions. On the other hand, a pivotal involvement of the RAS in the pathophysiology of cardiovascular and renal disease is extensively supported by both basic and clinical evidence. In particular, it is today recognized that angiotensin II (AngII), the biologic effector of the RAS, may prompt a number of relevant structural and functional abnormalities through the activation of a complex of cellular effects mostly mediated via its binding with the AT<sub>1</sub> subtype receptors. The key role of these AngII-linked mechanisms of disease is strongly corroborated by large

interventional studies. In fact, pharmacologic interference with RAS activity, by both preventing AngII formation with angiotensin-converting enzyme inhibitors or antagonizing its binding to cell membrane receptors by selective antagonists, is associated with highly beneficial outcomes in major disease conditions (hypertension, diabetes, renal failure, heart failure, myocardial infarction, stroke, and others). This article briefly reviews the current views on the biologic organization of RAS evidence supporting a pathogenic role of the RAS activity in promoting cardiac, vascular, and renal disease, and finally provides the basis for considering inhibition of RAS activity a major target for therapeutic interventions in these conditions.

In the last 20 yr, growing evidence has clearly pointed out that renin-angiotensin system (RAS) activity may represent an ideal target for pharmaceutical treatment in a number of cardiovascular diseases, including hypertension, atherosclerosis, congestive heart failure, renal disease, stroke, myocardial infarction, and others. In fact, evidence provided by the continuously increasing use of angiotensin-converting enzyme (ACE) inhibitors in the clinical practice as well as of angiotensin receptor antagonists has confirmed the value of inhibiting the RAS as an effective approach to reduce cardiovascular risk and cardiovascular and renal complications associated with major diseases (1,2).

Epidemiologic observational studies performed by measuring the levels of activity of the system, for instance on the basis of the plasma renin profile, support the concept that an enhanced activity of the RAS may be associated with higher risk of cardiovascular accidents, such as myocardial infarction. Further extensive evidence supporting this pathogenetic role of RAS derives also from studies performed in high-risk populations (3) and from studies of the polymorphism of RAS components and from transgenic animal models (4–7).

## *The Biologic Organization of the RAS*

To understand how the RAS may be implied in the pathogenesis of cardiovascular and renal disease, it may be useful to synthetically review the functional structure of the system and the role of its abnormalities in driving cardiovascular and renal pathology.

The RAS is classically viewed as an enzymatic proteic cascade, which through the generation of intermediate peptidic products finally leads to the production of angiotensin II (AngII), a small octapeptide. Through its binding with specific G protein-coupled receptors present on the cellular membranes of a number of tissues, AngII represents the terminal biologic effector of the system and is responsible of important and diverse functions that have fundamental relevance in both human physiology and pathology (8,9).

Under physiologic conditions, the biologic functions of AngII are particularly important for the homeostasis of the cardiovascular system, BP, perfusion pressure of a number of organs, salt and water balance, and the mechanisms of cellular growth and replication (10).

A modern view of the enzymatic proteic cascade of the RAS and its components and principal functions is represented in Figure 1. One key element in the activation and the capacity of regulation and response of the system is represented by the biosynthesis and release of renin, a step-limiting enzyme with a specific action on its substrate of cleavage, angiotensinogen, leading to the formation of the decapeptide AngI, which in turn is transformed by the action of the converting enzyme kininase II, which cuts two further amino acids, thus forming AngII. AngII is a biologically active peptide, which through its specific binding to the different angiotensin receptor subtypes with

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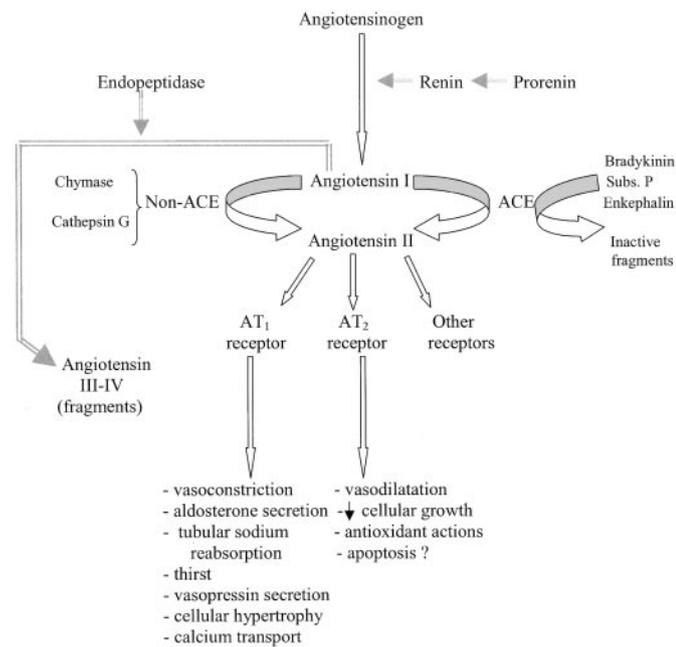


Figure 1. Enzymatic proteic cascade of the renin-angiotensin system (RAS), its compounds, and principal functions. ACE, angiotensin-converting enzyme.

a more marked affinity for the angiotensin receptor subtype AT<sub>1</sub> mediates the principal actions of the RAS in heart, vessels, kidney, brain, and at other levels. It is important to note that the major site of production of renin is localized in the cells of the juxtaglomerular apparatus in the kidney, but also in a number of other tissues in which all the components of the RAS have been identified and characterized (10,11).

The tissue RAS play independent functions and participate in the physiology of different organs and systems (12). These tissue RAS flank the action of the endocrine system by playing autocrine and paracrine functions, which appear to be particularly important in the development of disease processes. Another element that is of great interest today because of the potential therapeutic implications is represented by the existence of enzymatic pathways alternative to ACE such as chymase (13) and endopeptidases, which may produce AngII or other angiotensin fragments in the presence of an effective pharmacologic inhibition of the converting enzyme, thus suggesting the potential role of these alternative pathways in the generation of the AngII under specific physiologic or pathologic conditions. On the other hand, converting enzyme is a non-specific kininase II with a number of substrates different from AngI that may act on bradykinin, enkephalin, substance P, the vasoactive intestinal peptide, and other products. ACE has an ubiquitous distribution, although it is mostly produced at the level of pulmonary endothelium. Finally, AngII, produced through the above-illustrated sequence of biochemical steps, binds mostly to its AT<sub>1</sub> receptors, which mediate most of its biologic effect at the cardiovascular and renal level and at a minor degree to other receptor subtypes, AT<sub>2</sub>, AT<sub>3</sub>, and AT<sub>4</sub>. AngII may then be rapidly degraded to biologic inactive frag-

ments or smaller peptides, which may play relevant action in different tissues (8,14).

### Regulation of the RAS

Multiple factors may regulate biosynthesis and secretion of renin in the juxtaglomerular apparatus. To understand the pathophysiologic impact of the RAS, it is important to point out the dynamic nature of the system, with particular reference to its regulation (10).

One of the most important regulatory factors of the activity of the RAS is represented by the hydrostatic pressure at the level of glomerular and afferent arterioles so that the juxtaglomerular baroreceptor signals inhibit the production of renin when BP is elevated. In contrast under conditions of reduced pressure at this level, increased production and release of renin followed by an enhancement of the activity of the whole renin-angiotensin cascade are observed. A thorough comprehension of this mechanism appears to be fundamental to the understanding of how in the presence of arterial hypertension even normal levels of plasma renin may be inappropriate for the hemodynamic condition, and therefore drug inhibiting the RAS may nonetheless result effective in reducing BP. Other important mechanisms in the regulation of renin are represented by the sympathoadrenergic drive through the action of  $\beta$ -adrenoceptors, by the distal delivery of sodium at the level of macula densa and by the levels of AngII that may influence the production and release of renin through negative feedback mechanisms. Other factors controlling the RAS activity through the production of renin are potassium levels, atrial natriuretic peptide, endothelin, and others. With regard to the influence of the sodium chloride load at the level of macula densa, this represents a fundamental servomechanism that regulates not only the state of activity of the system but also the level of natriuresis, because AngII may in turn influence natriuresis by promoting proximal tubular reabsorption of sodium at the proximal level through direct action as well as through an indirect action by modifying the peritubular interstitial pressure and at distal level through the indirect stimulation of aldosterone. Also the sodium-renin servomechanism appears to be very important for the pathophysiologic interpretation of the RAS. To interpret the activity of the system, in fact, the circulating levels of renin or AngII need to be normalized on the basis of sodium intake or sodium excretion. Also the efficacy of drugs inhibiting the RAS is strongly affected by the state of repletion or depletion of salt and water of the subject. It is unreasonable to expect substantial effectiveness of these drugs in sodium-repleted individuals, whereas a slightly hyposodic diet or the association with a small dose of thiazidic diuretic or a loop diuretic may enhance significantly the responsiveness to these drugs (10).

In summary, under physiologic conditions the RAS plays an important biologic homeostatic function to preserve and to defend the blood volume and salt-water balance, thus affecting the levels of BP and tissue perfusion through a number of multiple complex actions, which integrate in a global effect of vasoconstriction and sodium retention.

Beyond these classical actions of the RAS that we have so far

illustrated, it is important to summarize more recently discovered effects of the RAS that seem to have an important role in regulating growth and remodeling processes in the body. In fact, AngII acts as a growth factor at a number of tissue sites and may also be involved in the processes of inflammation and oxidation (15,16). These actions of AngII need to be better defined; in particular, it is not clear whether AngII is a growth factor *per se* or whether it mostly acts as an amplifier of other growth factors and cytokines. Whatever the case, the reported beneficial actions of drugs antagonizing the RAS in the processes of ventricular hypertrophy in hypertension, or vascular hypertrophy or hyperplasia in atherosclerosis and hypertension, or cardiac remodeling in heart failure (17), or structural and functional abnormalities in the kidney in chronic renal failure strongly support the relevance of the inhibition of trophic action of the RAS. The trophic effect of AngII and its integrated action with other growth factors, such as growth hormone (GH), thyroid stimulating hormone (TSH), insulinlike growth factor-1 (IGF1), endothelin, epidermal growth factor (EGF), fibroblast growth factor (FGF), catecholamines, or cytokines, have been demonstrated, although further definition of these interactions are required, because most of these agonists and AngII share common intracellular pathways of post-receptorial signaling transduction (18).

**Pathophysiology of the RAS**

Although it is clear how the RAS may help to control homeostatic equilibrium of salt-water balance and tissue perfusion in a number of pathophysiologic conditions, such as dehydration, thirst, shock, postural changes, and other situations, it is uncertain how the activity of the RAS is implied in the pathophysiology and progression of important cardiovascular diseases. In the presence of conditions predisposing to hypertrophy, hyperplasia, and tissue remodeling, such as hypertension, atherosclerosis, diabetes, and others, even a normal activity of the RAS may result in inadequately elevated and may thus cause a further progression of the disease.

An experiment performed by John Hall from Arthur Guyton's group (19) several years ago clearly illustrates this concept as a paradigmatic example. The infusion of a low dosage of AngII in the presence of the servomechanism on renal arteries, which prevented the renal autoregulatory ability of kidneys, rapidly led to a marked increase in BP as well as to dramatic sodium retention with a consequent increase of cumulative sodium balance, thus resulting in fluid retention associated with a condition of pulmonary edema. The removal of the servomechanism in the presence of the same degree of AngII infusion was associated with an acute decrease in BP, a brisk rise in natriuresis, and the resolution of the condition of pulmonary edema. This example illustrates how the exposure to the same levels of AngII may produce opposite effects, depending on the pathophysiologic substrate.

If one transfers these concepts to human pathophysiology, it may be more easily understood how the same level of activity of the RAS and thus the same levels of AngII may be an important regulatory factor under physiologic conditions, and may indeed lead to further detrimental conditions and accelerate the progression of the disease in a number of pathologic

conditions. Figure 2 illustrates how AngII may thus represent a key factor in the pathophysiology and development of hypertension, renal disease, atherosclerosis, diabetes and heart failure. In these conditions, in fact, AngII may contribute to produce both vascular and tissue dysfunction, leading respectively to endothelial dysfunction, remodeling and hypertrophy of tissue, fibrosis and atherosclerosis, and loss of cells fibrosis remodeling in ischemia (16). These patterns of changes in the tissue structure represent a reasonable pathophysiologic basis for cardiovascular and renal disease.

Emerging new therapeutic strategies to inhibit the RAS on the basis of angiotensin receptor antagonist use have clarified how AngII may contribute to promote pathologic processes through its cellular effects.

Biological actions of AngII are in fact mediated mostly by two plasma membrane receptors, identified as the AT<sub>1</sub> and AT<sub>2</sub> subtypes. In normal conditions and in adult tissues, AT<sub>1</sub> receptors are more largely expressed and mediate the principal effects of AngII, whereas AT<sub>2</sub> receptors appear to be poorly expressed (8). However, under pathologic conditions, as well as during chronic AT<sub>1</sub> blockade, AT<sub>2</sub> receptor expression may be stimulated and lead to effects that are opposite to those mediated by AT<sub>1</sub> receptor (20), such as vasodilation and inhibition of vascular smooth muscle cell growth, as well as of cardiovascular remodeling and fibrosis (21,22). A specific role of AT<sub>2</sub> receptor in human pathophysiology continues to be poorly defined, and most of the functions of AngII are linked to its binding with the AT<sub>1</sub> subtype receptor and the activation of the related intracellular post-receptorial signaling pathway. AT<sub>1</sub> receptors belong to the seven-membrane domain superfamily of G protein-coupled receptors and are expressed in a number of different tissues, including heart, brain, kidney, lung, liver, adrenal glands, and mostly vascular smooth muscle cells. AT<sub>1</sub> receptors are coupled to a variety of intracellular signaling molecules, including phospholipases, adenylate cy-

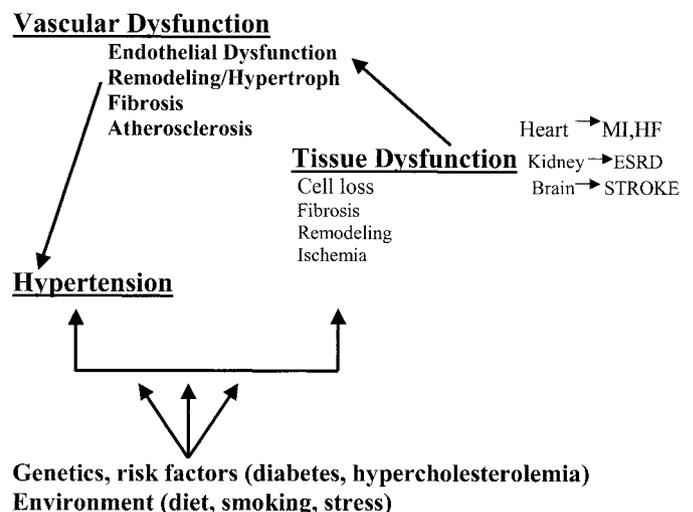


Figure 2. AngII as a key factor in pathophysiology and development of cardiovascular disease. MI, myocardial infarction; HF, heart failure; ESRD, end-stage renal disease.

class, voltage-dependent calcium channels, and a variety of kinases involved in phosphorylation cascades. Depending on the cell and organ type, stimulation of these signal transduction pathways leads to cellular contraction, hypertrophy proliferation, and/or apoptosis (8,23).

Recent work from our laboratory has shown the opposite influence of AT<sub>1</sub> and AT<sub>2</sub> receptors on growth and has particularly clarified how the two different subtype receptors may influence the growth and remodeling by integrating the processes linked to different growth factors of agonists

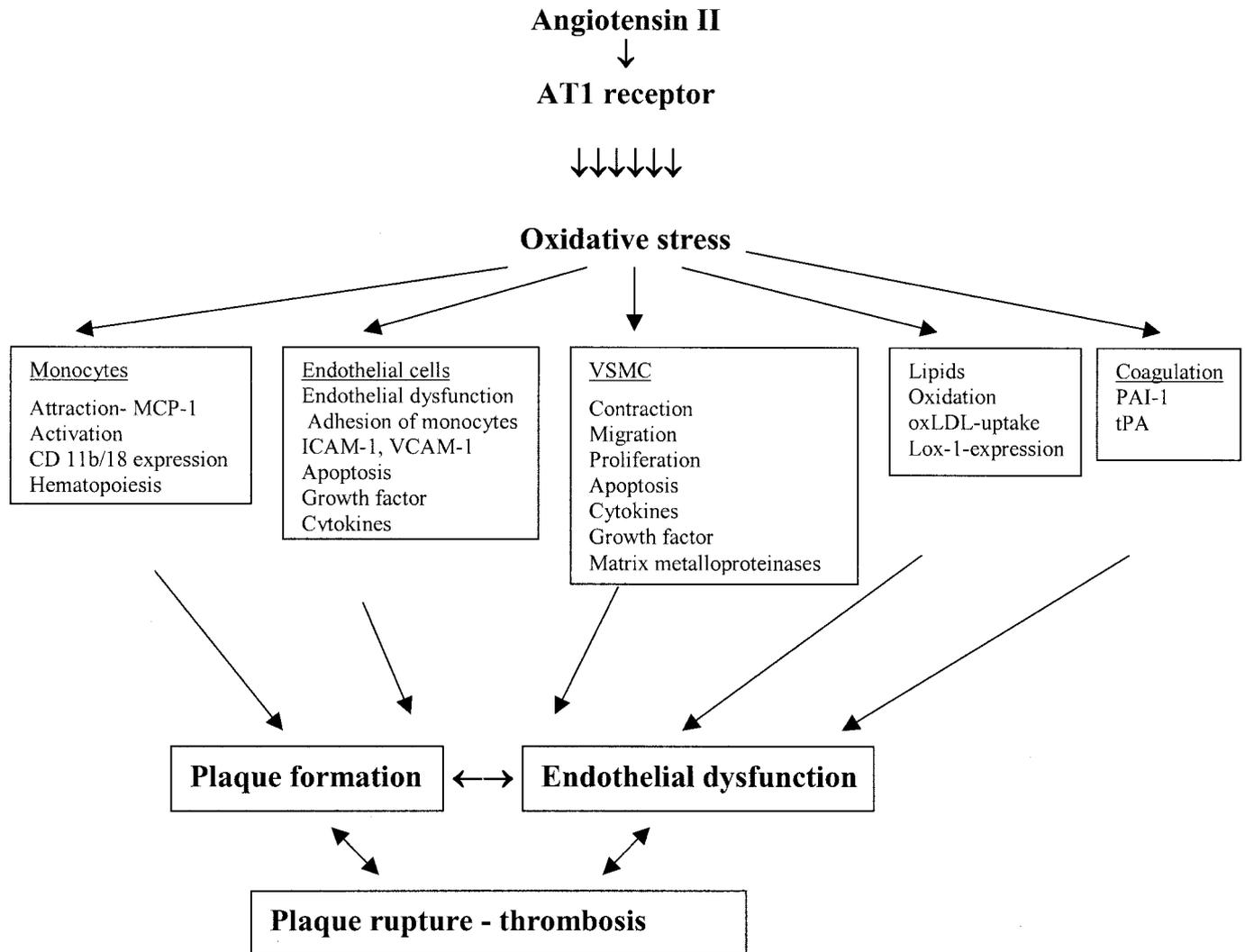


Figure 3. AT<sub>1</sub> induces oxidative stress and atherosclerosis. MCP-1, monocyte chemoattractant protein-1; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1; VSMC, vascular smooth muscle cells; LOX-1, oxLDL receptor; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator.

Table 1. Proven benefits of blocking the RAS<sup>a</sup>

Patient Type	Evidence of Benefit		
Hypertension <sup>b</sup>	↓ Mortality	↓ Heart failure	↓ Ischemic events
High-risk patients	↓ Mortality	↓ Heart failure	↓ Ischemic events
CAD without LVD	↓ Mortality	↓ Heart failure	↓ Ischemic events
Acute MI	↓ Mortality	↓ Heart failure	
LVD	↓ Mortality	↓ Heart failure	↓ Ischemic events
Heart failure	↓ Mortality	↓ Heart failure	↓ Ischemic events
Renal disease	↓ ESRD/mortality	↓ Heart failure	
Stroke	↓ Mortality		↓ Ischemic events

<sup>a</sup> CAD, coronary artery disease; LVD, left ventricular dysfunction; MI, myocardial infarction.

<sup>b</sup> Hypertension with LVD or DM.

(18). Elucidation of the interplay in the AngII receptor network represents an important area of research and may lead to significant advances in the treatment of cardiovascular disease.

Finally, in the last few years, increasing attention has been focused on the influence of AngII on the production and release of reactive oxygen species. This mechanism, which is selectively stimulated via the AT<sub>1</sub> receptor subtype and most likely reduced by the stimulation of AT<sub>2</sub> receptors, has a central role in the development of atherosclerosis and degenerative processes in cardiovascular and renal diseases (24,25).

Figure 3 synthesizes how AT<sub>1</sub> receptors may promote oxidative stress and how the effect of oxidative stress may contribute, through a complex and integrated action, to plaque formation, endothelial dysfunction, and thrombosis (15). It is clear that the AT<sub>1</sub> and AT<sub>2</sub> angiotensin receptor network may thus play an important role in oxidative stress and atherogenesis, and this novel field of research may provide the basis for a better understanding of the efficacy of intervention aimed at reducing the effects of the activation of the RAS at the cardiovascular and renal levels. In fact, although we have learned that inhibition of the RAS by ACE-inhibition or by AngII receptor antagonists may provide a number of favorable effects in terms of organ protection and reduction of events in the most important cardiovascular conditions (Table 1), it still represents a challenge to define exactly how these drugs achieve this important cardiovascular and renal end points in terms of cellular mechanism (26–31).

## References

- Khalil ME, Basher AW, Brown EJ, Alhaddad IA: A remarkable medical story: Benefits of angiotensin-converting enzyme inhibitors in cardiac patients. *J Am Coll Cardiol* 37: 1757–1764, 2001
- Yusuf S, Sleight P, Bosch J, Davies R, Dagenais G: The heart outcomes prevention evaluation study investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 342: 145–153, 2000
- Volpe M, Lembo G, De Luca N, Lamenza F, Indolfi C, Condorelli G, Trimarco B: Converting enzyme inhibition prevents the effects of atrial natriuretic factor on arterial baroreflexes. *Circulation* 81: 1214–1221, 1990
- Volpe M, Camargo MJF, Mueller FB, Campbell WG Jr, Sealey JE, Pecker MS, Sosa RE, Laragh JH: Relation of plasma renin to end organ damage and to protection of K<sup>+</sup> feeding in stroke-prone hypertensive rats. *Hypertension* 15: 318–326, 1990
- Roig E, Perez-Villa F, Morales M, Jimenez W, Orus J, Heras M, Sanz G: Clinical implications of increased plasma angiotensin II despite ACE inhibitor therapy in patients with congestive heart failure. *Eur Heart J* 21: 14–16, 2000
- Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L: Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Consensus Trial Study Group. *Circulation* 82: 1730–1736, 1990
- Volpe M, Lembo G, De Luca N, Lamenza F, Tritto C, Ricciardelli B, Molaro M, De Campora P, Condorelli G, Rendina V: Abnormal hormonal and renal responses to saline load in hypertensive patients with parental history of cardiovascular accidents. *Circulation* 84: 92–100, 1991
- Timmermans PB, Wong PC, Chiu AT, Herblin WF, Benfield P, Carini D, Lee RJ, Wexler RR, Sayre JA, Smith RD: Angiotensin II receptors and angiotensin II antagonist. *Pharmacol Rev* 45: 205–211, 1993
- de Gasparo M, Catt KJ, Inagami T, Wright JW, Unger T: International union of pharmacology. XXIII. The angiotensin receptors. *Pharmacol Rev* 52: 415–472, 2000
- Laragh JH, Sealey JE: The renin-angiotensin-aldosterone hormonal system and regulation of sodium, potassium, and blood pressure homeostasis. In: *Handbook of Physiology*, edited by Orloff J, Berliner RW, Bethesda, MD, American Physiological Society, 1973, pp 831–907
- Elding O, Gohlke P, Paul M, et al.: The RAS (renin angiotensin system): Physiology and pathophysiology. In: *ACE Inhibitors. Current Use and Future Prospects*, edited by Schachter M, London, Martin Dunitz, 1995, pp 3–41
- Johnston CI: Renin-angiotensin system: A dual tissue and hormonal system for cardiovascular control. *J Hypertens Suppl* 10: S13–S26, 1992
- Urata H, Nishimura H, Ganten D: Chymase-dependent angiotensin II forming systems in humans. *Am J Hypertens* 9: 277–284, 1996
- Goodfriend TL, Elliot ME, Gatt KJ: Angiotensin receptors and their antagonists. *N Engl J Med* 334: 1649–1654, 1996
- Nickenig G, Harrison DG: The AT<sub>1</sub>-type angiotensin receptor in oxidative stress and atherogenesis. Part I: Oxidative stress and atherogenesis. *Circulation* 105: 393–396, 2002
- Nickenig G, David G, Harrison DG: The AT<sub>1</sub>-type angiotensin receptor in oxidative stress and atherogenesis. Part II: AT<sub>1</sub> receptor regulation. *Circulation* 105: 530–536, 2002
- Wolny A, Clozel JP, Rein J, Mory P, Vogt P, Turino M, Kiowski W, Fischli W: Functional and biochemical analysis of angiotensin II-forming pathways in the human heart. *Cir Res* 80: 219–227, 1997
- De Paolis P, Porcellini A, Savoia C, Lombardi A, Gigante B, Frati G, Rubattu S, Musumeci B, Volpe M: Functional cross-talk between Angiotensin II and EGF receptors in NIH3T3 fibroblast. *J Hypertens* 20: 693–699, 2002
- Hall JE, Granger JP, Hester RL, Coleman TG, Smith MJ jr, Cross RB: Mechanisms of escape from sodium retention during angiotensin II hypertension. *Am J Physiol* 246: F627–F634, 1984
- De Paolis P, Porcellini A, Gigante B, Giliberti R, Lombardi A, Savoia C, Rubattu S, Volpe M: Modulation of AT<sub>2</sub> subtype receptor gene activation and expression by AT<sub>1</sub> receptor in endothelial cells. *J Hypertens* 17: 1873–1877, 1999
- Horiuchi M, Lehtonen YYA, Daviet L: Signaling mechanism of the AT<sub>2</sub> angiotensin II receptor: Crosstalk between AT<sub>1</sub> receptors in cell growth. *TEM* 10: 391–396, 1999
- Horiuchi M, Akishita M, Dzau VJ: Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. *Hypertension* 33: 613–621, 1999
- Unger T, Chung O, Csikos T, Culman J, Gallinat S, Gohlke P, Hohle S, Meffert S, Stoll M, Stroth U, Zhu YZ: Angiotensin receptors. *J Hypertens Suppl* 14: S95–S103, 1996
- Horiuchi M, Hayashida W, Kambe T, Yamada T, Dzau VJ: Angiotensin type 2 receptor dephosphorylate Bcl 2 by activating mitogen activated protein kinase phosphatase 1 and induces apoptosis. *J Biol Chem* 272: 19022–19026, 1997
- Tsutsumi Y, Matsubara H, Masaki H, Kurihara H, Murasawa S, Takai S, Miyazaki M, Nozawa Y, Ozono R, Nakagawa K, Miwa T, Kawada N, Mori Y, Shibasaki Y, Tanaka Y, Fujiyama S, Koyama Y, Fujiyama A, Takahashi H, Iwasaka T: Angiotensin I

- type 2 receptor overexpression activates the vascular kinin system and causes vasodilation. *J Clin Invest* 104: 925–935, 1999
26. The SOLVD Investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 325: 293–302, 1991
  27. Dries DL, Exner DV, Gersch BJ, Cooper HA, Carson PE, Domanski MJ: Racial differences in the outcome of left ventricular dysfunction. *N Engl J Med* 340: 609–616, 1999
  28. Progress Collaborative Group: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 358: 1033–1041, 2001
  29. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klingner GH, Neaton J, Sharma D, Thiyagarajan B: Effect of losartan compared with captopril on mortality in patients with the symptomatic heart failure: Randomised trial-the Losartan-Heart Failure Survival Study ELITE II. *Lancet* 355: 1582–1587, 2000
  30. Dickstein K: Elite II and Val-HeFT are different trials: Together what do they tell us? *Curr Control Trials Cardiovasc Med* 2: 240–243, 2001
  31. Brenner BM, Cooper ME, Zeeuw Dd D, Grunfeld JP, Keane WF, Kurokawa K, McGill JB, Mitch WE, Parving HH, Remuzzi G, Ribeiro AB, Schluchter MD, Snavely D, Zhang Z, Simps R: The losartan renal protection study-rationale, study design and baseline characteristics of RENAAL (reduction of Endpoints in NIDDM with angiotensin II antagonist losartan). *J Renin Angiotensin Aldosterone Syst* 1: 328–334, 2000