Angiotensin II plays a central role in the regulation of systemic arterial pressure through its systemic synthesis via the renin-angiotensin-aldosterone cascade. It acts directly on vascular smooth muscle as a potent vasoconstrictor. In addition, it affects cardiac contractility and heart rate through its action on the sympathetic nervous system. Angiotensin II also alters renal sodium and water absorption through its ability to stimulate the zona glomerulosa cells of the adrenal cortex to synthesize and secrete aldosterone. Furthermore, it enhances thirst and stimulates the secretion of the antidiuretic hormone. Consequently, angiotensin II plays a critical role in both the acute and chronic regulation of blood pressure through its systemic endocrine regulation.

A potent neurohormone that regulates systemic arterial pressure, angiotensin II also affects vascular structure and function via paracrine and autocrine effects of local tissue-based synthesis. This alternate pathway of angiotensin II production is catalyzed in tissues via enzymes such as cathepsin G, chymostatin-sensitive angiotensin II–generating enzyme, and chymase. Intratissue formation of angiotensin II plays a critical role in cardiovascular remodeling. Upregulation of these alternate pathways may occur through stretch, stress, and turbulence within the blood vessel. Similar processes within the myocardium and glomeruli of the kidney may also lead to restructuring in these target organs, with consequent organ dysfunction. Additionally, angiotensin II may increase receptor density and sensitivity for other factors that modulate growth of vascular smooth muscle, such as fibroblast growth factor, transforming growth factor β-1, platelet-derived growth factor, and insulin-like growth factors. Atherosclerosis may also be related, in part, to excessive angiotensin II effect on the vessel wall, which causes smooth muscle cell growth and migration. It also activates macrophages and increases platelet aggregation. Angiotensin II stimulates plasminogen activator inhibitor 1 and directly causes endothelial dysfunction. Other postulated effects of angiotensin II on vascular structure that could promote atherogenesis include inhibition of apoptosis, increase in oxidative stress, promotion of leukocyte adhesion and migration, and stimulation of thrombosis.

Inhibition of angiotensin II synthesis with an angiotensin-converting enzyme inhibitor has been demonstrated to be beneficial in modifying human disease progression. This is clearly apparent in clinical trials involving patients with diabetic nephropathy, postmyocardial infarction, or advanced degrees of systolic heart failure. Thus, angiotensin II is an excellent target for pharmacologic blockade. Not only does it play a pivotal role in both the acute and chronic regulation of systemic arterial pressure, but it also is an important modulator of cardiovascular structure and function and may be specifically involved in disease progression. Modification of angiotensin II effect may therefore serve a dual purpose. Not only will blood pressure reduction occur with less stretch, stress, and turbulence of the vascular wall, but there will also be less stimulation, either directly or indirectly, for restructuring and remodeling of the cardiovascular tree.


KEY WORDS: Angiotensin II, type 1 receptor, type 2 receptor, structure, function.
A substantial evolution in hypertension therapeutics has occurred over the past four decades. Only in the past 20 years have efforts been focused on pharmacotherapy that attenuates the activity of the renin-angiotensin-aldosterone system (RAAS). Three major therapeutic classes of drugs have this capability: β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers. Each therapeutic class exerts its inhibitory effect in different ways. β-Blockers primarily inhibit renin production, thus dampening the systemic RAAS. On the other hand, ACE inhibitors inhibit the converting enzyme responsible for the cleavage of peptide fragments off angiotensin I to create the active moiety angiotensin II. Angiotensin receptor blockers do not inhibit the formation of angiotensin II, but occupy its high-affinity type 1 (AT1) receptor, thus inhibiting its ability to exert its biologic activity.

The RAAS modifies blood pressure through a variety of effects in different tissues, including alterations in vascular tone, augmentation of the activity of the sympathetic nervous system, changes in structure and function of cardiovascular beds, and renal salt and water homeostasis. As will be discussed next, these far-reaching effects of this single system make it an ideal target to antagonize therapeutically. Not only is this system an important regulator of blood pressure homeostasis, but it also has a critical influence on cardiovascular remodeling and restructuring (Figure 1). This interesting dichotomy illustrates the need for improved understanding of angiotensin II, both its primary and secondary effects and how it influences vascular biology in health and in disease.

ACUTE VERSUS CHRONIC EFFECTS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

When the kidneys sense diminished effective arterial blood volume, renin is released by the macula densa of the juxtaglomerular apparatus. Once in the circulation, renin catalyzes the conversion of angiotensinogen, which is released by the liver, to angiotensin I. When angiotensin I comes into contact with the angiotensin-converting enzyme, which sits on the surface of vascular endothelium, it is converted to the active moiety angiotensin II. Angiotensin II preferentially binds to its high-affinity AT1 receptor site in a variety of tissues and exerts its biologic activity. This acute response of the endocrine RAAS to perturbations in systemic arterial pressure is critical for the fight-or-flight response and our ability to assume upright posture. Through multiple efferent pathways, this system can raise blood pressure, but primarily by increasing vasoconstriction and extracellular fluid volume. Not only is angiotensin II a powerful vasoconstrictor, it also directly stimulates the reabsorption of sodium in a proximal tubule in the kidney and augments adrenal production of aldosterone, which enhances distal tubular sodium reabsorption. Angiotensin II also alters glomerular hemodynamics, predominantly by inducing postglomerular vasoconstriction, thus increasing peritubular capillary colloid osmotic pressure and decreasing peritubular capillary hydrostatic pressure. These changes result in enhanced sodium and water transfer from the tubular lumen to the peritubular capillary. Angiotensin II can also raise blood pressure by augmenting catecholamine release from sympathetic nerve endings, thus enhancing myocardial contractility. It also is the most potent dipsogen known.

Despite the important benefits of the RAAS in regulating blood pressure homeostasis, there is concern that chronic production of angiotensin II may result in remodeling and restructuring in various cardiovascular organs, specifically blood vessels, the heart, and the kidneys. Although the peripheral or systemic RAAS as we classically understand it may be involved in this process, it is the autocrine or paracrine production of angiotensin II through a variety of different pathways that may be most important in promoting cardiovascular restructuring and remodeling. There are several enzymes that may catalyze the production of angiotensin II within tissues, including cathepsin G, chymostatin-sensitive angiotensin II–generating enzyme, and chymase (Figure 2). It is this intratissue formation of angiotensin II that may play a critical role in the progression of vascular disease. Additionally, it is well known that upregulation of these alternate pathways for angiotensin II synthesis within the blood vessel wall may occur after vascular injury or during stretch, stress, turbulence, and mechanical injury. It is likely that similar processes occur within the myocardium during pressure or volume overload, leading to systolic heart failure, or in the glomeruli of the kidney during glomerular capillary hypertension, in which the associated shearing stress and turbulence ultimately lead to the development of glomerular sclerosis. Thus, the relationship among angiotensin II, blood pressure homeostasis, and cardiovascular restructuring and remodeling is a delicate one. Angiotensin II can elevate blood pressure through a variety of different mechanisms on different target organs. An increase in pressure can result in mechanical stress and physical injury to the vessel wall, leading to localized upregulation of angiotensin II synthetic pathways. Similarly, angiotensin II, produced either systemically or within the vessel wall, may also upregulate similar synthetic pathways, ultimately leading to alterations in the structure and function of blood vessels. These latter changes may alter the compliance of blood vessels and elevate systemic arterial pressure, thus resulting in a vicious circle leading to progressive vascular injury. Therefore, therapeutic strategies that are
geared toward aggressive blood pressure reduction and that antagonize the effects of angiotensin II may be optimal in protecting vascular structure and function.

ANGIOTENSIN II–MEDIATED SIGNAL TRANSDUCTION VIA THE AT₁ RECEPTOR

The majority of the known cardiovascular activities of angiotensin II are mediated through the binding of angiotensin II to its high-affinity AT₁ receptor site (Figure 3).³,¹¹–¹³ This receptor is a member of the seven transmembrane domain receptor superfamily and is coupled to various G proteins. Its effectors include adenylate cyclase, phospholipases C, D, and A, and even a calcium channel. Stimulation of the AT₁ receptor may also trigger a variety of different tyrosine kinases and stimulate the early gene response controlling cell growth.¹¹–¹³ A single transduction event stimulated by angiotensin II is similar to those stimulated by other growth factors. Some of the similarities between angiotensin II and other growth factors include the activation of phospholipase C, inositol triphosphate formation, calcium mobilization, activation of protein kinase C, induction of proto-oncogenes, and protein tyrosine phosphorylation.¹⁴–¹⁸ In fact, it is the reversible protein phosphorylation that is a common mechanism by which many cell types regulate growth stimulatory signals. Protein phosphorylation is regulated by the balanced action between the protein kinases and the protein phosphatases present in every cell. Angiotensin II has been demonstrated to be involved in the vascular smooth muscle cell growth seen in disease as well as in clinical situations such as atherosclerosis and restenosis of vascular beds after angioplasty.⁵–⁸,¹⁹,²⁰ It has therefore been important to identify and understand the regulation of the activity of the various protein kinases and phosphatases involved in angiotensin II–mediated signal transduction.

Angiotensin II exerts substantial influence on the blood vessel wall and, in particular, vascular smooth muscle, through a variety of effects, predominantly by transducing signals leading to growth, remodeling, and restructuring (Figure 4). It is important to realize that blood pressure itself is an important instigator of this process, through mechanical stress, stretch, and turbulence. Additionally, vascular injury may also stimulate local production of angiotensin II through a variety of different mechanisms and result in a proliferative process and progressive atherosclerotic changes.

Angiotensin II not only has direct stimulatory effects on transducing signals, leading to restructuring and remodeling, but it can also affect factors that modulate the structure and function of cultured vascular smooth muscle cells. For example, angiotensin II can increase the activity of fibroblast growth factor, transforming growth factor β-1, platelet-derived growth factor...
factor, and insulin-like growth factors in remodeling and restructuring.\textsuperscript{5–8,18,21} In particular, its relationship with transforming growth factor $\beta$-1 can form a vicious circle, as this growth factor is also a renin secretagogue, which can lead to greater production of angiotensin II.\textsuperscript{21} Likewise, angiotensin II can also upregulate transforming growth factor $\beta$-1 production.\textsuperscript{22} Thus, both by direct and indirect mechanisms, angiotensin II promotes vascular smooth muscle cell growth.

Angiotensin II has numerous hypothesized atherosclerotic effects. In addition to promoting smooth muscle cell growth and migration, it can also activate macrophages and increase their ability to attach to and invade the vascular wall, ultimately creating a foam cell that can evolve into an atherosclerotic plaque.\textsuperscript{23} This occurs through alteration of the redox state, whereby redox-sensitive genes, including MCP-1 and VCAM, are activated and serve as chemoattractants to circulating monocytes, which facilitates not only their migration but also adherence and their ability to interpose themselves between the endothelium and vascular smooth muscle. Angiotensin II also increases platelet aggregation, stimulates plasminogen activator inhibitor 1, and promotes endothelial dysfunction and oxidative stress of the blood vessel.\textsuperscript{24–27} One of the expected outcomes from stimulation of oxidative stress is the upregulation of expression of adhesion molecules and the initiation of the inflammatory response that mediates atherosclerosis. All of these activities can be blocked by antagonizing the ability of angiotensin II to bind to its high-affinity AT$_1$ receptor binding site.

In summary, angiotensin II, through a variety of different mechanisms, whether direct or indirect, can substantially affect the structure, function, and atherosclerotic risk of a blood vessel. Angiotensin II stimulates growth, inhibits apoptosis, and promotes smooth muscle cell growth and migration through a variety of different mechanisms, predominantly by causing oxidative stress and altering the redox potential of the blood vessel (Figure 5). Angiotensin II promotes platelet aggregation and thrombosis and causes endothelial dysfunction. All of these factors are known to increase vascular tone, promote remodeling and restructuring, and augment atherosclerotic risk.

**THE FUNCTION OF OTHER, LOWER-AFFINITY, ANGIOTENSIN II BINDING SITES**

At least three other angiotensin II binding sites have been described.\textsuperscript{8,11–13} Only the type 2 (AT$_2$) receptor binding site has been reasonably well studied. The function of this receptor is still poorly understood. It, like the AT$_1$ receptor binding site, is a seven transmembrane domain receptor, but it is coupled to a different G protein and has totally different and opposite actions, compared with the AT$_1$ site, when stimulated.\textsuperscript{8} It activates a phosphatase that will dephosphorylate, whereas the AT$_1$ receptor turns on a kinase that tends to phosphorylate when activated. This effect results in the inactivation of a key enzyme known as mitogen-activated protein kinase, which is a critical kinase in the pathway leading to the transduction of angiotensin II signal for vascular smooth muscle cell growth.\textsuperscript{33,34} Thus, stimulation of the AT$_2$ receptor counterbalances or possibly opposes the effects of AT$_1$.
receptor stimulation. The result is inhibition of proliferation, vasodilation, and natriuresis and stimulation of apoptosis.

However, the clinical significance of AT2 receptor stimulation is not known. It is transiently expressed during fetal life. Increased expression of the AT2 receptor occurs during various pathologic situations such as cardiac failure or vascular injury. In the human heart, the AT2 to AT1 ratio increases in the failing myocardium, suggesting a possible involvement of the AT2 receptor subtype in the pathophysiology of progressive cardiac dysfunction. Thus, this receptor may serve as a modulator of growth signals, particularly in situations of disease such as the failing heart, in which there is marked activation of catecholamines, angiotensin, growth factors, cytokines, etc. Experimental studies have demonstrated that AT1 receptor blockade attenuates cardiac hypertrophy and interstitial fibrosis in a rat after coronary ligation. However, if an AT2 receptor antagonist is also administered, the benefit of AT1 receptor blockade is abolished. This simple experimental study suggests that part of the action of AT1 receptor antagonism is to shunt angiotensin II binding to lower-affinity binding sites such as the AT2 receptor, which may exert an effect diametrically opposite to that which would have resulted from AT1 stimulation, perhaps even amplifying the effect of AT1 receptor blockade (Figure 6). If one considers all of the possible AT1 receptor-mediated effects after angiotensin binding, one could imagine that AT1 receptor blockade could be beneficial by shifting angiotensin binding to the AT2 receptor in the hope of attenuating and perhaps reversing vascular damage, particularly in already damaged tissues.

ANGIOTENSIN II AND THE HEART

The cardiac response to mechanical stretch, stress, tension, and turbulence is similar to that which occurs in the blood vessel. As shown in Figure 7, there are known clinical scenarios that result in left ventricular pressure overload. This is particularly true for hypertension itself, particularly systolic hypertension. With cardiovascular senescence, the aorta loses much of its elastic recoil. Consequently, a marked increase in left ventricular pressure occurs with each systolic contraction of the heart, resulting in a substantial increase in left ventricular wall tension. Over time, this increasing wall tension and workload results in hypertrophic changes of the heart. One can see similar findings with other cardiac pressure overload scenarios, such as aortic stenosis and coarctation of the aorta.

Additionally, volume overload situations also increase left ventricular work and wall tension. Immediately after myocardial infarction or after acute valvular insufficiency, increases in ventricular volume cause an increase in left ventricular diameter. Laplace’s law notes that an increase in radius increases wall tension. Whatever the clinical situation, either left ventricular pressure overload or left ventricular volume overload, or both, the result is an increase in left ventricular wall tension and size and augmentation of angiotensin II synthetic pathways, leading to myocardial hypertrophy and, ultimately, systolic dysfunction.

Reducing blood pressure results in a reduction in ventricular pressure and helps attenuate hypertrophic changes of the heart. In clinical disease states such as systolic heart failure and post–myocardial infarction with left ventricular dysfunction, in which there are high circulating levels of catecholamines and activation of the RAAS, pharmacologic blockade of angiotensin II formation assumes even more importance. Reducing blood pressure and either inhibiting the synthesis of angiotensin II or blocking the AT1 receptor result in a reduction in the rate of progression of left ventricular remodeling and improved patient surviv-
Proposed Angiotensin II Influence on the Kidney

- Renal Injury
- Glomerular Hypertrophy
- Blood Pressure

Induction of Angiotensin II Pathways at the Tissue Level
(mesangial cells/vascular endothelium)

- Local Angiotensin II Production
- Glomerulosclerosis


Thus, an important cause-and-effect relationship exists between pressure and volume overload in the heart, augmented synthesis of angiotensin II, and the rate of progression of cardiac remodeling and restructuring.

ANGIOTENSIN II AND THE KIDNEYS

Progressive deterioration of renal function in patients with hypertension, diabetes, and primary renal diseases is a continuing medical problem. Once clinical signs of progressive deterioration of renal function commence, even aggressive efforts to control the underlying disease frequently fail to forestall the progression of renal failure. A variety of mechanisms may be involved in the inevitable decline of renal function associated with hypertension, diabetes, and other primary renal diseases, but angiotensin II likely plays a primary role. Abnormalities of systemic blood pressure, glomerular hemodynamics, and mesangial matrix production and degradation involve a number of the processes that may be influenced by angiotensin II and can adversely influence the rate of progression of renal disease.

With declining numbers of filtering nephron segments, adaptive mechanisms facilitate the ability of the kidney to maintain net overall function. The changes that occur include increases in glomerular size, glomerular capillary pressure, and systemic pressure (Figure 8). These perturbations result in increasing mechanical stress and shearing forces in intrarenal vascular beds and within the glomeruli, and activate intrarenal production of angiotensin II.

Experimental studies have demonstrated the therapeutic advantage of inhibiting angiotensin II formation in the kidney. The associated reduction in both systemic and glomerular capillary pressure and the improvement in glomerular perme selectivity to albumin and proteins result in a stabilization of renal function. The therapeutic benefit of ACE inhibitors has been demonstrated convincingly in both experimental and human clinical studies. However, the exact mechanism (in addition to blood pressure and glomerular capillary pressure reduction) whereby inhibition of angiotensin II results in an improved ability to delay progression of renal disease is not thoroughly understood.

One consideration is that the accumulation of extracellular matrix in the mesangial region and collapse of the glomerular capillary wall may be critical factors in progressive renal dysfunction. In vitro studies have shown that angiotensin II can stimulate the production and inhibit degradation of extracellular matrix independent of the systemic milieu. Moreover, it has been well demonstrated that shearing force and stress within the glomeruli can also augment extracellular matrix production. Extracellular matrix can be accumulated not only by the upregulation of its synthesis but also by downregulation of its degradation. Angiotensin II stimulates such inhibitors of extracellular matrix degradation as plasminogen activator inhibitor-1 via both AT1 and non–type 1 receptor–dependent pathways. Consequently, angiotensin II can not only upregulate extracellular matrix production but can also inhibit its degradation. This dual effect can have a significant impact on the development of glomerulosclerosis. Moreover, some of the experimental benefits of an ACE inhibitor in delaying progression of glomerulosclerosis may be related to its ability to activate matrix degradation by inhibiting plasminogen activator inhibitor formation.

The antiproteinuric properties of drugs that inhibit the RAAS may also have a substantial impact on the rate of development of renal disease. Clinical studies have demonstrated that suppression of proteinuria is associated with attenuation of progressive loss of glomerular filtration rate. One mechanism that may be important is related to proteinuria-induced activation of the complement cascade, which could lead to inflammatory interstitial changes. Proteinuria can also affect lipid metabolism, leading to lipoprotein abnormalities that can cause vascular disease, including that of the kidney. Moreover, there is concern that in patients with diabetes, glycosylated albumin may be nephrotoxic, inciting an inflammatory response leading to glomerular and interstitial damage.

In summary, both experimental and clinical trials have demonstrated that inhibition of the angiotensin II
effect, in addition to reducing blood pressure, can provide a substantial advantage in delaying progression of renal disease. This benefit is in large part related to both systemic and glomerular capillary pressure reduction, reduction of urinary albumin and protein excretion, inhibition of mesangial matrix production, and augmentation of matrix degradation. These benefits in delaying progression of renal disease may also be related to inhibition of angiotensin II formation as well as to inhibition of other known growth factors or soluble mediators of fibrosis such as transforming growth factor β-1, whose activity is influenced by angiotensin II.

ANGIOTENSIN II, SALT, AND BLOOD PRESSURE

Angiotensin II plays a primary role in the regulation of blood pressure, as previously discussed, but its importance in the salt-replete state has come into question. Patients with low peripheral renin activity and blood pressure salt sensitivity are considered to be less responsive to antihypertensive drugs that block the RAAS, compared with other therapies. However, in light of what is known about the effects of angiotensin II on both glomerular hemodynamics and renal tubular sodium and water handling, an alternate view is that the excessive vasoconstriction occurring in the kidney might interfere with renal perfusion and thus diminish renal salt and water excretion. Additionally, excessive angiotensin II–dependent effluent glomerular arteriolar vasoconstriction can reduce peritubular capillary hydrostatic pressure, increase peritubular colloid osmotic pressure, and enhance the driving force for sodium and water reabsorption. Consequently, it may make more physiologic sense to use a dose of a drug that blocks angiotensin effect in the kidney sufficient to improve renal blood flow, facilitate sodium and water excretion, and ultimately lower blood pressure. In fact, this is what has been described in clinical studies in which sufficient doses of either ACE inhibitors, renin inhibitors, or angiotensin receptor blockers have been used as renal vasodilators to facilitate blood pressure reduction. Comparative clinical trials suggest an advantage of the angiotensin receptor blocker or a renin inhibitor over the ACE inhibitor for renal vasodilation. These data suggest that inhibition of angiotensin II effect is the critical factor with regard to renal vasodilation, as opposed to augmentation of bradykinin production, as would also occur with the ACE inhibitor.

CONCLUSIONS

Angiotensin II plays a critical role in the regulation of systemic arterial pressure and influences vascular structure and function and disease progression. This is predominantly mediated through an effect on its high-affinity AT1 receptor binding site. Angiotensin II is an excellent target for pharmacologic blockade, as blood pressure reduction will occur not only through vasodilation and enhanced natriuresis, but also through inhibition of structural changes that could alter vascular compliance. This dual mechanism of benefit may be particularly advantageous in patients with advanced target organ injury, such as those with systolic heart failure or diabetic nephropathy. This is not to say that blocking the RAAS is a substitute approach for adequate blood pressure reduction. It is not. Aggressive blood pressure control and pharmacologic blockade of the RAAS makes the most physiologic sense in reducing the likelihood of vascular changes in hypertensive disease. Early clinical trials demonstrate that angiotensin receptor blockers have hemodynamic properties similar to those of ACE inhibitors and similar ability to reduce proteinuria. Short-term results from clinical trials using angiotensin receptor blockers in patients with heart failure suggest that they may be as good as ACE inhibitors—and perhaps may even have some advantages over ACE inhibitors—in reducing withdrawal from therapy and maybe even in reducing the incidence of death. Thus, the experimental and clinical data presented herein suggest that the RAAS is an excellent target for hypertension management.

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