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Reviews

Angiotensin-II Receptors: New Targets for Antihypertensive Therapy

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Summary: The renin–angiotensin system regulates blood pressure and sodium homeostasis through a series of coordinated substrate–enzyme interactions. These interactions result in the production of angiotensin II (AII), which exerts a number of diverse biologic effects mediated through AII cell-surface receptors. Dysregulation of this system is implicated in the pathogenesis of various forms of hypertension. Traditional therapy for hypertension has included angiotensin-converting enzyme inhibitors, which block the production of AII. However, a new class of drugs, AT_1-receptor blockers, now offers a number of benefits by specifically blocking the effects of AII at its physiologically relevant receptor.

Key words: hypertension, renin–angiotensin system, angiotensinogen, angiotensin II, AT_1 receptor, AT_1-receptor blocker, losartan

Introduction

The renin–angiotensin system is a key regulator of extracellular fluid volume and arterial blood pressure. This system consists of a cascade of coordinated interactions between substrate and enzymes that results in the production of the multifunctional peptide angiotensin II (AII) (Fig. 1). In every organ system, the biologic effects of AII are mediated through its interaction with specific receptors on cell membranes. In this article, we review developments in the understanding of the biology of angiotensin receptors and discuss the implications of new antihypertensive agents that target angiotensin receptors.

The renin–angiotensin system plays a critical role in the control of systemic blood pressure, and dysregulation of the renin–angiotensin system causes hypertension in humans. As Figure 1 shows, the first step in the renin–angiotensin system cascade involves renin acting on angiotensinogen to form the decapeptide angiotensin I. Most of the substrate molecule angiotensinogen is produced in the liver, although smaller quantities of angiotensinogen are produced in several other tissues, such as the kidney. While the effects of increased levels of plasma renin on blood pressure have long been recognized, recent observations suggest that alterations in angiotensinogen levels also affect blood pressure.[1] Jeunemaitre *et al.*[1] recently noted an association between variants of the angiotensinogen gene and elevated blood pressure levels in large groups of patients in the United States and France who have hypertension. In these patients, elevations in blood pressure were associated with increased levels of circulating angiotensinogen. Recently, Kim *et al.*,[2] by use of gene targeting in a mouse model, confirmed the ability of incremental increases in plasma angiotensinogen concentrations to raise blood pressure.

Angiotensin-converting enzyme (ACE) converts angiotensin I to the octapeptide AII. For the circulating renin–angiotensin system, this activity occurs primarily in the lung, although ACE present in other tissues may also contribute to this biochemical process. Similar to renin and angiotensinogen, variations in the ACE gene have been associated with hypertension in some experimental models.[3,4] Moreover, some clinical data suggest that ACE contributes to cardiac remodeling in ischemic heart disease.[5]

Pharmacologic inhibition of ACE is an effective method of lowering blood pressure. ACE inhibitors lower blood pressure levels primarily by blocking the formation of AII. Also, as shown in Figure 1, ACE is also a kininase and is involved in the breakdown of vasodilator kinin peptides. Thus, the potentiation of the vasodilator effects of kinins may contribute to decreases in blood pressure levels by ACE inhibitors. In addition, kinins also have potent proinflammatory effects, and the enhancement of kinin actions may play a role in some of the untoward effects associated with ACE inhibition, including cough.

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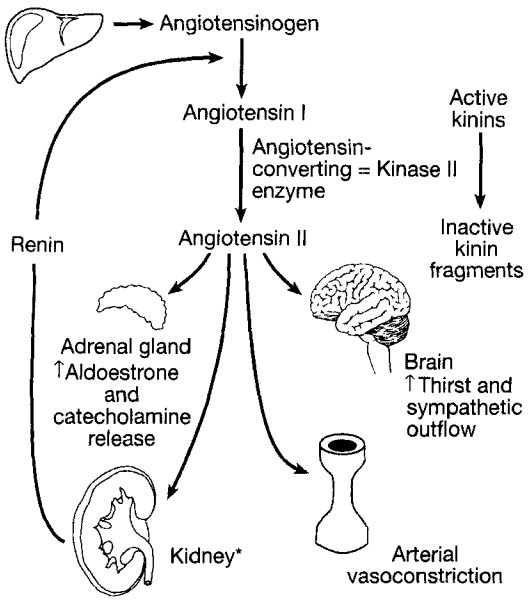

FIG 1. In the renin–angiotensin system, the multifunctional peptide angiotensin II is synthesized from the substrate molecule angiotensinogen through the coordinated actions of renin and angiotensin-converting enzyme (ACE). ACE also functions as kininase II, which degrades vasoactive kinin peptides.

Physiologic Effects of AII Related to Blood Pressure Regulation

As shown in Table I, AII causes a number of diverse biologic effects. AII acts as a potent vasoconstrictor and exerts pressor effects to cause acute elevations in blood pressure. However, according to the Guyton hypothesis,[6] long-term elevations in blood pressure levels cannot be sustained without a commensurate alteration in sodium handling by the kidney. AII may affect renal sodium handling through several distinct mechanisms: effects on renal hemodynamics, direct stimulation of renal tubular sodium reabsorption, and stimulation of aldosterone production by the adrenal glands.[1-3,7]

TABLE I Physiologic effects of angiotensin II

Increases in blood pressure
Vasoconstriction
Stimulation of renal sodium reabsorption
Aldosterone release
Negative feedback for renin release
Vasopressin release
Stimulation of thirst
Catecholamine release (adrenal and neuronal)
Prostaglandin release

In the first circumstance, the net effect of AII in the glomerular circulation is increases in sodium and water reabsorption through its actions on peritubular factors. Direct effects of AII on renal sodium reabsorption have been demonstrated in vivo using suppressor infusions of AII and in vitro in microperfused rabbit proximal tubules. Aldosterone production is primarily regulated by AII, and aldosterone stimulates sodium and water reabsorption in the kidney. However, the effects of aldosterone are quantitatively less than the direct intrarenal effects of AII that stimulate sodium reabsorption.[7]

Angiotensin II Receptors

The physiologic effects of AII are elicited through binding to specific receptors on cell membranes. As shown in Figure 2, angiotensin receptors can be divided into two distinct classes, which are designated as type 1 (AT_1) and type 2 (AT_2) according to their pharmacologic specificities.[8] Both classes of receptors bind AII and substituted AII peptides, such as saralasin, with high affinity. The AT_1 receptors are defined pharmacologically by their high-affinity binding to the nonpeptide receptor blocker losartan (DuP 753). AT_1 receptors mediate the known physiologic functions of AII. AT_2 receptors exhibit high-affinity binding to receptor blockers PD 123177 and CGP 42112 and do not bind to losartan. However, the physiologic functions and signaling mechanisms of AT_2 receptors are not known, and AT_2 receptors have no known role in the regulation of blood pressure.

The recent molecular cloning and sequencing of AT_1 and AT_2 receptors showed that these receptors belong to the large family of G protein–associated receptors.[9,10] Among the AT_1 receptors, two subtypes (AT_{1A} and AT_{1B}) have been identified.[11] These receptors are products of separate genes, share substantial sequence homology, and have wide tissue distributions. As shown in Table II, the AT_{1A} receptor seems to predominate in most tissues, except in the adrenal and anterior pi-

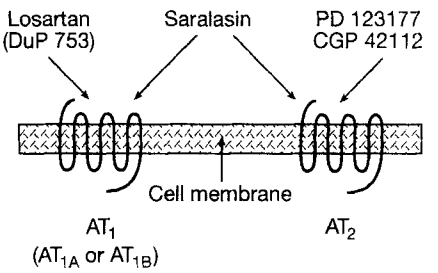

FIG 2. Angiotensin receptors are divided into two distinct classes, designated as type 1 (AT_1) and type 2 (AT_2) according to pharmacologic specificities. Both AT_1 and AT_2 receptors bind angiotensin II and saralasin with high affinity. The AT_1 receptors consist of two isoforms designated AT_{1A} and AT_{1B} and are pharmacologically defined by their high-affinity binding to the nonpeptide receptor blocker losartan. In contrast, AT_2 receptors bind the receptor blockers PD 123177 and CGP 42112 with high affinity but do not bind to losartan.

TABLE II Tissue distribution of AT_1 receptor subtypes

Heart	1A>>1B
Lung	1A>>1B
Kidney	1A>1B
Arteries	1A>1B
Adrenals	1A≥1B
Pituitary	1B>1A

tuitary glands.[12,13] Expression of the AT1B receptor is upregulated by sodium depletion, and expression of AT_{1A} and AT_{1B} receptors may be differentially regulated in the heart and the adrenal glands.[14] This differential tissue distribution and regulation of AT_1-receptor subtypes may serve to modulate the biologic effects of angiotensin II. However, the individual functions of the two AT_1 subtypes have been difficult to define pharmacologically because available AT_1-receptor blockers do not discriminate between the AT_{1A} and AT_{1B} receptors.

To define the physiologic function of the AT_{1A} receptor, we created mice lacking AT_{1A} receptors using gene targeting.[15] In AT_{1A} receptor-deficient mice, pressor responses to AII were essentially absent, and resting blood pressures were reduced by 20 mmHg. This suggests that the AT_{1A} gene locus plays an important role in regulating blood pressure.

Angiotensin$_1$-Receptor Blockers as Antihypertensive Therapy

Nonpeptide AT_1-receptor blockers have been developed for human use as antihypertensive agents. Losartan, which is the prototype AT_1 blocker, effectively lowers blood pressure and specifically inhibits AII-mediated physiologic responses such as systemic and renal vasoconstriction, sodium reabsorption by the renal proximal tubule, dypsogenic responses, and stimulation of aldosterone and adrenergic hormone release by the adrenal gland.[8]

Double-blind, placebo-controlled studies[16–18] have shown losartan to be clinically effective in lowering systolic and diastolic blood pressure levels. In clinical trials, approximately 2,900 patients who had essential hypertension were treated with losartan, either alone or in combination with another antihypertensive. Losartan monotherapy at a dosage of at least 50 mg/day produced reductions in trough blood pressures comparable to those obtained with dosages of 20 mg/day of enalapril. Whereas losartan dosages >50 mg/day did not produce greater reductions in blood pressure, additional reductions were obtained when losartan was combined with hydrochlorothiazide.

Since the characterization of the first orally active AII-receptor blocker, losartan, many pharmaceutical companies have synthesized and characterized a large number of chemically novel compounds that possess potent AII-receptor antagonism. These compounds may be subdivided into several chemical classes: biphenyl tetrazoles, which are derivatives of losartan (i.e., candesartan, ICI D8731, SC-52458, irbesartan, and FK 739); nonbiphenyl tetrazoles (i.e., eprosartan and BIBR-277); and a nonheterocyclic compound (i.e., valsartan). These compounds are undergoing further in vitro and in vivo pharmacologic characterization and are being tested in clinical trials, or both.

Like ACE inhibitors, AT_1-receptor blockers lower blood pressure by inhibiting the renin–angiotensin system. However, their mechanisms of action are fundamentally different. AT_1 blockers inhibit the interaction of AII with AT_1 receptors, but do not directly affect kinin metabolism. Thus, the effects of enhanced kinin generation on changes in blood pressure or the incidence of side effects such as cough should not occur after use of an AT_1-receptor blocker. This hypothesis was tested in a randomized, double-blind, controlled study comparing the incidence of cough associated with losartan, lisinopril (an ACE inhibitor), or hydrochlorothiazide in patients who previously reported cough while taking an ACE inhibitor.[19] The incidence of cough was significantly lower in patients taking losartan than in patients taking lisinopril, and was similar in patients taking hydrochlorothiazide.

As the AT_1 receptor also mediates stimulation of adrenal function by AII, AT_1-receptor blockers would be expected to cause hyperkalemia in susceptible patients in a manner similar to that observed during ACE inhibition. The efficacy of AT_1 receptor blockers depends on a specific interaction of the drug with the receptor and is independent of levels of circulating AII. Thus, AT_1-receptor blockers may provide additional therapeutic benefits in settings such as chronic heart failure in which suppression of AII generation by ACE inhibitors may be incomplete.

Conclusion

The renin–angiotensin system is a powerful regulator of blood pressure and sodium homeostasis, and dysregulation of this system is implicated in the pathogenesis of hypertension. The effects of AII are mediated through cell-surface receptors, which are divided pharmacologically into two subtypes: AT_1 and AT_2. The recognized physiologic effects of AII are mediated by AT_1 receptors; the function of AT_2 receptors is not known. Clinically, there are now two approaches to inhibiting the activity of the renin–angiotensin system:[1] ACE inhibitors, which inhibit the production of AII,[2] and AT_1-receptor blockers, which block the effects of AII at its physiologically relevant receptor. The potential clinical applications of AT_1-receptor blockers are now being actively investigated.

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