

THE RENIN-ANGIOTENSIN SYSTEM: PHYSIOLOGY, PATHOPHYSIOLOGY, AND PHARMACOLOGY

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I have lectured on the renin-angiotensin system for many years to medical, pharmacy, and other professional and graduate students. I find it to be a most worthwhile and satisfying subject to teach, mainly because there is so much that is relevant in the areas of physiology, pathophysiology, and pharmacology. The renin-angiotensin system is also of interest because it continues to be a major field of biomedical research. Finally, it is of considerable interest from the historical point of view.

From the standpoint of physiology, teaching the renin-angiotensin system is particularly worthwhile because it combines elements of renal physiology (control of renal hemodynamics and sodium excretion), cardiovascular physiology (blood pressure regulation), endocrinology (secretion of aldosterone and other hormones), and neurophysiology (actions of angiotensin on the brain and autonomic nervous system). Thus learning about the renin-angiotensin system serves to integrate major areas of physiology that are usually taught as separate subjects and, I hope, gives students an understanding of how diverse systems work together.

I find that students, especially medical students, do not really start to get interested in the renin-angiotensin system until the subject of pathophysiology is introduced. The renin-angiotensin system has lots to offer here, especially in the areas of high blood pressure and congestive heart failure. The fact that angiotensin contributes to the pathogenesis of hypertension, arterial disease, cardiac hypertrophy, heart failure, and diabetic renal disease serves to show that understanding the system really is important.

The pharmacology of the renin-angiotensin system is of particular interest to pharmacy students. Again, the renin-angiotensin system has plenty to offer, particularly because converting-enzyme inhibitors and angiotensin receptor antagonists are being used increasingly in the treatment of hypertension and congestive heart failure. The development of orally active renin inhibitors is also an interesting and potentially important area.

The renin-angiotensin system is a hotbed of research, and there is a seemingly endless amount of new information appearing in the literature every day. It is tempting to present some of this in lectures, but I find that most professional students are not interested in new developments unless their clinical relevance is readily apparent. In addition, the renin-angiotensin system is my own area of research, and it is easy to get carried away and lose sight of the forest for the trees. For these reasons, and because of lack of time, I generally steer clear of current research. Nevertheless, the opportunity to discuss new developments often comes up when responding to students' questions.

Last but not least, the renin-angiotensin system is of interest from the historical point of view. The progression of ideas from the recognition of the relationship between renal disease and hypertension by Bright to the production of experimental renal hypertension by Goldbatt and the discovery of angiotensin by Page ("angiotenin") and Braun-Menendez ("hypertensin"), culminating in a veritable explosion of research during the past three decades, makes a fascinating story. Once again, however, this does not particularly excite the students, and I generally pass it by.

The following section contains excerpts from my physiology syllabus together with some of my favorite figures to show how I teach this intriguing system.

PHYSIOLOGY

Because I generally teach in physiology courses, the physiology of the renin-angiotensin system is the major component of my lectures. I start with an overview of the system by describing the biochemical pathway of angiotensin II formation. My major emphasis here is on the control of renin secretion, because the rate of renin secretion is the primary determinant of the activity of the system, and on the actions of angiotensin II.

Biosynthesis of Angiotensin II

The renin-angiotensin system is shown in Fig. 1. The principal steps include enzymatic cleavage of angiotensin I from angiotensinogen by renin, conversion of angiotensin I to angiotensin II by converting enzyme, and degradation of angiotensin II by peptidases.

Renin. Renin is a very specific protease that catalyzes the release of the decapeptide angiotensin I from angiotensinogen. It is synthesized as a preprohormone that is processed to prorenin, which is inactive, and then to active renin, a glycoprotein consisting of 340 amino acids. Renin in the circulation originates in the kidneys. Enzymes with reninlike activity are present in some extrarenal tissues, but no physiological role for these enzymes has been established. Within the kidney, renin is synthesized and stored in a specialized area of the nephron, the juxtaglomerular apparatus, the major components of which are the afferent and efferent arterioles and the macula densa (Fig. 2). The afferent arteriole and, to a lesser extent, the efferent arteriole contain specialized granular cells called juxtaglomerular cells, which are the site of synthesis, storage, and release of renin. The macula densa is a specialized tubular segment closely associated with the afferent and efferent arterioles. The vascular and tubular components of the juxtaglomerular apparatus, including the juxtaglomerular cells, are innervated by the sympathetic nervous system.

Control of renin secretion. The rate at which renin is secreted by the kidney is the primary determinant of activity of the renin-angiotensin system. Renin secre-

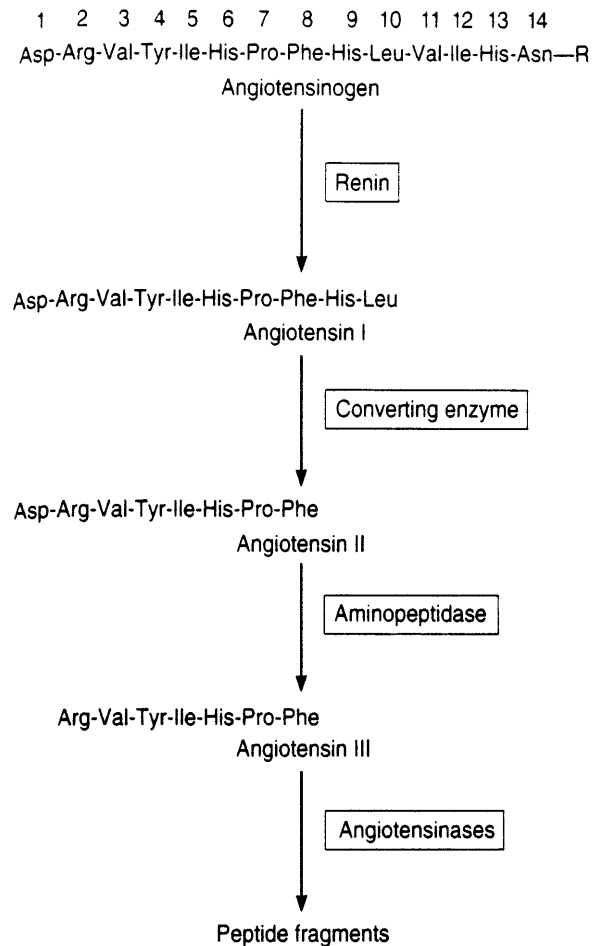


FIG. 1. Chemistry of renin-angiotensin system. Amino acid sequence of amino terminus of human angiotensinogen is shown. R, remainder of molecule.

tion is controlled by a renal baroreceptor, the macula densa, and the sympathetic nervous system, with short-loop feedback by angiotensin II (4).

Renal baroreceptor. The renal baroreceptor monitors renal perfusion pressure and signals an increase in renin release when perfusion pressure falls. The relationship between renin secretion and renal perfusion pressure is shown in Fig. 3. It can be seen that when renal perfusion pressure is above a threshold of ~80 mmHg, renin secretion is low and alterations in pressure cause little change in renin secretion. However, when pressure falls below this threshold, renin secretion is stimulated, increasing in a linear fashion as renal perfusion pressure falls. The receptor is appar-

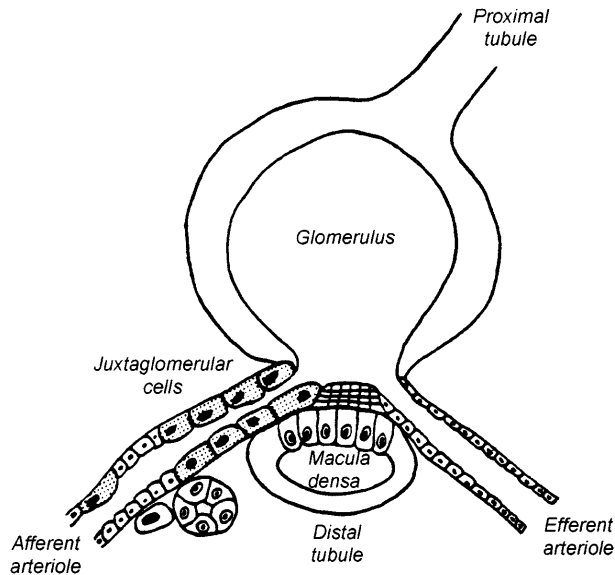


FIG. 2.

Juxtaglomerular apparatus. Note close contact between macula densa cells of distal tubule and renin-secreting cells of afferent arteriole.

ently located in the afferent arteriole, and it is possible that the juxtaglomerular cells themselves are sensitive to changes in stretch. As is discussed in *Role of Angiotensin in Body Fluid and Blood Pressure Regulation*, the renal baroreceptor plays an important role

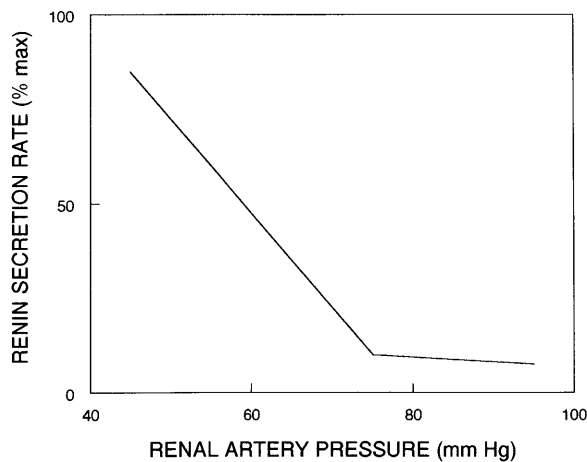


FIG. 3.

Relationship between renin secretion [as a percentage of maximum (%max)] and renal artery pressure. When renal perfusion pressure falls below a threshold of ~80 mmHg, renin secretion is stimulated. Note that this threshold is close to normal resting arterial pressure.

in detecting and minimizing changes in arterial pressure.

Macula densa. The close anatomic relationship between the macula densa and the afferent arteriole suggests that there are functional interactions between these tubular and vascular components of the juxtaglomerular apparatus. It is now known that the macula densa functions as a NaCl sensor and that changes in NaCl concentration in the tubular fluid passing the macula densa cells alter the secretion of renin by the juxtaglomerular cells in the afferent arteriole (6). Chloride is the major signal, with decreased chloride concentration stimulating renin secretion, and vice versa (Fig. 4). These changes are mediated by way of a luminal $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter that is sensitive to changes in luminal Cl^- concentration. In sodium-deficient states, decreases in plasma NaCl concentration and glomerular filtration rate (GFR) result in decreased delivery of NaCl to the macula densa, and the resulting activation of the renin-angiotensin system helps to prevent further loss of sodium (see *Role of Angiotensin in Body Fluid and Blood Pressure Regulation*).

A key question that has stimulated considerable research but that still remains unanswered is how the macula densa communicates with the renin-secreting cells of the afferent arteriole. Substances that have

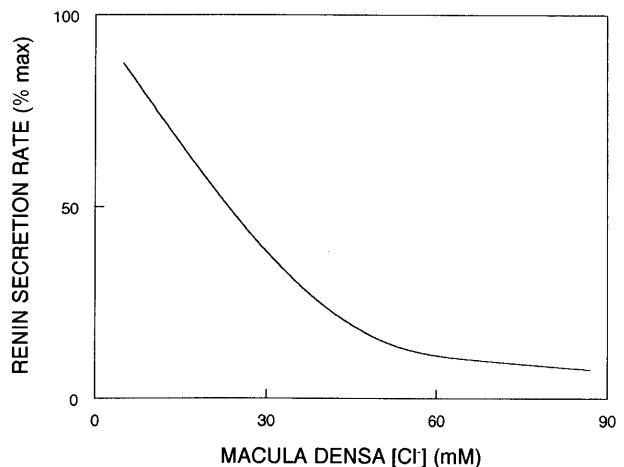


FIG. 4.

Relationship between renin secretion and chloride concentration ($[\text{Cl}^-]$) at macula densa. In sodium deficient states decreased delivery of NaCl to the macula densa causes stimulation of renin secretion.

been proposed as mediators include adenosine, prostaglandins, and, most recently, nitric oxide.

Sympathetic nervous system. Similar to the other vascular and tubular components of the kidney, the juxtaglomerular cells are innervated by sympathetic postganglionic neurons. Renin secretion increases when the renal nerves are stimulated and decreases when the kidneys are denervated (2). The relationship between renin secretion and renal sympathetic nerve activity is shown in Fig. 5. Neural effects on renin secretion are mediated by locally released norepinephrine acting on β_1 -adrenergic receptors. This activates adenylyl cyclase and increases the formation of the intracellular messenger cAMP. In some situations, sympathetic stimulation increases renin secretion indirectly by stimulating α -adrenergic receptors, causing constriction of the afferent arteriole with resultant activation of the renal vascular receptor and decreased delivery of sodium chloride to the macula densa. The reflex increases in sympathetic activity elicited by hemorrhage, standing, and exercise stimulate renin secretion and thus help defend blood pressure in these situations.

Angiotensin. Angiotensin II inhibits renin secretion by increasing blood pressure and by acting directly on the juxtaglomerular cells. The latter action forms the basis of a short-loop negative feedback mechanism controlling renin secretion, a feature common to most

endocrine systems. Interruption of this feedback with inhibitors of the renin-angiotensin system (see **Drugs That Inhibit Renin Secretion**) results in stimulation of renin secretion.

The regulation of renin secretion is summarized in Fig. 6.

Angiotensinogen. Angiotensinogen is the circulating protein substrate for renin. It is a glycoprotein with a molecular weight of $\sim 57,000$ and is synthesized in the liver. The 14 amino acids at the amino terminus of the molecule are shown in Fig. 1. The concentration of angiotensinogen in plasma is less than the Michaelis-Menten constant of the renin-angiotensinogen reaction and is therefore a determinant of the rate of formation of angiotensin.

Angiotensinogen production is increased by glucocorticoids and estrogens. Thus plasma angiotensinogen concentration is increased in patients with Cushing's syndrome and in patients being treated with glucocorticoids. It is also elevated during pregnancy and in women taking estrogen-containing oral contraceptives. The increased angiotensinogen concentration is thought to contribute to the hypertension that occurs in some of these situations. In this context, it is of interest that there is evidence for a genetic linkage between the angiotensinogen gene and essential hypertension.

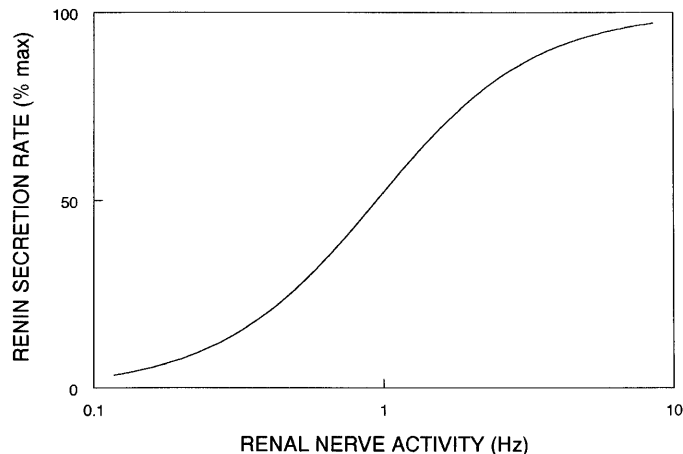


FIG. 5. Relationship between renin secretion and renal sympathetic nerve activity. Reflex increases in renal nerve activity elicited by stimuli such as hemorrhage, standing, and exercise stimulate renin secretion.

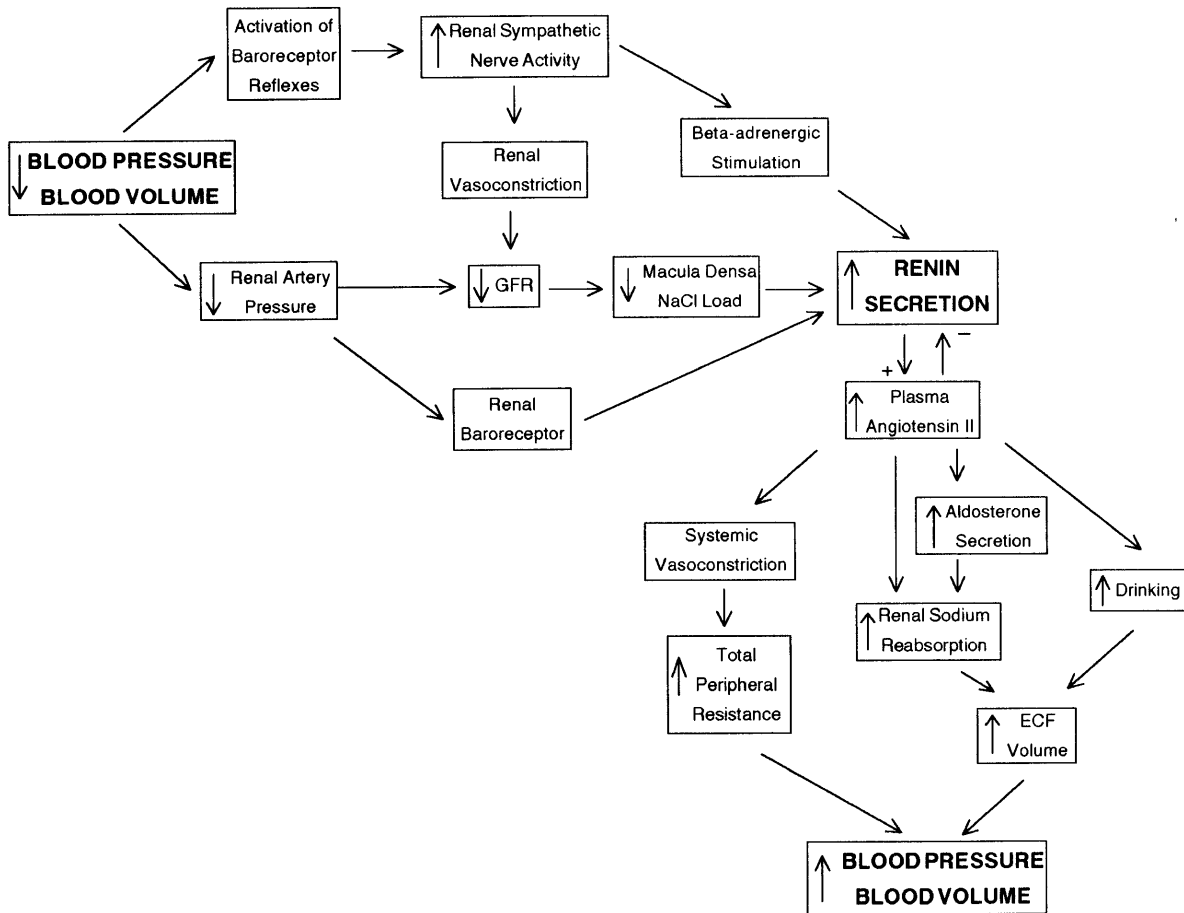


FIG. 6.

Summary of control of renin secretion and major cardiovascular and renal actions of angiotensin II. Decreases in blood volume and/or pressure stimulate renin secretion by way of renal baroreceptor, macula densa, and renal sympathetic nerves. Plasma angiotensin II concentration increases, causing vasoconstriction, increasing renal sodium and water reabsorption, and stimulating drinking, thus restoring blood volume and pressure. Excessive secretion of renin causes sodium and water retention, hypertension, and other abnormalities. ECF, extracellular fluid; GFR, glomerular filtration rate.

Angiotensin I. Angiotensin I contains the peptide sequences necessary for all of the actions of the renin-angiotensin system, but it has little or no biologic activity. Instead, it must be converted to angiotensin II by converting enzyme (Fig. 1). Angiotensin I may also be cleaved by plasma or tissue aminopeptidases to form [des-Asp¹]angiotensin I; this in turn is converted to [des-Asp¹]angiotensin II (commonly known as angiotensin III) by converting enzyme.

Converting enzyme. Converting enzyme is a dipeptidyl carboxypeptidase. Its most important substrates are angiotensin I, which it converts to angiotensin II,

and bradykinin, which it inactivates. It also cleaves enkephalins and substance P, but the physiological significance of this action has not been established. The action of converting enzyme is restricted by a penultimate prolyl residue, and angiotensin II is therefore not hydrolyzed by converting enzyme. Converting enzyme is located on the luminal surface of vascular endothelial cells throughout the circulation.

Angiotensinase. Angiotensin II is removed rapidly from the circulation, with a half-life of less than one minute. It is metabolized during passage through most vascular beds (an exception being the lungs) by

several peptidases collectively referred to as angiotensinase. Most metabolites of angiotensin II are biologically inactive, but the initial product of aminopeptidase action, [des-Asp¹]angiotensin II, retains considerable biologic activity.

Actions of Angiotensin II

Angiotensin II acts at several sites in the body, including vascular smooth muscle, adrenal cortex, kidney, and brain (3). Through these actions, the renin-angiotensin system plays a key role in the regulation of fluid and electrolyte balance and arterial blood pressure (Fig. 6).

Angiotensin receptors and signaling pathways.

Angiotensin II receptors are located on the plasma membrane of target cells throughout the body. Two distinct receptor subtypes, termed AT₁ and AT₂, have been identified (3). Most of the known actions of angiotensin II are mediated by the AT₁-receptor subtype. This receptor, which belongs to the G protein-coupled receptor superfamily, is a peptide containing ~360 amino acids that spans the cell membrane seven times. Binding of angiotensin II to AT₁ receptors in vascular smooth muscle results in the phospholipase C-mediated generation of inositol trisphosphate [Ins(1,4,5)P₃] and diacylglycerol (DAG). Ins(1,4,5)P₃ mobilizes calcium from endoplasmic reticulum, whereas calcium and DAG activate enzymes, including protein kinase C and calcium-calmodulin kinases, that catalyze phosphorylation of proteins. These events result in smooth muscle contraction within seconds. They also initiate slower responses to angiotensin, including vascular growth and ventricular hypertrophy. The function and signal transduction pathways for AT₂ receptors are still being investigated.

Blood pressure. Angiotensin II is a potent pressor agent, considerably more potent than norepinephrine. The pressor response to angiotensin II is rapid in onset (10–15 seconds) and sustained during long-term infusions of the peptide. A large component of the pressor response to intravenous angiotensin II is due to direct contraction of arteriolar smooth muscle. However, angiotensin II also increases blood pressure through actions on the brain and autonomic nervous system. In particular, it acts centrally to increase

sympathetic outflow and peripherally to facilitate sympathetic transmission by increasing the release and reducing the reuptake of norepinephrine at adrenergic nerve terminals (5). It also has a less important direct positive inotropic action on the heart. The pressor response to angiotensin is usually accompanied by little or no reflex bradycardia because the peptide acts on the brain to reset the baroreceptor reflex control of heart rate to a higher pressure (5).

Adrenal cortex. Angiotensin II acts on the zona glomerulosa of the adrenal cortex to stimulate aldosterone biosynthesis. Aldosterone in turn increases sodium reabsorption in the distal tubule.

Kidney. Angiotensin II acts on the kidney to cause renal vasoconstriction, increase proximal tubular sodium reabsorption, and inhibit the secretion of renin.

Brain. Angiotensin II acts on the central nervous system to increase blood pressure, stimulate drinking (dipsogenic action), and increase the secretion of vasopressin and ACTH. The physiological significance of these effects is still under investigation.

Cell growth. Angiotensin II is mitogenic for vascular and cardiac muscle cells and may contribute to the development of cardiovascular hypertrophy.

Role of Angiotensin in Body Fluid and Blood Pressure Regulation

The major physiological function of the renin-angiotensin system is to defend extracellular fluid volume and blood pressure. Consider the response of the renin-angiotensin system to acute loss of blood (Fig. 6). Decreases in blood volume and arterial pressure result in decreased firing of the low- and high-pressure baroreceptors, causing a reflex increase in sympathetic discharge. The increase in renal sympathetic nerve activity, together with decreases in renal artery pressure, GFR, and macula densa NaCl load, causes stimulation of renin secretion. Plasma angiotensin II concentration increases, causing vasoconstriction, stimulation of aldosterone secretion, and increased renal sodium and water reabsorption. These responses combined with increased fluid intake serve

to restore extracellular fluid volume and blood pressure.

Note that the renin-angiotensin system helps to defend blood pressure and blood volume in other situations such as standing and sodium deficiency. With standing, the major stimulus to renin secretion is increased renal sympathetic nerve activity, whereas with sodium deficiency the stimulus is decreased delivery of NaCl to the macula densa.

PATHOPHYSIOLOGY

Up to this point, the emphasis has been on the normal physiology of the renin-angiotensin system. This sets the stage for a brief review of the consequences of the excessive renin secretion that occurs in some forms of hypertension and congestive heart failure. The consequences of excessive renin secretion are readily predictable from the information presented in the preceding section.

Hypertension

The most common form of human hypertension is essential hypertension, the cause(s) of which is still unknown. Other forms of hypertension are caused by endocrine and renal disease. Some of these involve overactivity of the renin-angiotensin system, which is not surprising in view of the potent effect that angiotensin II has on blood pressure.

Overactivity of the renin-angiotensin system is usually caused by increased secretion of renin, with a result-

tant increase in plasma angiotensin II concentration. Excessive secretion of renin by renin secreting tumors causes severe hypertension. Fortunately, this form of hypertension is both rare and curable. The hypertension associated with narrowing of one or both renal arteries (renovascular or renal hypertension) and several types of renal disease are frequently associated with increased secretion of renin. Finally, renin secretion is increased in a subgroup of patients with essential hypertension.

Overactivity of the renin-angiotensin system can also result from increased production of angiotensinogen. As noted in **Angiotensinogen**, angiotensinogen production is increased by estrogen therapy, estrogen-containing oral contraceptives, and pregnancy, and this may contribute to the hypertension that sometimes occurs in these situations. Increased production of angiotensinogen may also contribute to the hypertension associated with glucocorticoid therapy or Cushing's syndrome.

Congestive Heart Failure

The initial pathological event in heart failure is decreased myocardial contractility, which is commonly caused by hypertension and coronary artery disease. Cardiac output and effective blood volume decrease, resulting in increased sympathetic discharge, which in turn stimulates renin secretion. Plasma angiotensin II concentration increases, causing retention of salt and water (Fig. 6) and edema.

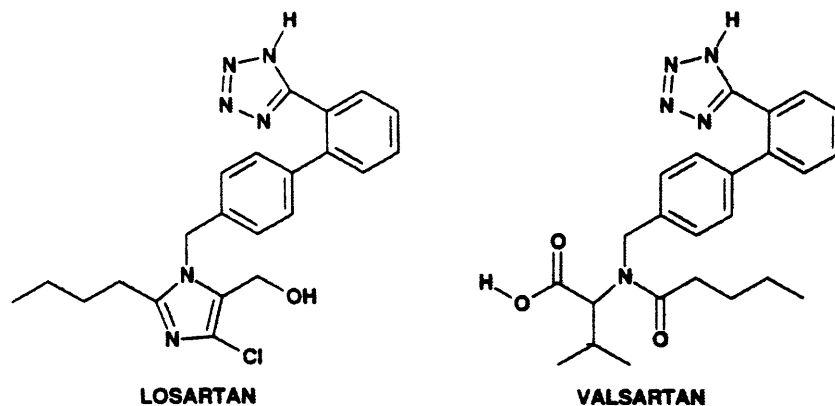


FIG. 7. Two orally active angiotensin II receptor antagonists, losartan and valsartan.

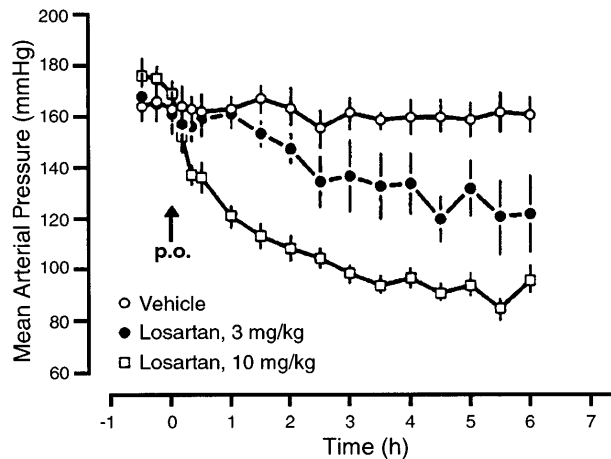


FIG. 8. Effect of angiotensin II receptor antagonist losartan on blood pressure in rats with renovascular hypertension [adapted from Wong et al. (7)].

PHARMACOLOGY

The fact that angiotensin contributes to the pathogenesis of several diseases stimulated the development of drugs that inhibit the renin-angiotensin system. This has been an exciting and fruitful area of research, particularly during the past decade, which has seen the development of potent and specific inhibitors of the formation or actions of angiotensin II. Drugs are now available that suppress renin secretion, block angiotensin II receptors, and inhibit the enzymatic action of renin and converting enzyme.

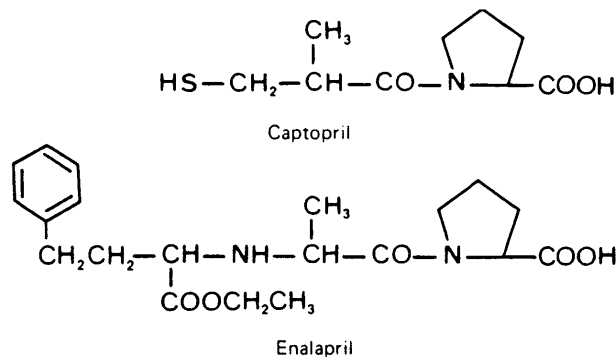


FIG. 9. Two orally active angiotensin converting-enzyme inhibitors, captopril and enalapril.

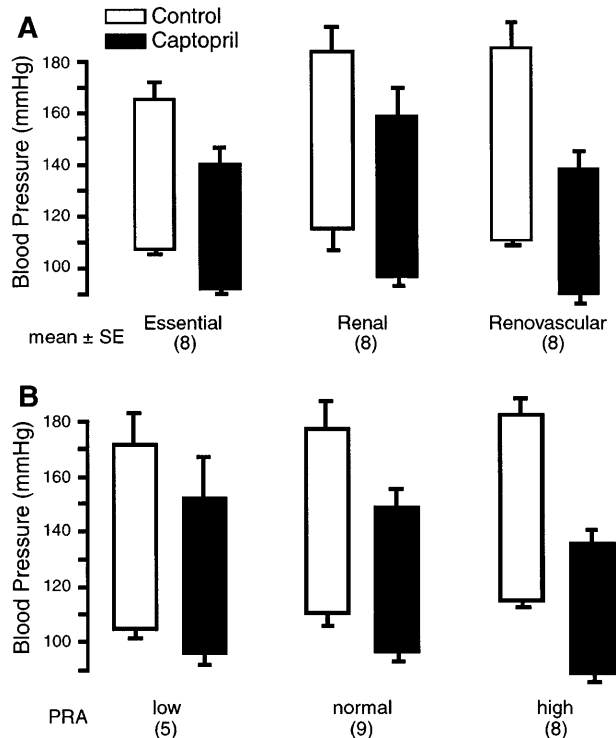


FIG. 10. Antihypertensive effect of captopril [adapted from Brunner et al. (1)]. In A, patients are classified on basis of cause of hypertension, whereas in B, patients are classified on basis of plasma renin levels. Note that although captopril is most effective when plasma renin is high, it also lowers blood pressure in patients with normal and even low plasma renin levels. This is due, at least in part, to decreased metabolism of bradykinin. PRA, plasma renin activity.

Drugs That Inhibit Renin Secretion

β-Adrenergic blocking drugs such as propranolol decrease renin secretion, and this may contribute to their antihypertensive action. Note, however, that these drugs also reduce blood pressure by actions unrelated to the renin-angiotensin system, including decreased cardiac output. Propranolol and other β-adrenergic blocking drugs suppress renin secretion by blocking renal β-adrenergic receptors (Fig. 6).

Angiotensin Receptor Antagonists

Substitution of aliphatic residues such as glycine, alanine, leucine, or threonine for the phenylalanine at the carboxyl terminus of angiotensin II results in the

TABLE 1
Comparison of major characteristics of angiotensin II receptor antagonists, converting-enzyme inhibitors, and renin inhibitors

	Angiotensin II Receptor Antagonists	Converting-Enzyme Inhibitors	Renin Inhibitors
Mode of action	Block AT ₁ receptors	Inhibit conversion of ANG I to ANG II	Inhibit ANG I formation
Location of target protein	Surface of vascular smooth muscle cells	Surface of vascular endothelial cells	Blood
Renin secretion	Increased	Increased	Increased
Plasma renin enzyme activity	Increased	Increased	Decreased
AT ₁ receptors	Blocked	Not stimulated (plasma ANG II↓)	Not stimulated (plasma ANG II↓)
AT ₂ receptors	Stimulated (plasma ANG II↑)*	Not stimulated	Not stimulated
Bradykinin levels	No change	Increased	No change
Main hemodynamic effect	Vasodilation	Vasodilation	Vasodilation
Renal blood flow	Increased	Increased	Increased
BP in normotensive sodium-replete subjects	Little or no change	Little or no change	Little or no change
BP in normotensive sodium-depleted subjects	Decreased	Decreased	Decreased
Indications approved in humans	Hypertension, congestive heart failure	Hypertension, congestive heart failure	None yet
Mode of administration	Oral, once daily	Oral, once daily	Oral availability too low

*Role of AT₂ receptors is not clear. ANG I or II, angiotensin I or II; BP, blood pressure; ↑, increase; ↓, decrease.

formation of competitive antagonists of the action of angiotensin II. Substitution of sarcosine for the amino-terminal aspartic acid prolongs the half-life of the peptides, enhancing their activity. The best-known of these antagonists is [Sar¹,Val⁵,Ala⁸]angiotensin II, or saralasin (Sar-Arg-Val-Tyr-Val-His-Pro-Ala).

Saralasin. Saralasin possesses some agonist activity and may elicit a pressor response, particularly when circulating angiotensin II levels are low. Saralasin must be administered intravenously, and this severely restricts its use as an antihypertensive agent. However, it can be useful in the detection of renin-dependent hypertension and other hyperreninemic states.

A new class of drugs that block angiotensin II receptors was developed recently (3). An example is losartan, which is a potent and selective antagonist of angiotensin AT₁ receptors (Fig. 7). These drugs interact with amino acids in the transmembrane domains of AT₁ receptors, preventing the binding of angiotensin II. They are orally active and lower blood pressure almost as effectively as converting-enzyme inhibitors but with fewer side effects (see *Converting-Enzyme*

Inhibitors). They lower blood pressure in animals with experimental hypertension (Fig. 8; Ref. 7) and in hypertensive patients and are used increasingly in the treatment of hypertension and congestive heart failure.

Converting-Enzyme Inhibitors

A nonapeptide inhibitor of converting enzyme was originally isolated from the venom of a South American snake. The synthetic form of this peptide, teprotide, is an effective inhibitor of converting enzyme but is active only when administered intravenously. An important class of orally active converting-enzyme inhibitors, directed against the active site of converting enzyme, is now extensively used. Captopril and enalapril are typical (Fig. 9). Many potent new converting-enzyme inhibitors are now available. It should be noted that converting-enzyme inhibitors not only block the conversion of angiotensin I to angiotensin II but also inhibit the degradation of other peptides, including bradykinin. This latter effect contributes to the antihypertensive action of converting-enzyme inhibitors and may be responsible for side effects such

as cough and angioedema. Extensive studies document the value of the converting-enzyme inhibitors in hypertension (Fig. 10; Ref. 1) and congestive heart failure. Indeed, converting-enzyme inhibitors are so effective that they have become one of the cornerstones of the treatment of congestive heart failure. Recent evidence suggests that these drugs may also protect against renal vascular injury in diabetes and other conditions.

Renin Inhibitors

Recently, orally active renin inhibitors have been developed (8). These drugs suppress plasma renin activity, thus decreasing plasma angiotensin II concentration. They lower blood pressure in hypertensive patients and have the potential to be as effective as converting-enzyme inhibitors and angiotensin receptor antagonists. However, significant improvement of their oral bioavailability is required.

The major characteristics of angiotensin II receptor antagonists, converting-enzyme inhibitors, and renin inhibitors are compared in Table 1.

SUMMARY

The renin-angiotensin system is an important control system that plays a major role in the regulation of fluid and electrolyte balance and of blood pressure. In particular, the system helps defend blood pressure and volume in situations such as hemorrhage, sodium depletion, and changes in posture. Excessive secretion of renin can cause hypertension and exacerbate

the abnormalities that occur in other diseases such as congestive heart failure. Several potent orally active drugs that block the formation or actions of angiotensin II are now available and have proven to be very effective in the treatment of hypertension and congestive heart failure.

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