The Role of Renin in Normal and Pathological Cardiovascular Homeostasis

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SUMMARY Recently, the availability of a number of specific inhibitors of the renin-angiotensin system has made it possible to address certain critical questions concerning the role of angiotensin II in physiologic homeostasis and in a number of pathologic states. These studies indicate that angiotensin II does not have an obligatory role in blood pressure maintenance in the normal, sodium replete individual, but it is essential following sodium depletion. The role of angiotensin II in feedback control of renin secretion is confirmed as is its importance in aldosterone stimulation both in relation to posture and sodium depletion. Angiotensin II is responsible for the initial pressor response of experimental renovascular hypertension and appears to be important in the initiation of chronic renovascular hypertension. Converting enzyme blockers and competitive inhibitors of angiotensin II are helpful in the diagnosis of clinical renovascular hypertension and in the identification of renin dependent hypertensives. Homeostatic mechanisms leading to maintenance of blood pressure and accumulation of edema in experimental congestive heart failure appear to be dependent on angiotensin II.

IT MAY BE WORTH INQUIRING why the renin-angiotensin system should be the subject of a lecture some 77 years after its initial description. With the rapid advance of our understanding of physiology, this ancient system should appropriately be relegated to standard textbooks, its primary importance as one element of the basic information with which we approach new problems. Yet, in spite of the efforts of many skillful and imaginative investigators, we still do not completely understand its role in normal and abnormal cardiovascular function. The history of the study of the renin-angiotensin system is marked by periods of activity and productivity, by uncovering new facets of its function, followed by times in which little progress is made. At times we have attached great importance to the regulatory function of renin. These cycles of interest often are related — as is our present one — to the development and application of new tools in chemistry or physiology.

Tigerstedt and Bergman named renin in a classic paper published in 1898. They showed that hypertension could be induced in dogs by injecting a crude extract of kidney.1 Drawing on developments in physiological investigations in animals and effective methods for measuring a variety of hemodynamic variables, made during the 1930s, Goldblatt devised an elegant series of experiments which called attention to renal mechanisms of blood pressure control.2 The mechanism of renin’s action remained unclear, however, until Page and Helmer3 demonstrated that it was probably an enzyme that acted upon another substance to release an active principle, which they called angiotensin. Braun-Menédez and colleagues, working independently, made a similar observation.4 Characterization of angiotensin, later called angiotensin (a synthesis of Page and Helmer’s term angiotensin and Braun-Menédez’s term hypertensin), hinged on developments in the field of protein and peptide isolation and of peptide sequencing.

Ultimately the structure of angiotensin II as the final product of renin action was identified.6 With the advent of more facile peptide synthetic methods the hormone was synthesized.6,7 The double isotope derivative method, which allowed the measurement of aldosterone concentration in body fluids,8 was decisive in physiological experiments that successfully demonstrated that a potent aldosterone-stimulating hormone was secreted by the kidney,9 and that synthetic angiotensin II increased the rate of aldosterone excretion.10,11

The radioimmunoassay method was soon applied to the measurement of angiotensin II concentrations in plasma12-14 as well as to the more accurate and efficient estimates of renin activity.15-18 These methods provided further understanding of the interconversion of the components of the system. Tools in modern membrane biochemistry allowed what first seemed a daring examination of the direct interactions of hormones and their receptors but which yielded characterization of the angiotensin receptor in a variety of tissues.19-21

Advances in protein fractionation, particularly affinity chromatography, have, after many unfruitful years, led to the purification of renin.22-25 Before long we may expect that
its detailed structure and mechanism of action will be understood.

One of the most direct ways to uncover the essential functions of an endocrine organ is to ablate it. This cannot be done with the juxtaglomerular apparatus, the source of renin, since it maintains such an intimate structural linkage with one of the organs it regulates, the kidney. Now we have several inhibitors, each specific to one of the several steps in the transition between renin secretion and angiotensin action on end organ receptors. These inhibitors allow temporary and reversible ablation of the renin system. These are the new tools that have generated the recent resurgence of interest in the renin system and have more precisely defined its role in normal and pathological cardiovascular homeostasis.

The Renin-Angiotensin System

A Feedback Loop

Renin is synthesized and stored in membrane-bound cytoplasmic granules at the vascular pole of the renal glomerulus. Both the afferent and efferent arterioles are anatomically and functionally associated with a group of specialized cells at the origin of the distal tubule that form the macula densa. The entire structure is referred to as the "juxtaglomerular apparatus" (fig. 1). This site is the center of a feedback loop, which serves to regulate blood pressure and probably intravascular volume by modulating the rate of renin secretion. Factors directly affecting the rate of secretion of renin by the juxtaglomerular apparatus include sodium concentration in the distal tubule, blood pressure in the afferent arteriole, plasma angiotensin II concentration, and the impulse traffic of the renal sympathetic nerves.

The secretion of renin ultimately results in the production of angiotensin II, which has both direct and indirect effects on blood pressure and blood volume. Angiotensin II is a potent vasoconstrictor, thereby directly raising blood pressure. It also acts on the central nervous system to increase peripheral vascular resistance. The adrenal gland may be stimulated by angiotensin II or its metabolic product, angiotensin III, to produce aldosterone, a potent mineralocorticoid that promotes sodium retention in the renal tubule. Sodium retention, in turn, increases vascular volume and blood pressure.

The feedback loop is completed when vasoconstriction and sodium retention increase blood pressure and decrease renin secretion by acting directly on the baroreceptors in the juxtaglomerular apparatus. Stimulation of a chemoreceptor for sodium in the kidney, and several vascular baroreceptors located elsewhere in the circulation, also serve to regulate renin secretion. Some of these feedback loops are pictured in figure 1, and these concepts are reviewed in considerably more detail elsewhere.

Chemistry of the Renin-Substrate Reaction

Renin has no known direct physiologic effect but acts only to cleave its substrate, angiotensinogen, which is an alpha II globulin synthesized in the liver. The amino acid sequence of the amino terminal 14 residues of renal substrate is known (fig. 2). Renin cleaves between the two leucine residues at positions 10 and 11 to release the decapeptide angiotensin I. Angiotensin I is in turn cleaved between residues 8 and 9 by a converting enzyme to yield the active pressor hormone, angiotensin II. Aminopeptidases further degrade angiotensin II by removing the amino terminal aspartic acid. The resultant heptapeptide, sometimes called angiotensin III, is believed by some investigators to be the primary mediator of}

![FIGURE 1. Feedback regulation of renin release. Several feedback loops are shown. An increase in angiotensin II concentration results in decreased renin secretion by: 1) increased sodium retention resulting in increased extracellular fluid volume; 2a) a direct negative feedback; 2b) increased blood pressure through the central nervous system; 2c) increased blood pressure through direct systemic vasoconstriction; 3) direct sodium effects on the macula densa. From Oparil S, Haber E. Reprinted, by permission, from the New England Journal of Medicine (291: 393, 1974).]
adrenal-cortical aldosterone secretion.\textsuperscript{29, 30} Angiotensin II and III have very short half-lives in the circulation and are further degraded to smaller inactive peptides.\textsuperscript{31}

**Determinants of Renin Secretion in Normal Man**

In the normal unstimulated individual the major determinants of renin secretion are posture, sodium intake, and time of day. Figure 3 depicts renin activity and plasma aldosterone and cortisol concentrations determined at varying times of day at three levels of sodium intake in normal subjects.\textsuperscript{32}

Very low levels of both renin activity and plasma aldosterone concentration are observed at the highest sodium intake, 240 mEq per day. There seemed to be little variation during the course of the day. At 100 mEq sodium intake, renin activity is low during sleep but rises by a factor of nearly ten, reaching a maximum the middle of the day. By 8 p.m. it has declined to early morning levels, even though the subjects have remained upright at normal activity throughout this period. Plasma aldosterone levels follow renin activity faithfully. At a low sodium intake, 10 mEq per day, nighttime levels of both renin and aldosterone are higher and plasma aldosterone seems to peak at a still higher level.

On the other hand, plasma cortisol, which reflects ACTH secretion, follows a different and independent diurnal pattern. Cortisol peaks at 8 a.m. and gradually falls during the course of the day. Its magnitude is independent of sodium intake. If normal individuals are kept in bed for 24 hours, diurnal cycles of renin secretion can still be observed, but the height of the peaks is considerably blunted.\textsuperscript{32, 34}

**Inhibitors of the Renin-Angiotensin System**

The ability to measure renin activity and angiotensin II concentration by radioimmunoassay proved to be most helpful to the physiologist and clinical investigator in understanding the response of the renin-angiotensin system to a variety of interventions. However, it was not until specific inhibitors were available that it became possible to define precisely the role of renin in any given physiologic or pathologic situation. Inhibitors may 1) interfere with the action of renin on its substrate, 2) block converting enzyme in its action on angiotensin I to produce angiotensin II, and 3) compete in the interaction of angiotensin II with its receptor site in blood vessels or in the adrenal cortex (fig. 4).

**Renin Inhibitors**

Antirenin antibody was the earliest inhibitor used in physiologic studies.\textsuperscript{35-37} The removal or inactivation of renin from the circulation with a specific antibody should also remove whatever physiologic consequences its presence might engender. Antirenin antiserum lowered blood pressure in experimental renovascular hypertension, but the specificity of the antibody, and consequently the interpretation of the results, was not confirmed. Since extracts of kidney of varying purity were used as the immunogen, the antibodies produced were likely to be highly heterogeneous. One would expect to find antibodies directed against a variety of renal cellular constituents including functionally important membrane structures and receptors. Such antibodies may simultaneously affect several of the kidney's functions, thereby obscuring or distorting the result of their inhibition of renin.

Even if functionally homogeneous renin antibodies were available, the reaction of this antibody with its antigen would lead to the formation of immune complexes, which in turn activate the complement system. A number of peptides released in the course of complement activation have independent vascular effects, again confounding the investigator.

If the antibody is raised in a heterologous species, it may only be used for a short time since the formation of antibodies to a foreign protein would result in rapid elimination by immune action.

Pepstatin is a nonspecific acid protease inhibitor which also inhibits renin.\textsuperscript{38} Conflicting data cast doubt on its efficacy in vivo however.\textsuperscript{39}
A new class of competitive renin inhibitors based on substrate structure has been synthesized recently in our laboratory. Skeggs and co-workers reported that octapeptide I in table 1 was the shortest peptide that was able to act as a substrate for renin and had kinetic properties similar to the natural tetradecapeptide as isolated from the substrate protein by enzymatic cleavage. We showed that this compound was, as expected, a competitive inhibitor of the action of renin on the tetradecapeptide substrate.

A number of analogs were synthesized that had a less strong inhibitory effect than the parent octapeptide. The most successful of the first group was characterized by substitution of the D-stereoisomer of leucine at position 6, immediately carboxyterminal to renin's cleavage site (6 in table 1). At pH 5.5 its inhibitory constant with respect to the tetradecapeptide substrate was 3 μM and with respect to protein substrate in plasma, 32 μM. The D-leu substitution prevented cleavage of the leu-D-leu bond by renin. Unfortunately this inhibitor was inactive at pH 7.4 and could not be used in physiologic studies. Other analogs that were soluble and active at physiologic pH were then synthesized. The most potent of these (11 in table 1) is characterized by a phenylalanine substitution for leucine carboxyterminal to the cleavage site and a proline residue at the amino terminus of the peptide. It was capable of inhibiting the action of renin on both the tetradecapeptide and on its natural protein substrate in plasma at pH 7.4 with nearly equal effectiveness. Preliminary studies in vivo in the squirrel monkey show promise that this group of compounds offers a new physiologic tool in the investigation of renin action in vivo.
**Table 1. Inhibitors of Renin**

<table>
<thead>
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<th>Peptide</th>
<th>$K_i$ (μM)</th>
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*Inhibition studies were performed at pH 7.4 and solubility studies at pH 7.5. *6 Absence of inhibition with one-third saturated solution.

**Converting Enzyme Inhibitors**

A series of peptides originally isolated from snake venom are effective inhibitors of angiotensin-converting enzyme.44 They act to block the cleavage of angiotensin I and thereby prevent the formation of angiotensin II.44 The synthetic nonapeptide PYR-TRP-PRO-ARG-PHE-GLN-ILE-PRO-PRO will be described in detail subsequently.

**Competitive Inhibitors of Angiotensin II**

Sarcosine8alanine8angiotensin II (Sar8Ala8AII);47 (fig. 4) is an example of a series of effective and specific inhibitors that compete with angiotensin II at its receptor sites. These peptides are based on variants of the structure of angiotensin II. The critical site of amino acid substitution, which determines the efficacy of an inhibitor, is the carboxyterminal position. Substitutions at the amino terminal position serve to enhance activity. These compounds have now found both experimental and clinical applications.49-54

**Renin and Sodium Balance**

The intravenous infusion of converting enzyme inhibitor (CEI) has no discernible effect either on blood pressure or plasma renin activity in a normal experimental animal maintained on an adequate sodium intake.57-58 The angiotensin II competitive inhibitor Sar8Ala8AII results in a brief pressor response in the normal animal, followed by the prompt return of blood pressure to normal levels even though infusion of the drug may continue.49 50

Sodium deprivation, however, uncovers a very different response.50 Figure 5 shows the results of a typical experiment in a trained conscious dog. This animal had undergone prior adrenalectomy and was subsequently maintained on 25 mg

![Figure 5](https://example.com/figure5.png)  
*Figure 5. Similarity of degree of hypotension induced in an adrenalectomized, sodium-depleted dog given [Sar8, Ala8] angiotensin II (20 μg/min) and the nonapeptide converting enzyme inhibitor (5 mg). Note that the initial pressor response to the angiotensin II analog is absent with the CEI. From Samuels AI, Miller ED Jr, Fray JCS, Haber E, Barger AC. Fed Proc (in press).*
cortisone and 1 mg DOCA. On a normal intake of sodium (50–60 mEq/day), CEI did not lower blood pressure. However, on a 10 mEq/day diet, very different results were obtained. Baseline blood pressure levels were within the normal range. The animal was alert and manifested normal activity and behavior. Plasma renin activity was moderately elevated. Upon administration of Sar²Ala⁸AII, blood pressure levels first rose and then fell sharply below control levels. These hemodynamic changes were associated with a striking rise in plasma renin activity. Blood pressure soon returned to control levels coincident with a fall in renin activity. The subsequent administration of CEI resulted in a prompt fall in blood pressure without the initial rise noted when Sar²Ala⁸AII was used. Renin activity also rose coincidently with the hemodynamic change. Similar observations were made in 13 experiments in four such dogs. The results of these experiments are consistent with earlier reports.⁴⁹-⁵₂, ⁵⁷-⁶⁰

A fall in blood pressure in a sodium-depleted animal consequent to blockade of the action of renin by two very different methods suggests that, in the presence of a limited extracellular fluid volume, the hormone plays a major role in blood pressure maintenance. Is the immediate rise in renin activity simply the result of baroreceptor stimulation or reflex increase in sympathetic activity secondary to a lowered blood pressure? Or are other mechanisms involved? An answer is suggested by the following experiment.⁶¹ A

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**Figure 6.** A) Substantiated hypotension induced by infusion of nonapeptide converting enzyme inhibitor in adrenalectomized, sodium-depleted animal associated with a rise in plasma renin activity. B) Prevention of rise in plasma renin activity during administration of CEI in sodium-depleted, adrenalectomized dog by infusion of angiotensin II sufficient to produce modest elevation of pressure. Note rapid rise of PRA following cessation of AII infusion. C) Rise of PRA during infusion of CEI in sodium-depleted, adrenalectomized dog given an equipressor dose of phenylephrine (compare with B). From Samuels AI, Miller ED Jr, Fray JCS, Haber E, and Barger AC⁶¹ (Fed Proc, in press).
prolonged infusion of CEI administered to a sodium-depleted adrenalec-tomized dog resulted in hypotension throughout the duration of the infusion (fig. 6A). Renin activity rose until it reached levels over 12-fold of that of the control period. When angiotensin II was infused at a sufficient rate to maintain normal blood pressure during the CEI infusion, renin activity did not rise (fig. 6B). These results indicate that if both blood pressure and angiotensin II concentration are maintained, CEI alone does not alter plasma renin activity. If the alpha-adrenergic agonist phenylephrine, which itself has no effect on renin activity, is used to maintain blood pressure instead of angiotensin II during CEI blockade, a rise in renin activity still occurs, though to a somewhat lesser degree (fig. 6C). To exclude reflex beta-adrenergic stimulation as the cause of renin release, a blocking dose of propranolol was given prior to the injection of the inhibitor. Even though heart rate did not change as blood pressure fell, plasma renin activity increased significantly. These experiments indicate that the rate of renin secretion is controlled by both blood pressure and angiotensin II concentration. Thus another feedback loop is uncovered: the direct modulation of renin secretion by angiotensin II.

In earlier experiments, the intravenous infusion of angiotensin II had been shown to decrease renin release or plasma renin activity in human subjects64 and other species.65-66 Blair-West et al.67 showed that this inhibition could be demonstrated at physiologic concentrations of the hormone and that it was independent of changes in renal arterial pressure and sodium concentration. More recently Freedman et al.68 demonstrated that infusions of either angiotensin II or the heptapeptide des-1-Asp-angiotensin II at rates that do not significantly affect renal blood flow, arterial blood pressure, or sodium excretion, results in a decrease in plasma renin activity. These reports further support direct negative feedback of angiotensin II on renin secretion.

**Studies in Normal Human Subjects**

Does the renin angiotensin system come into play only at the extremes of extracellular fluid volume depletion, or does it also have a role in blood pressure regulation at lesser degrees of physiologic stress? Studies in human subjects have addressed this question.69 Four normal young subjects were in sodium balance on a 110 mEq intake. They were first studied in the supine position, then tilted upright to 70° before and after administration of CEI. The nature and duration of the tilting stress was judiciously chosen so that none of these normal subjects would become either hypertensive or faint. During the study heart rate and blood pressure were monitored and frequent blood samples were obtained for plasma renin activity and aldosterone concentration.

As can be seen from figure 7, prior to the administration of CEI, upright tilting resulted in little hemodynamic change, a minimal narrowing of pulse pressure, and a slight tachycardia. However, a rise in both plasma renin activity and plasma aldosterone concentration occurred. The administration of CEI did not result in significant hemody-
dynamic changes either in the supine position or on tilting. Renin activity increased both in the supine position and on tilting, but no corresponding rise in aldosterone concentration was apparent. After sodium depletion, either by diet or after the administration of a diuretic, an average weight loss of 2.6 kg was observed. Supine renin and aldosterone plasma values were higher during the control period; the hemodynamic response to tilting was somewhat more marked than on the higher sodium intake. After administration of CEI, tilting was associated with a striking fall in blood pressure to hypotensive levels accompanied by an even greater elevation in renin activity; again, there was no change in plasma aldosterone concentration.

To determine the effects of prolonged infusion of CEI in the supine posture, another group of five normal subjects was given 80 mg of furosemide; they sustained a weight loss of 1.54 kg (fig. 8). The administration of CEI was followed by a transient drop in diastolic blood pressure associated with a brief tachycardia. Blood pressure and heart rate returned to control values and remained there during a constant infusion of CEI for the next 145 minutes. Renin activity rose rapidly to very high levels immediately after the initiation of CEI infusion. At the same time plasma aldosterone values fell.

These observations in normal man extend and reinforce the conclusions of earlier experiments in sodium-depleted animals. A marked fall in blood pressure and a rise in heart rate on tilting in the sodium-depleted, but not in sodium-replete subjects, indicates that angiotensin II is an essential element of blood pressure control, even in states of only modest extracellular fluid volume depletion. The rise of plasma renin activity in the supine position subsequent to CEI (fig. 8), in the absence of a fall in blood pressure, suggests that angiotensin II exerts direct feedback control on renin secretion. The absence of the expected rise in plasma aldosterone after CEI, both on tilting or sodium-depletion in the presence of an exaggerated renin activity, suggests that angiotensin II is the primary stimulus to aldosterone secretion in response to sodium-depletion or postural change.

Experimental Renovascular Hypertension

The importance of renin in the genesis and maintenance of renovascular hypertension has been subject to conflicting interpretations and, at times, apparently irreconcilable experimental data. An elevation in renal vein renin has proven to be a most useful diagnostic test for curable unilateral renal arterial stenosis. Yet in chronic experimental or clinical renovascular hypertension, plasma renin activity is often normal.

Acute experimental studies are difficult to interpret because anesthesia, surgical trauma, and blood loss all modify the response of the renin-angiotensin system. Renal function has been shown to be altered as long as one to two weeks after surgery. To circumvent some of these problems studies were performed on trained, conscious animals appropriately prepared and examined at least two weeks subsequent to surgery. The animals had undergone unilateral nephrectomy. An external catheter allowed inflation of a cuff around the renal artery while catheters proximal and distal to the cuff permitted precise adjustment of the gradient created by this stenosis. Blood samples could be obtained either in the renal vein or in the vena cava.

Figure 9 summarizes the events during the first hour of constriction. A substantial gradient is established between

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**Figure 8.** Mean data of five sodium-depleted subjects studied in the supine position and during tilting, with and without converting enzyme inhibitor. Modified from Sancho J, Re R, Burton J, Barger AC, Haber E.
the aorta and the renal artery and is maintained at a constant level by adjustment of the cuff. A rapid rise in mean aortic pressure to hypertensive levels occurs and is associated with an early elevation of plasma renin activity. The administration of CEI results in a prompt fall in blood pressure to near normotensive levels associated with a striking rise in plasma renin activity. These observations indicate that the renin-angiotensin system is responsible for the initial rise in systemic blood pressure that results from renal artery hypotension. Blockade of the conversion of angiotensin I to II promptly reduced blood pressure to normal.

During chronic renal artery constriction associated with persistent hypertension, plasma renin activity is elevated for several days, but it then returns to control levels as sodium and water retention occur.75 We looked at the question of whether or not an elevation of angiotensin II concentration is a necessary prerequisite for chronic renovascular hypertension. A constant infusion of CEI was begun prior to renal artery constriction and maintained for several days.84 Figure 10 shows two successive experiments in the same dog. In the first series of observations, the renal artery was constricted and blood pressure rose over the course of four days from a mean pressure of 85 mm Hg to 120 mm Hg. Plasma renin activity rose, peaking on the second day and then declining to control levels by the third day. During a subsequent experimental period, the artery was constricted during an infusion of CEI. Renin activity rose to much higher levels than during the first experimental period, but no elevation of blood pressure occurred over the course of four days. Such experiments provide strong evidence that elevated angiotensin II concentrations are essential in the initiation of chronic renovascular hypertension. They do not delineate the role of angiotensin II in the maintenance of established renovascular hypertension at a time when plasma renin activity is normal.31

Wakerlin et al.72 reported the lowering of blood pressure in chronic renovascular hypertensive dogs as a result of immunization with renin. More recent evidence, however, has not supported the view that angiotensin II plays a significant role in the maintenance of chronic hypertension in the one-kidney Goldblatt rabbit60 or rat.81,79,74 After the initiation of chronic renovascular hypertension in the dog, a single intravenous injection of CEI produces a significant fall in blood pressure during the first three days. After the fourth day, the effect becomes progressively less marked.85 These results are in essential agreement with those of Bumpus and co-workers46 who employed the Sar1Ile6 analog of angiotensin II. They reported that blockade was effective in reducing blood pressure in the conscious dog within three to six days after renal artery constriction but not later. Similarly, Johnson and co-workers86 reported that Sar1Ala4II did not lower blood pressure in one-kidney Goldblatt dogs two to seven weeks after constriction of the renal artery.

All of these observations further confirm the earlier report of Pals et al.53 that the blockade of angiotensin II in the one-kidney Goldblatt rat lowers blood pressure only within the first two weeks after an artery constriction. Although Bing and Nielsin65 suggested that the Sar1Ala4II analog was effective in lowering blood pressure one to two months after renal artery constriction in the rat, three of their seven animals did not have a drop in blood pressure, and in only one animal did blood pressure fall below 160 mm Hg at the time of the maximum effect of the drug. Thus, the decreasing effectiveness of CEI and angiotensin II antagonists in lowering blood pressure in chronic one-kidney renovascular hypertension suggests that over time other factors begin to play an increasingly important role in the maintenance of elevated blood pressure.

Tobian and co-workers59 and Guyton et al.24 have stressed the importance of sodium and water retention in the
maintenance of the elevated blood pressure of chronic renovascular hypertension. Tagawa et al.\textsuperscript{71} have shown that in a unilaterally nephrectomized dog with a normal sodium intake, sodium retention and increased water intake followed the chronic constriction of the renal artery. Gavras and co-workers\textsuperscript{80} showed that in the sodium-depleted one-kidney Goldblatt rat, Sar'Ala\textsuperscript{8}AII resulted in a large drop in blood pressure, whereas after sodium repletion no fall in blood pressure could be demonstrated with this agent.

There are two phases of renovascular hypertension: initially, elevated blood pressure is maintained by the direct pressor actions of angiotensin II; during a later chronic phase, blood pressure is maintained largely as a result of hypervolemia, mediated by sodium and water retention. Whether sodium retention is simply the direct effect of diminished renal arterial pressure on kidney function or is mediated indirectly via angiotensin II through its action on mineralocorticoid secretion remains to be determined. The lack of response to single injections of either CEI or angiotensin II analogs in chronic renovascular hypertension is not conclusive. Even upon release of renal artery constriction, a period of 24 hours is required to effect a diuresis with a consequent normalization of blood pressure.\textsuperscript{71} A brief removal of angiotensin II effect is not enough to bring about this long-term homeostatic adjustment. A critical experiment, which has not yet been reported, is the chronic infusion of either a receptor blocker (angiotensin II analog) or CEI after the establishment of chronic renovascular hypertension. If angiotensin II is ultimately responsible for maintenance of hypertension, a sodium diuresis should occur with a return of blood pressure to normal levels.

**Renin-dependent Hypertension in Human Subjects**

While the etiologic role of the renin-angiotensin system in chronic renovascular hypertension remains to be established, it is generally agreed that the determination of renin activity in renal venous blood is a most useful diagnostic aid. When renal vein renin activity from the affected kidney is greater than that of the uninvolved side, the probability of improvement in blood pressure after surgery is considerable.\textsuperscript{77,81} Prior treatment to stimulate renin release by either a decrease in circulating angiotensin II concentration or blockade of the angiotensin receptor has been shown to enhance selectively renin release from the affected kidney.\textsuperscript{77,82} This technique improves diagnostic accuracy of renal artery stenosis.

Figure 11 shows a study in a patient in whom severe right renal artery stenosis was demonstrated later. At the time of bilateral renal venous catheterization, a single intravenous dose of CEI was administered. An unanticipated and striking fall in blood pressure occurred. Right renal vein renin ac-

**Figure 10.** Comparison of changes in mean arterial pressure and basal plasma renin activity induced by renal artery constriction in the same dog without CEI (---) and during chronic infusion of CEI (---). From Miller ED Jr, Samuels AI, Haber E, Barger AC.\textsuperscript{88} Reprinted, by permission, from the American Journal of Physiology (228: 450, 1975).

**Figure 11.** Changes in systolic and diastolic blood pressure, pulse, renin activity in the renal veins, and a peripheral vein and plasma aldosterone concentration in a 54-year-old man with chronic hypertension in response to converting enzyme inhibitor (CEI). Blood pressure during the previous year had averaged 170/100 mm Hg despite therapy with hydrochlorothiazide, triamterene, hydralazine, and guanethidine. Furosemide (80 mg) had been administered 24 hours prior to the study. Arrow indicates the time of administration of CEI (unpublished data of Duhme DW, Sancho J, Athanasoulia C, Haber E, Koch-Weser J; modified from Lancet 1: 408, 1974).
tivity rose to very high levels. The small increase in left renal vein renin simply reflected the increase in systemic renin activity. The ratio between right and left renal venous renin activity, which is utilized as a diagnostic index, rose from 5.5 to 14.0. While the diagnosis of unilateral renal artery stenosis was not difficult to make in this patient, a marked selective stimulation of this kind may be of value in many patients who exhibit marginal lateralization in renal venous renin activities. (The undesirable hypotension experienced by this patient was probably the result of sodium depletion by diuretics prior to CEI administration. Hypotension has not occurred in individuals in normal sodium balance undergoing this diagnostic treatment.)

Several investigators have suggested that a fall in blood pressure in response either to CEI or angiotensin II analogs may be of value in identifying patients with renin-dependent hypertension.84-86 Gavras et al.88 stress that sensitivity of detection may increase if subjects have been previously sodium depleted. A fall in blood pressure under these circumstances must be interpreted with the greatest caution, however. Under the circumstances of testing, we only learn that blood pressure maintenance is in part dependent on angiotensin II, which is the normal physiologic state in volume depletion in normal patients as well as in those with hypertension of other than a renin basis.

Utilization of inhibitors in the identification of renin-dependent hypertension may require that testing be carried out while subjects are in a state of normal sodium balance. An example is shown in figure 12. The patient was a 28-year-old woman with chronic bilateral pyelonephritis and persistent hypertension. She was studied while in sodium balance on a daily 110 mEq sodium diet. Plasma renin activities were abnormally elevated (normal values on this diet are 1.02 ± 0.21 ng/ml/hr). The administration of CEI resulted in a prompt fall in blood pressure to the normotensive range. There was a further rise in plasma renin activity, accompanied by a fall in plasma aldosterone that confirmed blockade of angiotensin production.

The Renin-Angiotensin System in Experimental Congestive Heart Failure

The role that the renin-angiotensin system plays in congestive heart failure remains uncertain. Early experiments of Deming and Leutscher84 demonstrated sodium-retaining activity in the urine of patients with cardiac failure. Davis et al.86 later suggested that increased circulating angiotensin II levels were responsible for hypersecretion of aldosterone in experimental heart failure. A variety of subsequent clinical and experimental studies, however, presented conflicting results. Plasma renin activity during cardiac failure was shown to be high, low, or normal.86, 87 Watkins et al.88 addressed this question directly by employing CEI in a congestive failure model in the conscious dog. Either the thoracic inferior vena cava or the pulmonary artery were compressed by an externally controlled inflatable cuff. As either of the cuffs was inflated, blood pressure fell and plasma renin activity and plasma aldosterone levels rose rapidly. Sodium excretion fell to nearly zero, plasma volume, and body weight increased. When ascites and edema were manifest, blood pressure was gradually restored. Upon hemodynamic compensation, plasma renin activity and aldosterone fell to control levels and sodium excretion rose. A new equilibrium was established in a volume-expanded animal. However, if CEI was administered while plasma renin activity was elevated and prior to the development of volume expansion, a 25–30 mm Hg drop in blood pressure occurred. Chronic infusion of CEI prevented the establishment of the new equilibrium. Plasma aldosterone concentration did not rise, volume expansion did not occur, and hypotension persisted.

Similar observations were reported by Johnson and Davis89 utilizing an angiotensin II analog. Thus, congestive heart failure appears to be analogous in a number of ways to renovascular hypertension. The renin-angiotensin-aldosterone system is essential in initiation of compensatory adjustments that are the hallmark of this pathophysiologic state, particularly the increase in plasma volume and consequent development of edema.

Conclusion

The renin-angiotensin-aldosterone system has been more fully characterized since inhibitory agents have become available. It now seems that angiotensin II does not play a crucial role in the normal animal or human subject in sodium balance, but it does become a central element in the maintenance of blood pressure after sodium deprivation. Angiotensin II is essential in the initiation of renovascular hypertension. When free sodium and fluid intake is per-
mitted in the unilaterally nephrectomized Goldblatt hypertensive animal, angiotensin II loses its importance in the maintenance of chronic hypertension. In a similar fashion, compensatory fluid retention in experimental congestive failure requires the mediation of angiotensin II. In its absence, hemodynamic equilibrium cannot be restored and blood pressure remains at hypotensive levels.

Angiotensin antagonists may be most useful clinically in identifying renin-dependent hypertension, though great caution must be exercised in interpreting a blood pressure fall in a sodium-depleted subject since this is also seen in normal individuals. These compounds may be particularly helpful in the diagnosis of unilateral renal artery stenosis, since renin secretion on the affected side is selectively stimulated. Studies with antagonists have also confirmed that angiotensin II is the major stimulus to aldosterone secretion in response to posture or sodium deprivation and that angiotensin II acts as a feedback repressor of renin.

We look forward to the next breakthrough which will probably be heralded by new technological advances. New inhibitors of the action of renin itself may become available. Soon purified renin will have been isolated. Renin antibodies will make direct measurement of renin concentration possible. Both discoveries will be progressive steps toward full characterization of the catalytic site and mechanism of action of this important enzyme.

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