A Steady-State Control Analysis of the Renin-Angiotensin-Aldosterone System

By Edward H. Blaine, James O. Davis, and Patrick D. Harris

ABSTRACT

This communication develops a steady-state block diagram about the configuration of the renin-angiotensin-aldosterone system in relation to the mineralocorticoid-dependent reabsorption of sodium. Two principal mechanisms appear to be involved in the control of renin secretion. The baroreceptor hypothesis suggests that decreased stretch of the afferent glomerular arteriole produces increased renin secretion. The macula densa theory, on the other hand, suggests that renin secretion responds to alterations either in sodium load or in sodium concentration at the macula densa. These two receptors are presented as parallel feedback pathways which are independently capable of altering renin secretion. This concept of independent receptor function is supported by literature in which one of the receptor pathways was eliminated. The system configuration for the renin-angiotensin-aldosterone system suggests the hypothesis that the vascular receptor controls renin secretion in the autoregulatory range of blood pressure and that macula densa control dominates at pressures below the autoregulatory range. The control system diagram also calls attention to certain unique features of the renin-angiotensin-aldosterone system; it indicates that (1) a chronic low-sodium diet involves changes in both input variables (extracellular fluid volume) and parameters (hepatic blood flow) to maximize sodium reabsorption, (2) thoracic inferior vena cava constriction opens the feedback loop so that the renal receptors do not perceive increases in extracellular fluid volume, (3) congestive heart failure reduces the overall gain of the system, and (4) a small nonhypotensive hemorrhage primarily increases renin secretion through renal sympathetic nerve stimulation.

KEY WORDS mineralocorticoid-dependent sodium reabsorption renal baroreceptor hypothesis congestive heart failure renal autoregulation low-sodium diet hemorrhage constriction of thoracic vena cava macula densa receptor

In general, physiological mechanisms may be organized into control systems with identification of feedback loops, controlled variables, and control functions. This form of organization emphasizes the properties of the system which are related to the configuration of the system or the interconnections within it rather than to the characteristics of individual components. In addition, this organizational plan facilitates a predictive form of thinking in which anticipated responses can be compared to experimental results. Most of the literature on the renin-angiotensin-aldosterone (R-A-A) system is concerned with the characteristics of particular segments, but few authors have addressed themselves to an integrated view of the entire system. Among them, Guyton and co-workers have provided a significant mathematical model of nephron dynamics (1) and have analyzed the open-loop characteristics of the renin-angiotensin...
system in the dog (2). The present communication analyzes available data to develop a steady-state block diagram as a hypothesis about the configurational properties of the R-A-A system.

The present model is concerned primarily with the mineralocorticoid-dependent reabsorption of sodium; the mechanisms which control antidiuretic hormone or thirst have not been included. The R-A-A system can be divided into four segments: (1) relation of renin secretion to the plasma concentration of aldosterone, (2) relation of plasma aldosterone concentration to renal afferent arteriolar pressure, (3) effect of sodium delivery to the macula densa on renin secretion as a feedback pathway, and (4) effect of afferent arteriolar stretch on renin secretion as a feedback pathway.

This format for subdivision of the system emphasizes the two principal mechanisms which have been hypothesized for control of renin secretion. In the baroreceptor or stretch hypothesis, the receptor is located in the afferent glomerular arteriole and responds to decreased stretch of the vascular wall by producing increased renin secretion (3–6). The macula densa theory, on the other hand, maintains that renin secretion responds to alterations either in sodium load (7–9) or in sodium concentration at the macula densa (10–12). The present model assumes that two distinct receptors exist and postulates that two pathways function as parallel additive limbs in a negative-feedback control system. The alternative hypothesis that either receptor modifies the sensitivity (or gain) of the other is discarded in the development of the system configuration.

This system description is represented by numbered blocks which show components where an input variable functionally determines an output variable. These steady-state relationships are indicated by graphs (Figs. 1–6) which are based on a synthesis of existing information from published data. In some instances, hypothetical relationships are presented to conform with the other components of the system. In most blocks, a normal operating point is indicated. Variables in the system are illustrated as arrows to and from the sides of the blocks with the output, or dependent variable, on the ordinate and the input, or independent variable, on the abscissa of the graphs within the blocks. In many of the blocks, arrows enter from the top or the bottom of the blocks to represent factors which alter the basic relationship between the input and output variables. By convention, these factors are called "parameters" in the system.

RELATION OF RENIN SECRETION TO THE PLASMA CONCENTRATION OF ALDOSTERONE (FIG. 1)*

Block 1.—A certain portion of the total amount of renin secreted by the kidneys is metabolized by the liver (14, 19–21). Thus, the plasma level of renin reflects a dynamic balance between its secretion and destruction, which is expressed by the equation:

\[
\text{plasma renin concentration (GU/liter)} = \frac{\text{renin secretion rate (GU/day)}}{\text{metabolic clearance rate (liter/day)}}.
\]

Several authors (14, 19–21) have found that the percent of renin extracted by the liver remains relatively constant over wide variations in plasma renin concentration. This means that changes in renin secretion result in linearly related changes in plasma renin concentration. Schneider et al. (22) showed that the amount of renin extracted by the liver is also a function of acute changes in hepatic plasma flow. Therefore, in accordance with the Fick principle, hepatic plasma flow is a

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*The literature citations for Figures 1–5 indicate the sources for the normal operating points and for the shape of the curves. The normal operating points represent generally accepted values for man. We recognize that different experimental techniques in different laboratories have provided a wide range of normal values for these variables; however, for simplicity in the figures, a single representative value from the literature is presented. In some instances, these representative values have been calculated or estimated from published data. GU is the abbreviation for Goldblatt unit.
Effect of renin secretion on the plasma concentration of aldosterone. Normal human operating points are the values shown on the axes in each block. Renin secretion rate (dR/dt) (13, 14), plasma renin concentration (R) (13), rate of angiotensin II production (dAII/dt) (15), plasma angiotensin II concentration (AII) (15), aldosterone secretion rate (dAl/dt) (16), and plasma aldosterone concentration (Al) (17, 18).

Parameter which can alter the slope of this relationship.

Block 2.—A relationship between the plasma concentration of renin and the rate of angiotensin II formation in the blood of anesthetized dogs was qualitatively demonstrated by Regoli and Vane (23). The quantitative relationship is based on data by Pickens et al. (24) who used a standard bioassay technique to measure the amount of angiotensin II which was generated by the addition of standard amounts of partially purified human renin to an incubation mixture. This measurement depended on the presence of excess renin substrate in the incubation mixture to give a zero-order kinetic reaction (13). Although this degree of excess substrate does not exist in the in vivo condition (25), it seems likely that renin substrate is continually replenished by the liver as substrate is converted to angiotensin I. Thus, although renin substrate concentrations in vivo indicate first-order kinetics in some conditions such as liver disease, the reaction rate is usually linearly dependent on enzyme concentration. Since these extreme alterations in renin substrate concentration alter the relationship between plasma renin concentration and angiotensin II production rate, renin substrate concentration is a parameter. Angiotensin I is converted to angiotensin II on passage through the pulmonary circulation (26). Since any alteration in pulmonary conversion rate also alters the slope of this curve, this conversion by the lungs is also a parameter.
Block 3.—The relationship between the rate of angiotensin II production and the plasma concentration of angiotensin II has been studied by Doyle et al. (27), using a radioactive analogue of angiotensin II. These investigators observed a linear relationship between the rate of phenylthiocarbamyl angiotensin II-35S infusion and its plasma level in the steady state. Thus, any change in production rate of natural angiotensin II probably produces a linear change in vivo in the plasma concentration of angiotensin II. Plasma and tissue angiotensinases are a parameter for this function, but as pointed out by Biron and Huggins (28) they are probably of minor significance due to the slow action of these enzymes as compared to the rapid extraction of angiotensin II by the peripheral vascular beds.

Block 4.—Many investigators (29) have provided evidence that angiotensin II stimulates aldosterone secretion. The work of Blair-West et al. (30) in sheep indicated that angiotensin II infusion into the arterial supply of an isolated adrenal gland affected the rate of aldosterone production according to a typical sigmoid dose-response curve. In the majority of mammals, including man, angiotensin II is the primary regulator of aldosterone production, but the plasma levels of sodium and potassium also influence the secretion of aldosterone (30, 31) as does the level of adrenocorticotropic hormone (ACTH) (32).

Block 5.—Ayers et al. (33), Tait et al. (34), and Davis et al. (35) have indicated that the liver is the principal site of aldosterone metabolism. In normal man (36) and in both normal dogs and dogs with experimental heart failure (35), the hepatic extraction of aldosterone approaches 100% and is relatively constant at various plasma levels of aldosterone. These data indicate a linear relationship between the rate of aldosterone secretion and the plasma concentration of aldosterone. However, since aldosterone extraction is almost complete in one passage through the liver, its metabolism is flow limited (34, 35). Consequently, hepatic blood flow is a parameter which can alter the slope of the relationship between aldosterone secretion and plasma aldosterone concentration. The role of the kidneys in the metabolism of aldosterone is minor and has been omitted from the diagram.

RELATION OF PLASMA ALDOSTERONE CONCENTRATION TO RENAL AFFERENT ARTERIOLAR PRESSURE (FIG. 2)

Block 6.—Aldosterone promotes sodium reabsorption in distal nephrons and in extra-renal sites such as salivary glands, sweat glands, and intestinal epithelium. Since the evidence is conflicting in regard to an effect of aldosterone on proximal renal tubules, only the distal nephron will be considered in this segment of the control diagram. Investigators have demonstrated the sodium-retaining effects of aldosterone or the less potent mineralocorticoid, desoxycorticosterone acetate (DOCA), in dogs (38), sheep (39), and humans (40). The data showed that, with increased levels of aldosterone or DOCA, sodium excretion decreased. Since sodium reabsorption is reciprocally related to sodium excretion, the data on the sodium retention observed by these investigators provide the function which represents the effect of plasma aldosterone on sodium reabsorption.

Block 7.—This component is presented as a linear relationship between extracellular fluid volume and sodium reabsorption by the distal nephron. This linearity implies (1) that increased sodium reabsorption is associated with increased water reabsorption and (2) that increased sodium reabsorption is accompanied by increased antidiuretic hormone (ADH) secretion, which helps to provide an isotonic extracellular fluid. Recent evidence (41) also suggests that angiotensin II directly stimulates ADH secretion. This direct action of angiotensin II on ADH secretion is possibly a second mechanism for ensuring isotonic reabsorption of sodium and water during renal control of extracellular fluid volume.

Block 8.—Any change in extracellular fluid volume is associated with a similar directional change in vascular volume; however, the nonlinear compliance of the venous vascular
Effect of plasma aldosterone concentration on renal afferent arteriolar pressure. Normal human operating points are the values shown on the axes. Rate of sodium reabsorption by the distal nephron (dNa/dt) \( \text{dNa}_{\text{d}}/\text{dt} \) \( \text{dNa}_{\text{d}}/\text{dt} \) (37), extracellular fluid volume (ECF) \( \text{ECF} \) (37), vascular volume (BV) \( \text{BV} \) (38), mean arterial blood pressure \( \text{P}_{\text{art}} \) (37), and mean afferent arteriolar pressure \( \text{P}_{\text{aa}} \) (37).

tree and the presence of the cellular component of blood produces a nonlinear relationship. A plateau exists at the upper end of the curve since the maximum capacity of the vascular system is approached, and fluid will accumulate in the extracellular space with very little additional increase in the vascular space. Therefore, in this range of extracellular fluid volume, edema and ascites occur readily and are associated with capillary pressures in excess of 30 mm Hg (37). Vascular volume is dependent on Starling forces such as oncotic pressure, capillary pressure, and tissue pressure so these are illustrated as parameters which, if altered, would produce a new relationship. For example, a decrease in plasma oncotic pressure would shift the function downward and to the right since there would be a net movement of fluid into the interstitial space.

Block 9.—The pressure within the arterial system is determined by the volume of fluid (cardiac output) that is available to fill the arterial tree and by the size of the arterial space (that is, by changes in peripheral vascular diameters). Several factors including the sympathetic nerves, circulating catecholamines, intrinsic myogenic arteriolar tone, and perhaps angiotensin II contribute to the parameter “peripheral vascular tone.” Data presented by Coleman et al. (42) suggest that changes in peripheral resistance are important in maintaining an elevated blood pressure after expansion of the extracellular fluid space, since cardiac output rises initially and then returns to control levels. The relationship
between the degree of arterial filling and arterial pressure has not been determined experimentally since the arterial space has not been measured directly.

Block 10.—Although pressure in the renal afferent arteriole is slightly less than systemic arterial pressure, it is assumed that for a given state of the afferent arterioles, the distending pressure within these vessels is a linear function of the systemic arterial pressure. The parameters renal afferent and efferent arteriolar diameter can affect this relationship by altering the ratio of the pressure drops across the afferent and efferent arterioles. Also, changes in renal venous pressure or renal venous compliance will produce changes in the arteriolar diameters. All of these resistance changes can be influenced by the renal nerves and circulating catecholamines.

**EFFECT OF AFFERENT ARTERIOLAR PRESSURE ON THE MACULA DENS**

**ONE FEEDBACK PATHWAY (FIG. 3)**

Block 11.—By use of micropuncture techniques in rats, Gertz et al. (45) demonstrated that hydrostatic pressure within the glomerular capillaries is relatively constant above a mean systemic arterial pressure of approximately 90 mm Hg. This is related to the phenomenon of autoregulation of renal blood flow and, for a given diameter of the efferent arterioles, is determined primarily by resistance changes in the afferent arterioles (37). Below a mean arterial pressure of 90 mm Hg, glomerular capillary pressure is a linear function of the systemic pressure. Above this level, the pressure drop across the afferent arteriole becomes a linear function of systemic arterial pressure, i.e., as arterial pressure increases, afferent resistance increases proportionally. This provides a glomerular capillary pressure which is relatively constant and independent of changes in systemic arterial pressure above 90 mm Hg.

Block 12.—To obtain the effective filtration pressure, it is necessary to subtract from the glomerular capillary pressure the Starling forces which oppose filtration across the glomerular membrane. These forces are the oncotic pressure of the plasma and the pressure within the glomerular capsule.

Block 13.—Glomerular filtration rate is simply an expression of the rate of ultrafiltration by the glomerular membrane and is solely dependent on the effective filtration pressure for a given level of glomerular permeability. Hence, the curve relating glomerular filtration rate to effective filtration pressure is essentially a straight line. If one incorporates the concept that the rate of glomerular filtration influences hydrostatic pressure within the proximal tubule, the slope of the line changes.

Block 14.—This graph shows that the filtered load of sodium is directly proportional to the glomerular filtration rate for any given plasma concentration of sodium.

Block 15.—Approximately 85% of the filtered load of sodium is reabsorbed in the proximal renal tubules. Several investigators (46, 47) have indicated a glomerulotubular balance for the proximal tubules by suggesting that the percent reabsorption of sodium remains constant over wide ranges of filtered sodium load. If this is true, the relationship between proximal reabsorption and the filtered load of sodium is linear. However, other investigators (48, 49) have provided data which indicate that the glomerulotubular balance is not perfect. This means that proximal reabsorption of sodium does not increase to the same degree as an increase in the filtered load. In this event, the relationship between proximal sodium reabsorption and filtered load would be curvilinear.

Block 16.—This component indicates a mathematical relationship in which sodium reabsorption in the proximal tubule is subtracted from the filtered load of sodium to yield the sodium load which enters the loop of Henle.

Block 17.—Morgan and Berliner (43) used a continuous microperfusion technique to study sodium reabsorption in the short loops of Henle in the rat. When perfusion rate was increased from 10 nliters/min to 40 nliters/min, the amount of reabsorbed sodium as a fraction of delivered load decreased from 80% to 50%. This means that the graph for loop reabsorption of sodium as a function of...
Effect of afferent arteriolar pressure on the macula densa. Normal human operating points are the values shown on the axes. Glomerular capillary pressure (P\(_c\)), plasma colloid osmotic pressure (oncotic pressure), renal tubular pressure (tubular pressure), effective filtration pressure (P\(_{ef}\)), glomerular filtration rate (GFR), filtered load of sodium (F\(_{Na}\)), rate of proximal tubular sodium reabsorption (dN\(_{Na}\)/dt), and sodium load to the loop of Henle (dN\(_{Na}\)/dt) (43), sodium load to the macula densa segment (MD Load\(_{Na}\)) (37, 43), and rate of sodium transport by the macula densa cells (dN\(_{MD}\)/dt) (no data available). In a recent communication, Brenner et al. (44) reported a value of 60 cm H\(_2\)O for glomerular capillary pressure in a unique strain of Wistar rats with glomeruli on the renal cortical surface.

delivered load from the proximal tubules is curvilinear.

Block 18.—The sodium load which is presented to the macula densa is the sodium load which is delivered by the proximal tubule to the loop of Henle minus the amount of sodium reabsorbed by the loop.

Block 19.—This element represents a relationship between the sodium load at the macula densa and the rate of sodium reab-
sorption by the macula densa cells. According to the hypothesis of Vander and Carlson (8), the macula densa cells behave in a fashion qualitatively similar to the cells of the ascending limb of the loop of Henle. When the sodium load to the early distal tubule is increased, the macula densa cells increase their rate of sodium transport and presumably raise the intracellular concentration of sodium (8). Vander and Carlson (8) have suggested that these changes in macula densa sodium lead to a reduction in renin secretion. If these characteristics are assumed for the macula densa cells, the effects of such diuretics as furosemide (8, 11) on renin secretion can be explained adequately. Under these conditions, even though the sodium delivery to the macula densa segment is high, the diuretics might inhibit sodium transport by the ascending limb and macula densa and, consequently, decrease the intracellular concentration of sodium to enhance renin secretion (8). Postulation of this mechanism implies that aldosterone acts on the renal tubules at a site distal to the macula densa since Geelhoed and Vander (50) have shown that aldosterone does not have a direct inhibitory effect on renin secretion. In contrast, it has been postulated (10-12) that the macula densa receptor is sensitive to sodium concentration in tubule fluid rather than to sodium load, with an increase in sodium concentration being associated with increased renin secretion. In this hypothesis (1, 10), it has been suggested that the renin-angiotensin system participates in the regulation of renal blood flow and glomerular filtration rate through an intrarenal feedback mechanism.

**EFFECT OF HYDROSTATIC PRESSURE ON THE AFFERENT ARTERIOLE—A SECOND FEEDBACK PATHWAY (FIG. 4)**

**Block 21.**—Several investigators (51) have demonstrated that changes in the head of hydrostatic pressure in the afferent arteriole alter the resistance to flow through the afferent arterioles. These changes in resistance must reflect changes in radius of the afferent arteriole, which result from changes in the tone of the smooth muscle in the vessel wall. Although at the present time there are insufficient data to identify the actual output variable for this component, it is suggested that changes in afferent arteriolar radius and vascular tone alter the degree of “stretch” of some element in the wall of the afferent arteriole. It should be pointed out that decreased stretch does not necessarily imply decreased afferent arteriolar diameter. For example, renal autoregulation appears to involve a change in intrinsic smooth muscle contractility, and a decrease in arterial pressure is associated with renal arteriolar dilation and increased renin secretion. Presumably, this alteration in afferent arteriolar stretch affects the renin-release mechanism since Blaine et al. (5) reported increases in renin secretion with reduction in renal perfusion pressures in kidneys with no sodium delivery to the macula densa. Afferent arteriolar compliance is a parameter for this component and is affected by nerve activity, myogenic contractility of the afferent arterioles, the state of the elastic components of the vessel wall, and the renal interstitial pressure.

**Effect of hydrostatic pressure on the afferent arteriole. Normal human operating points are the values shown on the axes. Renal afferent arteriolar pressure (P<sub>aa</sub>) (37) and stretch of the afferent arteriolar wall (Stretch) (no data available).**

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EFFECT OF AFFERENT ARTERIOLAR STRETCH ON RENIN SECRETION—A CONCEPT OF PARALLEL FEEDBACK PATHWAYS (FIG. 5)

Block 20.—Vander and Carlson (8) postulated that renin secretion is inversely proportional to the rate of sodium transport by the macula densa cells. This implies the presence of a component which has a characteristic curve with a negative slope. Renin is stored in granules in the highly differentiated juxtaglomerular cells of the afferent arteriole (52), and it has been postulated that a substance is formed by the macula densa cells and influences the release of renin from these granules (53). Although nothing is known of such a “renin-releasing factor,” it could be a proteolytic enzyme that degrades the membrane which surrounds the granules. The presence of some factor—electrical, mechanical, or chemical—is necessary if one postulates an overall system configuration which has parallel or additive feedback pathways.

Block 22.—According to present hypotheses (3, 5) renin release is inversely proportional to hydrostatic pressure within the arteriole. Recently, convincing evidence (5, 6) has been provided for a renal vascular receptor which responds to changes in arteriolar hydrostatic pressure. This concept has been supported by several authors including Skinner et al. (4), who showed that graded constriction of the aorta above the renal artery gave proportional increases in renin secretion. This concept indicates the presence of a component which has a negative slope. As before, it is suggested that the output of this element is a hypothetical renin-releasing factor which acts on the renin storage granules to influence the rate of renin release.

Block 23.—This relationship represents simple addition of the two receptor outputs as parallel feedback pathways.

FIGURE 5
Effects of afferent arteriolar stretch and macula densa sodium transport on renin secretion. No quantitative data are available for these components. Macula densa sodium transport \( (\frac{dNa_{MD}}{dt}) \), renin-releasing factor \( (RRF) \), renin secretion rate \( (\frac{dR}{dt}) \).

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Block 24.—This component illustrates the concept that an increase in the postulated renin-releasing factor affects the membrane of the renin storage granules to increase renin secretion. This block also includes three factors as parameters which alter the synthesis, storage, or release of renin. Sodium intake may be of particular importance since sodium depletion produces increased renin concentration within the kidney (52, 54). Moreover, Bunag et al. (55) have shown that dogs on a low-sodium diet release more renin after reduction of renal perfusion pressure than do sodium-replete dogs. Experiments with hemorrhage as the stimulus for renin secretion have produced similar findings (56). Thus, a negative sodium balance shifts the characteristic curve upward and to the left. Recent data indicate that renal nerve stimulation and norepinephrine infusion (57) increase renin secretion in the nonfiltering kidney in which the afferent arterioles are dilated with papaverine. Thus, the renal nerves and circulating catecholamines also influence renin release, possibly by a direct action on the juxtaglomerular cells. Bunag et al. (58) and Vander (59) found that direct infusion of high levels of ADH into the renal artery suppresses renin secretion. More recently, Tagawa et al. (60) demonstrated renin suppression in sodium-depleted conscious dogs with more physiological levels of ADH. Since there was no detectable change in sodium excretion in these studies, it is likely that ADH acts directly on the renal arterioles or on the juxtaglomerular cells.

Action of Potassium and Angiotensin II on Renin Secretion.—Potassium is a factor which alters renin secretion but which has not been illustrated in the system diagram (Fig. 6). Increased plasma levels of potassium are associated with decreased renin secretion (61-64). In addition, direct infusion of a hyperkalemic solution into the renal artery rapidly reduces renin secretion (65). Thus, potassium could have a direct effect on renin release either by stabilizing the membrane of the renin storage granules or by altering the production of renin-releasing factor. Alternatively, potassium might act on the renal tubules upstream from the macula densa to inhibit sodium reabsorption (66) and thus increase the macula densa sodium load and reduce renin secretion. Preliminary experiments by Shade and Davis (unpublished) support the latter interpretation, since potassium infusion into the renal artery of a nonfiltering kidney had no influence on renin secretion.

Renal artery infusion of physiological levels of angiotensin II suppressed renin secretion (58, 67, 68). Also, angiotensin II has a natriuretic effect (69), and there is some evidence (70) that angiotensin II exerts its action on the distal tubule beyond the macula densa. In this event, the macula densa would not sense the change in renal tubule sodium, and, therefore, angiotensin II might act directly on block 24 to inhibit renin release. If inhibition of renin secretion is a physiological function of angiotensin II, there would be a negative feedback loop within the larger feedback loop of the R-A-A system. This smaller loop might have a relatively low gain which would allow the larger loop to be dominant during homeostasis.

FUNCTIONAL ROLE OF THE RECEPTOR PATHWAYS IN THE OVERALL SYSTEM (FIG. 6)

The proposed receptor pathways for renin secretion are illustrated as parallel limbs which are independently capable of altering renin secretion. In this configuration, it is assumed that one receptor is sensitive to the pressure in the arterial system and that the other is sensitive to changes in sodium delivery to the macula densa. This working hypothesis does not eliminate the possibility that the macula densa receptor may function by altering the sensitivity of the vascular receptor. The latter possibility is consistent with the evidence that a low sodium intake potentiates the renin response to a decrease in renal perfusion pressure (55). According to the system diagram (Fig. 6), one may test this concept of independent receptor function by eliminating, i.e., opening, one of the individual receptor pathways and providing experimental stimuli which are known to stimulate renin secretion in the normal kidney.
Vascular Receptor.—Selye and Stone (71) developed a renal model in rats in which the tubular elements were destroyed but the renal vasculature was intact. Although data on renin secretion were not available, this so-called “endocrine” kidney did exhibit a high content of a reninlike substance. Thus, these early studies suggested that intact tubular structures were not necessary for renin production and storage. In a somewhat similar manner, Blaine et al. (5) developed a nonfiltering kidney model in dogs for studies on the renin secretory mechanism. In the system diagram (Fig. 6), elimination of glomerular filtration would isolate the proposed renal vascular receptor. Thus, by using temporary renal ischemia and ureteral ligation in combination with renal denervation and adrenalectomy, blocks 12–20 in the control system and the effects of the renal nerves and circulating catecholamines (blocks 10, 21, 24) on the proposed vascular receptors could be eliminated. Using this model, Blaine and Davis (72) observed that renin secretion was stimulated in the anesthetized dog by a pressure reduction of only 10–15 mm Hg with no change in renal blood flow. This strongly supports the existence of a vascular receptor.
which can independently promote renin secretion during small fluctuations in arterial pressure.

Macula Densa Receptor.—Vander and Miller (7) showed that the increase in renin secretion which is produced by aortic constriction was prevented by simultaneously administering a diuretic which increased the sodium load to the macula densa. Subsequently, many investigators have interpreted data which were obtained with diuretics and hypertonic saline infusions to implicate the macula densa in the control of renin secretion. Unfortunately, many of these experimental techniques affected the distribution of blood flow within the kidney (73, 74) and conceivably could also have influenced the renal vascular receptor. Thurau et al. (10) attempted a direct stimulation of the macula densa by retrograde injection of hypertonic saline into the distal tubules and concluded that the macula densa was stimulated by an increased concentration of sodium. More recently, Cooke et al. (12) found that ethacrynic acid did not stimulate renin release in dogs which had obstructed ureters, but renin secretion increased immediately after reestablishment of urine flow. These findings are also evidence for the existence of a macula densa receptor.

Vander and Carlson (8) have suggested that the rate of sodium transport by the macula densa cells is the stimulus for renin secretion. They further hypothesized that the macula densa cells increase their rate of sodium transport when the sodium load to the macula densa increases. In this hypothesis, the macula densa cells behave similarly to the cells of the ascending limb of the loop of Henle, which also increase sodium reabsorption when sodium delivery is increased (74, 75). In this theory, then, the rate of sodium transport by the macula densa is a function of sodium load. This hypothesis implies that both sodium concentration and volume flow are involved and that the macula densa computes the product of the two factors, the sodium load, and responds to it. In this regard, the suggestion of Thurau et al. (10) that sodium concentration is sensed by the macula densa is a simpler hypothesis.

The system diagram (Fig. 6) emphasizes the important point that the function of the macula densa as a sodium receptor in the normal animal is strictly dependent on the rate of glomerular filtration (block 13); that is, autoregulation of glomerular filtration rate essentially determines the function of this receptor pathway. If autoregulation was perfect, that is, if there was no change in glomerular filtration rate with changes in renal perfusion pressure, there would be a zero slope for the relationship in block 11 and the gain of this entire receptor pathway would be zero. Thus, the role of the macula densa in renin release in the autoregulatory range depends on imperfect autoregulation of glomerular filtration rate. However, even if autoregulation is imperfect, the gain of this receptor pathway and, consequently, the effect of this receptor mechanism would be very low. Another mechanism which would produce an increase in gain of this pathway would be "parametric forcing," that is, a change in at least one of the parameters of this pathway. For example, alterations in plasma sodium concentration (block 14) could activate the macula densa receptor for renin release without a loss of autoregulation of glomerular filtration rate.

Implication of Parallel Feedback Pathways.—A parallel configuration, as illustrated in Figure 6, makes it functionally possible for the macula densa and the vascular receptor to compliment each other. In the normal range of blood pressure, autoregulation of glomerular filtration rate could sufficiently reduce the gain of the macula densa pathway to allow domination by the vascular receptor pathway in the control of renin release. At mean systemic pressures below approximately 90 mm Hg, autoregulatory phenomena would disappear and the gain of the macula densa pathway would be markedly increased. At blood pressures below 90 mm Hg, the afferent arteriole becomes fully dilated since the resistance drop across the afferent arteriole...
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becomes negligible (45). With maximal dilation, tension in the wall of the afferent arteriole would become relatively low and approximately constant. Thus, at pressures below the autoregulatory range, the gain of the vascular receptor pathway would be substantially reduced. These considerations, which are derived from our best estimate of the control system configuration for the R-A-A system, suggest that the receptors are anatomically in parallel but functionally in series. This system configuration also suggests the hypothesis that the vascular receptor dominates in the autoregulatory range of blood pressure and that the macula densa receptor dominates at pressures below the autoregulatory range. However, one must alter this concept if parameters beyond block 11, such as plasma sodium concentration, change to activate a subsequent segment of the macula densa pathway which could have high gain.

Discussion

STEADY-STATE RESPONSES TO PHYSIOLOGICAL AND PATHOLOGICAL CHANGES IN THE R-A-A SYSTEM (FIG. 6)

The renin-angiotensin-aldosterone system is responsive to several normal and abnormal conditions that occur in animals. This system reacts to these conditions by using negative feedback to move the system variables toward their normal operating points. Negative feedback is represented in the system diagram (Fig. 6) by blocks 20 and 22 since these components have characteristic curves with negative slopes. In the remainder of this discussion, the system diagram (Fig. 6) will be examined to ascertain the manner in which several physiological and pathological conditions influence the R-A-A system to elicit negative feedback and, therefore, to maintain system homeostasis.

Low Sodium Intake.—A chronic low sodium intake, as is known to occur in many alpine areas of the world, will decrease total extracellular fluid volume (block 8) and subsequently decrease glomerular filtration rate (block 13). This, in combination with a slightly decreased plasma sodium concentration (block 14) (76), could decrease the sodium load delivered to the macula densa (blocks 11-19) and could conceivably reduce sodium transport at the macula densa. According to this view (8), the sodium concentration in the macula densa cells will decrease to increase renin secretion (blocks 20, 24, 25). In a similar manner, a decrease in afferent arteriolar pressure will decrease stretch of the afferent arterioles (block 21) causing an increase in renin secretion (blocks 22-24). The increase in renin secretion by both receptor pathways will increase aldosterone production (block 4) and the plasma concentration of aldosterone (block 5), which in turn will increase sodium reabsorption (block 6) as a compensatory mechanism to restore the extracellular fluid volume. In addition to changes in the input and output variables for each component of the system, changes in several parameters of the system will augment the effect of the increased secretion of renin and aldosterone. For example, sufficient contraction of the extracellular fluid volume will decrease hepatic blood flow, which will decrease metabolism of both renin (block 1) and aldosterone (block 5). These reductions in metabolism will result in increased plasma concentrations of renin and aldosterone. Thus, a chronic low-sodium diet disturbs the system by both input variable (extracellular fluid volume) and parameter (hepatic blood flow) changes, both of which induce a compensatory system response to maximize sodium reabsorption and to increase extracellular fluid volume toward the normal operating point.

Caval constriction.—Thoracic inferior vena cava constriction is a potent stimulus to the R-A-A system (77, 78) in that constriction of the inferior vena cava above the diaphragm results in hepatic congestion and sequestration of a large portion of the blood volume in the large veins of the lower body. With venous pooling, venous and capillary pressures in the lower body rise to produce edema and ascites. An initial disturbance to the R-A-A system is a decrease in arterial pressure (block 9) as a result of reduced cardiac output (parameter in block 9) secondary to reduced venous return to the heart. The decrease in arterial
pressure will presumably activate both receptor pathways to give increased renin secretion, which subsequently induces high levels of circulating aldosterone (block 5) to enhance sodium reabsorption and expand the extracellular fluid volume. At this point, however, the system fails to provide compensation. The expansion of the extracellular fluid volume does not signal the kidneys to decrease renin secretion, because the increase in extracellular fluid volume is not distributed throughout the entire vascular system but is sequestered as edema and ascites or as blood in the veins of the lower body. Therefore, the system functions as an open-loop system, since the loop is opened between blocks 8 and 9, and extracellular fluid volume and vascular volume are no longer transduced into arterial pressure. Thus, the kidneys do not perceive the increased extracellular fluid volume and continue to respond with increased renin secretion. This interpretation is supported by the findings of Robb et al. (79), who could not demonstrate a reduction in plasma renin activity in dogs with constricted thoracic inferior vena cava after administration of large doses of DOCA. The normal animal will not continuously increase sodium reabsorption under excess mineralocorticoid stimulation (76, 80) but "escapes" from the sodium-retaining action of aldosterone. In dogs with constricted thoracic inferior vena cava, some other factor prevents the proximal rejection of sodium that is characteristic of the escape phenomenon in the normal animal. It has been suggested (81) that this factor is a natriuretic hormone.

Several parameters also function in caval constriction to elevate further the plasma aldosterone concentration. The metabolism of aldosterone is decreased (block 5) because of hepatic congestion (33) and decreased hepatic flow (34). The Starling forces (block 8) are altered in favor of increased sequestration of fluid as edema and ascites, because of increased capillary pressure and decreased colloid osmotic pressure. The latter is particularly important where paracentesis produces loss of protein and reduction of plasma protein concentration. Increased renal vein pressure induces afferent arteriolar dilation in addition to the dilation secondary to decreased arterial pressure (51). Increased renal vein pressure might also have a significant effect on glomerular filtration rate through increased intratubular pressure (block 12). Therefore, in constriction of the thoracic inferior vena cava, the secretion of aldosterone is markedly increased due to opening of the feedback loop at a point where increases in extracellular fluid volume cannot be perceived by the receptors controlling the system.

Congestive Heart Failure.—This is another pathological condition in which renin and aldosterone are elevated (82). A consistent finding early in congestive heart failure and frequently before the onset of failure is a reduction in renal blood flow which might be the result of an increase in sympathetic nervous outflow to provide cardiovascular compensation. Initially this would represent a parametric stimulus (blocks 10, 21, 24) to increase renin secretion either by a direct action on the release mechanism or by decreasing glomerular filtration rate and stretch of the afferent arteriole. However, congestive heart failure is primarily characterized by a decrease in cardiac output, since the heart fails as a pump. This acts as a reduction in overall gain of the R-A-A system by depression of the curve in block 9. Thus, the volume of blood in the arterial tree is reduced and subsequently afferent arteriolar pressure and macula densa sodium load are reduced to increase renin and, consequently, aldosterone secretion. Also, there is a tendency for venous pooling and development of edema which reduce the gain in blocks 9 and 10 and further reduce the overall gain of the system. Metabolism of aldosterone and renin are reduced since hepatic blood flow is frequently very low in congestive heart failure, and increased physical activity probably increases sympathetic nerve activity and reduces hepatic blood flow.

Thus, in contrast to constriction of the thoracic inferior vena cava, which opens the feedback loop, the R-A-A system is activated to differing degrees in congestive heart failure.
depending on the reduction in gain of component 9, which is dependent on the severity of cardiac compromise.

**Hemorrhage.**—In this condition, increased activity of the R-A-A system (83) results from a decrease in blood volume (block 8); however, depending on the severity of hemorrhage, different mechanisms are probably involved. Since a small nonhypotensive hemorrhage does not stimulate renin secretion in denervated kidneys (84), the renal nerves are a significant factor in activation of the R-A-A system. The renal sympathetic nerves could affect either the renin-releasing mechanism directly (block 24) or the tension in the afferent arteriole (block 21). In animals with innervated kidneys, small hemorrhages could increase tension in the afferent arteriole through an increase in sympathetic discharge or an increase in circulating catecholamines. With relatively constant perfusion pressure, a slight decrease in arteriolar lumen diameter would decrease the stretch of a vascular receptor (block 21) to signal for an increase in renin secretion. In the denervated kidney, there might be no change in arteriolar tension and diameter, and thus the vascular receptor would not be affected.

A large hypotensive hemorrhage will activate both receptor limbs in the system, especially if autoregulation of glomerular filtration rate is lost. There will be increased renin and aldosterone secretion to increase sodium reabsorption. In contrast to constriction of the thoracic inferior vena cava, hemorrhage does not open the system loop, and therefore the increase in sodium reabsorption will expand the extracellular fluid volume toward normal to raise arterial pressure as a compensatory mechanism. There are also alterations in system parameters which increase the response of the R-A-A system to hemorrhage. For example, decreased hepatic plasma flow will also increase the plasma concentration of renin and aldosterone (22).

**The Steady-State Approach.**—The development of a steady-state block diagram for the renin-angiotensin-aldosterone system serves to emphasize functional relationships. The concept of a double intrarenal receptor system focuses attention on parallel feedback pathways; these may conceivably function independently or in an additive manner. Analysis of the special situations considered here by this approach calls attention to certain unique features which might otherwise be overlooked. For example, the difference between the pathophysiological mechanisms of sodium retention in cirrhosis of the liver (exemplified in the model of caval constriction) and in congestive heart failure is evident by the opening of the feedback loop in the former situation and by a decrease in gain of a crucial component in the system in the latter. Finally, this type of analysis calls attention to the missing gaps in our knowledge of the renin-angiotensin-aldosterone system. So little information is available on how hyperkalemia decreases renin secretion that no attempt was made to include this relationship in the diagram; instead, the relationship was considered in the text. And, the necessity for postulation of a renin-releasing factor became clearly evident from the analysis. Thus, control system analysis not only emphasizes certain important functional relationships, but it focuses attention on specific problems for future research.

**References**


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