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The renal renin-angiotensin system

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Harrison-Bernard LM. The renal renin-angiotensin system. *Adv Physiol Educ* 33: 270–274, 2009; doi:10.1152/advan.00049.2009.— The renin-angiotensin system (RAS) is a critical regulator of sodium balance, extracellular fluid volume, vascular resistance, and, ultimately, arterial blood pressure. In the kidney, angiotensin II exerts its effects to conserve salt and water through a combination of the hemodynamic control of renal blood flow and glomerular filtration rate and tubular epithelial cell sodium chloride and water transport mechanisms. Pharmacological inhibition of the actions of the RAS are widely used in the treatment of patients with hypertension, congestive heart failure, left ventricular dysfunction, pulmonary and systemic edema, diabetic nephropathy, cirrhosis of the liver, scleroderma, and migraines. Therefore, a thorough understanding of the influences of the RAS on normal renal physiology is of major importance for first-year medical students.

angiotensin receptor; blood pressure regulation; kidney; sodium excretion; vasoconstriction

THE RENIN-ANGIOTENSIN SYSTEM (RAS) influences sodium balance, extracellular fluid (ECF) volume, and renal and systemic vascular resistance. Thus, the RAS serves as one of the most powerful regulators of arterial blood pressure. Pharmacological inhibition of the actions of the RAS are widely used in the treatment of patients with hypertension, congestive heart failure, left ventricular dysfunction, pulmonary and systemic edema, diabetic nephropathy, cirrhosis of the liver, scleroderma, and migraines. A thorough understanding of the influences of the RAS on normal renal physiology is therefore important for first-year medical students. In my experience, most first-year medical students are fearful of learning renal physiology. It may be the first time for many of them that they are being exposed to the unique renal vascular architecture and numerous epithelial cell transporters along the different segments of the nephron. My recommendation to them is to approach renal physiology by bringing to class concepts they have already learned in cardiovascular physiology, respiratory physiology, gross anatomy, histology, and clinical medicine. In this way, the students start the renal block with the realization that they already possess a strong foundation for the understanding of renal physiology.

In the Medical Physiology course taught to our first-year medical students, the RAS is not covered in a single lecture but is discussed in 5 of 10 renal physiology lectures (50 min each). The lecture titles in which a component of the RAS is presented include the following: *1*) structure and function of the kidneys, *2*) regulation of renal blood flow (RBF), *3*) transport of sodium and chloride by the nephron, *4*) regulation of potassium balance, and *5*) integration of salt and water bal-

ance. The learning objectives for understanding the importance of the RAS in renal physiology include the ability of the students to:

● Diagram the formation of angiotensin II (ANG II) from the substrate angiotensinogen.
● Identify three factors that promote renin release.
● Describe the influence of ANG II on RBF and the glomerular filtration rate (GFR).
● Describe the effects of ANG II on the regulation of sodium reabsorption along the nephron.
● Explain the role of the RAS in response to a decrease in blood volume.
● Recognize that the ultimate goal of the RAS is to maintain ECF volume and blood pressure within the normal physiological range.

These learning objectives have been adapted from the Renal Physiology Objectives developed by the American Physiological Society (1). The learning objectives and renal problems for the renal physiology block are included in the Supplemental Material.[1]

The Renal Failure Patient

I try to find "hooks" to motivate medical students to study and understand renal physiology. So, on the first day of the renal block, I present them with key findings of a patient with renal failure (Table 1). This represents a patient such as those they are likely to see, since there are currently 20 million Americans with kidney disease, and the number is rising due to the increasing prevalence of hypertension, obesity, and diabetes in this country and worldwide (5). The patient may present with elevated blood pressure and plasma parathyroid hormone, potassium, urea, phosphate, and sulfate levels relative to normal levels. Also, reductions in hematocrit, pH, plasma bicarbonate, and calcium may be evident. In some patients, an elevation in blood pressure may occur in response to overactivation of the RAS due to renal artery stenosis.

The RAS Cascade

ANG II is synthesized by cleavage of angiotensinogen, an α_2-globulin formed primarily in the liver and, to a lesser extent, in the kidney by the proteolytic enzyme renin to form angiotensin I (ANG I; Fig. 1). ANG I is a decapeptide that is rapidly converted by angiotensin-converting enzyme (ACE) and, to a lesser extent, by chymase to ANG II, an octapeptide. The actions of ANG II are mediated by two G protein-coupled receptors: angiotensin type 1 (AT_1) and angiotensin type 2 (AT_2) receptors. In the kidney, all of the actions of ANG II on hemodynamic and tubular function are thought to be mediated

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Table 1. *Renal failure patient*

Patient Data	Relative to Normal
Plasma potassium	↑
Blood urea nitrogen	↑
Blood pressure	↑
Plasma parathyroid hormone	↑
Plasma phosphate	↑
Hematocrit	↓
Plasma bicarbonate	↓
Plasma pH	↓
Plasma calcium	↓

↑, Increased; ↓, decreased.

via AT_1 receptors, including afferent and efferent arteriolar vasoconstriction and enhanced sodium and fluid reabsorption. Similarly, the ANG II-induced stimulation of aldosterone release from the adrenal cortex is mediated via the activation of AT_1 receptors.

Control of Renin Secretion

Since renin is the rate-limiting enzymatic step in the formation of ANG II, it is important to understand the factors that regulate renin secretion. Renin is synthesized and released from the juxtaglomerular cells of the afferent arteriole into the intravascular space and surrounding interstitium. Renin secretion is positively regulated by the second messenger cAMP; however, unlike most secretory cells, renin secretion from the juxtaglomerular cell is inversely related to extracellular and intracellular calcium concentrations (2). This novel relationship is referred to as the "calcium paradox." Inputs that compromise blood volume, ECF volume, and arterial blood pressure influence renin release (Fig. 2). There are three major mechanisms for the regulation of renin release: *1*) intrarenal barorecptors of the afferent arteriole, *2*) alterations in the delivery of sodium chloride to the macula densa cells, and *3*) the influence of sympathetic nerves on the arterioles of the
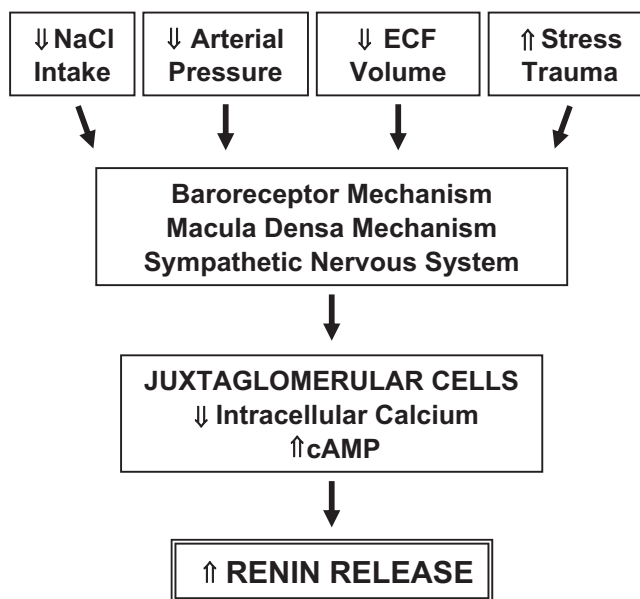

Fig. 2. Regulation of renin release by the juxtaglomerular cells. ECF, excellular fluid.

juxtaglomerular apparatus. These mechanisms stimulate the release of renin by the cells of the juxtaglomerular apparatus that cleaves angiotensinogen to form ANG I.

Intrarenal barorecptors. The juxtaglomerular cells of the afferent arteriole act as high-pressure barorecptors and are able to detect changes in blood pressure. An increase in renal arterial pressure inhibits renin release. A decrease in renal arterial pressure results in decreased stretch, decreased intracellular calcium concentration, and increased renin release from the juxtaglomerular cells. A decrease in renal arterial pressure may be caused by hemorrhage, by constriction of the aorta above the renal arteries, or by stenosis of the renal artery due to atherosclerosis. This narrowing of the vasculature can be viewed by a renal angiogram or by magnetic resonance angiography. Stenosis of the preglomerular arteries or arterioles may be caused by fibrosis of the arterial wall. The arterial stenosis leads to a reduction of the hydrostatic pressure distal to the stenosis that is sensed by the juxtaglomerular cells of the afferent arteriole. Activation of the intrarenal barorecptor mechanism results in the secretion of renin and increased formation of ANG II. Increased ANG II levels elevate renal artery perfusion pressure beyond the stenosis toward normal levels while leading to systemic hypertension. With early diagnosis of renal artery stenosis, treatment with ACE inhibitors or angiotensin receptor blockers may be effective in some patients. It is important to note that ACE inhibitors may precipitate renal ischemia in some patients with renal artery stenosis.

Alteration in delivery of sodium chloride. Increased distal delivery of sodium chloride to the macula densa cells of the thick ascending limb of the loop of Henle results in decreased renin secretion by the juxtaglomerular cells; decreased distal delivery of sodium chloride to the macula densa results in increased renin secretion. The primary pathway for the stimulation of renin secretion via the macula densa mechanism is the upregulation of cyclooxygenase 2 in the macula densa cells, increased production of PGE_2, activation of PGE_2 receptors (EP_4 receptors), stimulation of adenylyl cyclase, and increased
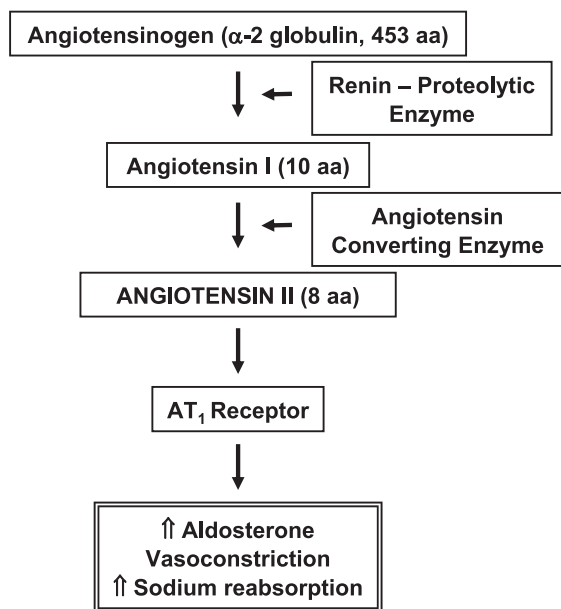

Fig. 1. Renin-angiotensin system cascade for the formation of angiotensin II. AT_1 receptors, angiotensin type 1 receptors.

intracellular cAMP (2). cAMP is the second messenger for renin secretion. Increased renin secretion leads to increased ANG II levels and increased blood pressure. This mechanism is important to maintain systemic arterial pressure and tissue perfusion under conditions of reduced vascular volume.

Influence of sympathetic nerves. The juxtaglomerular cells are innervated by sympathetic nerve fibers. Activation of renal sympathetic nerves and stimulation of β-adrenergic receptors increases the release of renin. Reduced sympathetic nerve activity diminishes renin secretion.

ANG II Influences Blood Pressure Through Multiple Pathways

ANG II has multiple actions on different vascular beds and organ systems that can ultimately elevate ECF volume and arterial blood pressure (4). ANG II causes vasoconstriction of renal and systemic arterioles, which increases total peripheral resistance and blood pressure. Activation of ANG II receptors in the brain increases sympathetic output to the heart and vasculature, which increases cardiac output and total peripheral resistance, thus increasing blood pressure. ANG II causes an increased release of arginine vasopressin from the posterior pituitary gland. Arginine vasopressin increases fluid retention in the renal collecting duct in the kidneys to help conserve blood volume. ANG II stimulates thirst, and the increased fluid ingestion expands blood volume, which raises blood pressure. Plasma ANG II increases aldosterone release from the adrenal cortex, which increases sodium chloride and fluid reabsorption in the distal nephron to increase ECF volume.

Hemodynamic Actions of ANG II

ANG II produces systemic vasoconstriction, which increases total peripheral resistance and leads to increased blood pressure. Exerting powerful vasoconstrictor actions on the kidney, ANG II decreases RBF and sodium excretion. ANG II has a direct effect on renal vascular smooth muscle cells, causing vasoconstriction of both the afferent and efferent arterioles, which results in reduced RBF. To demonstrate this point, I present a movie illustrating the efferent arteriole response to 10 nM ANG II (see Supplemental Material). This movie was prepared from research conducted in my laboratory using the mouse in vitro blood-perfused juxtamedullary nephron technique. This experimental tool allows for the real-time analysis of direct measurements of renal arteriolar diameter during a bath application of ANG II in the isolated perfused mouse kidney. The efferent arteriole diameter measures 20.0 μm under baseline conditions. ANG II (10 nM) was applied to the surface of the kidney at the 15-min time point. The efferent arteriole diameter measures 8.0 μm at the peak contraction to ANG II, which occurred 30 s after the application of the peptide. This rapid and potent vasoconstriction represents a 60% reduction in vessel diameter. At the 15:30-min time point, the arteriole has narrowed to the point that single red blood cells can be seen traveling within the vessel. During the steady-state contraction to ANG II, the efferent arteriole diameter was reduced by 30% of the control diameter. Upon removal of the peptide from the bath, the efferent arteriole diameter returned to the baseline diameter of 20.0 μm. ANG II causes contraction of mesangial cells, which is thought to decrease the ultrafiltration coefficient (K_f) and decrease GFR.

Increased intrarenal ANG II levels are responsible for the increased sensitivity of the tubuloglomerular feedback mechanism. The tubuloglomerular feedback mechanism links changes in solute concentration at the macula densa cells to the control of GFR to help ensure a relatively constant delivery of solutes to the distal tubule. The ultimate goal of the macula densa cells is to balance the amount of salt and water filtered by the glomerulus with the reabsorptive capabilities of each nephron. Increased sensitivity of the tubuloglomerular feedback mechanism occurs with decreased sodium chloride intake, which leads to the conservation of salt and water by the kidneys. ANG II decreases medullary blood flow, which aids in concentrating the urine and increases water retention by the kidney. Overall, the renal hemodynamic actions of ANG II lead to reductions in RBF and GFR to preserve ECF volume and blood pressure. Other vasoconstrictor hormones that reduce RBF and GFR include endothelin, arginine vasopressin, and norepinephrine. Stimulation of the sympathetic nerves also decreases RBF and GFR. Vasodilators that increase RBF and GFR include prostaglandins, nitric oxide, bradykinin, and atrial natriuretic peptide.

Tubular Actions of ANG II

Direct tubular effects of ANG II on sodium reabsorption. ANG II exerts several important effects on the kidney that contribute to sodium conservation. Many students are familiar with the effects of ANG II on the adrenal cortex to stimulate aldosterone release, which increases sodium reabsorption in the kidney. However, few students realize the importance of the direct tubular actions of ANG II to the overall effect of the RAS on the regulation of sodium and water excretion. AT_1 receptors for ANG II are located on luminal and basolateral membranes of proximal and distal nephron segments. Intraluminally produced and circulating ANG II directly increases sodium chloride and fluid reabsorption in these nephron segments via binding to AT_1 receptors. Activation of AT_1 receptors leads to increased activities of the proximal tubule apical sodium/hydrogen exchanger and of the basolateral sodium-bicarbonate cotransporter. ANG II also enhances the activity of the sodium-chloride cotransporter in the distal tubule and the epithelial sodium channel in the collecting duct. Therefore, ANG II directly increases salt and water reabsorption in multiple nephron segments via a receptor-mediated event to conserve ECF volume.

Indirect tubular effects of ANG II on sodium reabsorption via aldosterone. ANG II is a very powerful regulator of aldosterone release by the adrenal gland. The increased aldosterone levels synergize with the direct tubular effects of ANG II to enhance distal tubule sodium reabsorption. Aldosterone increases sodium reabsorption in the distal segments of the nephron by binding to the cytoplasmic mineralocorticoid receptor. On binding, the receptor complex migrates to the nucleus, where it induces gene transcription. Expression of proteins that stimulate sodium reabsorption is enhanced by the increased expression of proteins that stimulate sodium reabsorption by the following mechanisms:

- Increasing sodium-potassium ATPase protein and activity at basolateral membranes of distal nephron segments.
- Increasing the activity of enzymes of the tricarboxylic acid cycle.

- Increasing the production of ATP to be used as an energy source for the sodium-potassium ATPase pump.
- Increasing the expression and activation of epithelial sodium channels, which enhances sodium entry into the cell.
- Increasing the permeability of the apical membrane to potassium, which drives the ATPase pump.

Taken together, the activation of multiple sodium transport mechanisms leads to augmented sodium and water reabsorption by the kidney.

Effects of ANG II on tubuloglomerular feedback sensitivity. ANG II enhances the tubuloglomerular feedback sensitivity, which allows glomerular capillary pressure and GFR to be maintained at the reduced distal volume delivery rate that would occur as a consequence of ANG II effects to increase sodium reabsorption. The net effect is a reduced sodium excretion by the kidneys.

Effects of ANG II on potassium secretion. Increases in plasma potassium concentration directly increase the release of aldosterone from the adrenal cortex, independent of the actions of ANG II. Aldosterone increases potassium secretion in the distal segments of the nephron. Aldosterone stimulates potassium secretion by increasing the following:

- Sodium-potassium ATPase protein and activity at the basolateral membrane of distal nephron segments, which increases the electrochemical driving force for potassium entry into the cell and increases the secretion of potassium across the apical membrane.
- Activity of enzymes of the tricarboxylic acid cycle.
- Production of ATP to be used as an energy source for the sodium-potassium ATPase pump.
- The expression and activation of epithelial sodium channels, which enhances sodium entry into the cell and increases lumen negativity, which then increases the secretion of potassium.
- Permeability of the apical membrane to potassium by increasing the number of potassium channels and enhancing the activation of these potassium channels.

Therefore, increasing apical secretion of potassium increases potassium excretion by the kidneys.

ANG II is one of many other antinatriuretic hormones that increase sodium reabsorption and decrease sodium excretion by the kidneys, such as aldosterone and arginine vasopressin. Activation of renal sympathetic nerves also increases sodium reabsorption and decreases sodium excretion by the kidneys. In opposition, natriuretic hormones that decrease sodium reabsorption and increase sodium excretion by the kidneys include atrial natriuretic peptide, dopamine, prostaglandins, nitric oxide, and bradykinin.

Role of the RAS in Response to Changes in Effective Circulating Volume

An overview of the role of the RAS in response to alterations in effective circulating volume is valuable way to link the multiple pathways by which ANG II affects salt and water handling by the kidneys. The effective circulating volume is the critical parameter that the body recognizes as an index of changes in sodium content. The effective circulating volume is a functional blood volume that reflects the extent of tissue perfusion, as evidence by the fullness or pressure within the blood vessels. Normally, changes in the effective circulating volume parallel those in total ECF volume; however, this relationship may be indistinct in certain diseases. Variations in effective circulating volume affect four major regulatory systems: *1*) RAS, *2*) sympathetic nervous system, *3*) arginine
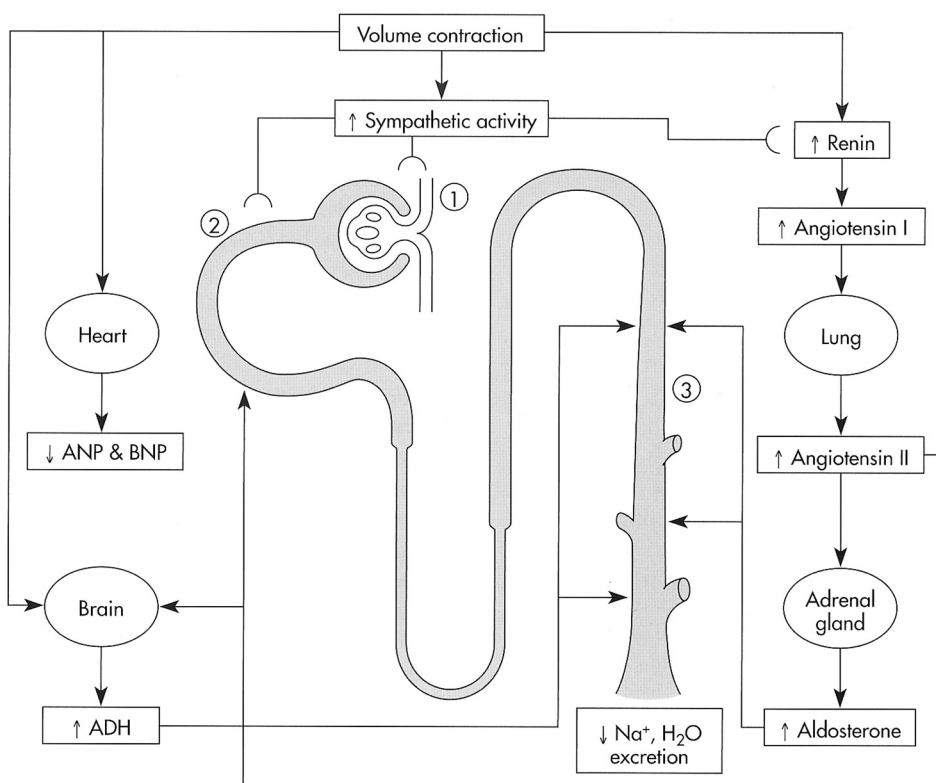

Fig. 3. Regulatory responses to ECF volume contraction. The integrated response of the nephron to ECF volume contraction results in the following: decreased glomerular filtration rate (*1*), increased NaCl and water reabsorption by the proximal tubule and loop of Henle (*2*), and increased NaCl and water reabsorption by the distal tubule and collecting duct (*3*). ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; ADH, antidiuretic hormone. [From Ref. 3.]

vasopressin, and *4*) atrial natriuretic peptide. The RAS is likely the quantitatively single most important factor in the hierarchy of the ECF volume control systems. During ECF volume contraction, the high-pressure and low-pressure vascular volume sensors decrease signals to the kidneys, which leads to reduced sodium and chloride and water excretion (Fig. 3) (3). There are four major signals that act on the kidneys, which include the following: *1*) increased activity of renal sympathetic nerves; *2*) increased renin secretion by the juxtaglomerular cells, which results in elevated ANG II levels and increased secretion of aldosterone from the adrenal cortex; *3*) inhibition of atrial natriuretic peptide and brain natriuretic peptide secretion from the heart; and *4*) stimulation of arginine vasopressin secretion from the posterior pituitary gland.

The integrated response of the nephron to volume contraction results in the following: *1*) decreased GFR, *2*) increased sodium chloride and water reabsorption by the proximal tubule and loop of Henle, and *3*) increased sodium chloride and water reabsorption by the distal tubule and collecting duct. The RAS is integrally involved in regulating GFR and enhancing sodium chloride and water reabsorption in proximal and distal nephron segments. The final outcome is a reduction in salt and water excretion and preservation of ECF volume and blood pressure.

Reduction in GFR. Increased renal sympathetic nerve activity causes afferent and efferent arteriolar vasoconstriction. The afferent arteriole constriction is greater than the efferent arteriole constriction, so glomerular capillary hydrostatic pressure falls and GFR is reduced. The renal plasma flow (RPF) decreases more than the GFR decreases, so the filtration fraction (GFR/RPF) actually increases. The decrease in GFR reduces the filtered load of sodium and contributes to reduced sodium excretion by the kidneys.

Increased sodium reabsorption by the proximal tubule and loop of Henle. Increased sympathetic nerve activity and ANG II directly stimulate sodium reabsorption in the proximal tubule and thick ascending limb of the loop of Henle. The decreased glomerular capillary hydrostatic pressure leads to a decrease in peritubular capillary hydrostatic pressure, which enhances the reabsorption of fluid. In addition, the increased filtration fraction results in an increase in the peritubular capillary oncotic pressure, which also favors fluid reabsorption from the tubular lumen back into the vasculature. The reduced filtered load and enhanced proximal tubule reabsorption decrease the delivery of sodium to the loop of Henle. Therefore, sodium reabsorption is enhanced in proximal tubules and the loop of Henle by mechanisms related to increased activity of tubular epithelial cell sodium transporters and fluid reabsorption by the renal capillaries.

Increased sodium reabsorption by the distal tubule and collecting duct. The small amount of sodium that is delivered to the distal tubule is almost completely reabsorbed by the late nephron segments due to the actions of aldosterone. Also, plasma levels of natriuretic peptides are decreased so inhibition of collecting duct sodium reabsorption is removed. Finally, water reabsorption is enhanced in the collecting duct by arginine vasopressin and so water excretion by the kidneys is reduced. Because both water and sodium are retained by the kidneys, euvolemia is reestablished.

During ECF volume expansion, the high-pressure and low-pressure vascular volume sensors send signals to the kidneys that increase sodium chloride and water excretion. There are five major signals that act on the kidneys, which include the following: *1*) decreased activity of renal sympathetic nerves; *2*) release of atrial natriuretic peptide and brain natriuretic peptide from the heart; *3*) inhibition of arginine vasopressin from the posterior pituitary and decreased action of arginine vasopressin on the collecting duct cells; *4*) decreased renin secretion by the juxtaglomerular cells and thus decreased formation of ANG II; and *5*) decreased aldosterone secretion, which is caused by reduced ANG II levels and elevated natriuretic peptide levels.

The integrated response of the nephron to volume expansion results in the following: *1*) increased RPF (without much change in GFR due to parallel dilation of afferent and efferent arterioles) and a decrease in filtration fraction, *2*) decreased sodium chloride and fluid reabsorption by the proximal tubule and loop of Henle, and *3*) decreased sodium reabsorption by the distal tubule and collecting duct.

Collectively, the various mechanisms discussed provide overlapping influences of the RAS that are responsible for the highly efficient regulation of sodium balance, ECF volume, blood volume, and arterial pressure. In normal physiology, the RAS plays a pivotal role in maintaining ECF volume and blood pressure; however, overactivation or inappropriate activation of the RAS may contribute to pathophysiological conditions of the cardiovascular and renal systems.

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