35

Control of Body Fluid Osmolality and Volume

LEARNING OBJECTIVES

Upon completion of this chapter the student should be able to answer the following questions:

1. Why do changes in water balance alter [Na^+] of extracellular fluid (ECF)?
2. How is the secretion of arginine vasopressin (AVP) controlled by changes in the body fluid osmolality, blood volume, and systemic blood pressure?
3. What cellular events are associated with the AVP action on the collecting duct and how do they increase the water permeability of this nephron segment?
4. What is the role of Henle's loop in the production of both dilute and concentrated urine?
5. What is the composition of the medullary interstitial fluid, and how does it contribute to urinary concentration?
6. What are the roles of *vasa recta* in the process of diluting and concentrating urine?
7. How is the diluting and concentrating ability of the kidneys quantitated?
8. Why do changes in Na^+ balance alter the volume of extracellular fluid?
9. What is the effective circulating volume, how is it influenced by changes in Na^+ balance, and how does it influence renal Na^+ excretion?
10. What mechanisms regulate the effective circulating volume?
11. What are the major signals for altering renal Na^+ excretion?
12. How do changes in extracellular fluid volume alter Na^+ transport in the different nephron segments and how these changes regulate renal Na^+ excretion?
13. What mechanisms contribute to edema formation and what roles do the kidneys play in this process?

Body fluid osmolality represents one of the most highly regulated parameters of human physiology. The kidney controls the osmolality and volume of body fluid by regulating excretion of water and NaCl, respectively. This chapter discusses the renal mechanisms of water and NaCl excretion. The composition and volumes of the various body fluid compartments are reviewed in Chapter 2.

Control of Body Fluid Osmolality: Urine Concentration and Dilution

As described in Chapter 2, water constitutes approximately 60% of the healthy adult human body. Water is distributed between two major compartments in the body—the intracellular fluid (ICF) and extracellular fluid (ECF)—that exist in osmotic equilibrium because aquaporins (e.g., AQP1) make the cellular membranes permeable to water. The major source of body water is oral intake of liquids and solid foods containing a liquid component. Water is also generated during metabolism of ingested foods (e.g., carbohydrates). Intravenous fluids are an important route of water supply during disease states.

The kidneys are responsible for regulating water balance and under most conditions are the major route for eliminating water from the body (Table 35.1). Water is also lost through the gastrointestinal tract. Fecal water loss is normally small (≈100 mL/day) but can increase dramatically with diarrhea (e.g., 20 L/day with cholera). Vomiting can also cause gastrointestinal water losses. The production of sweat is an active process of water and electrolyte elimination. The water loss through kidneys, gastrointestinal tract, and sweat glands is termed **sensible water loss** because the person is aware of its occurrence. Other routes of water elimination from the body are evaporation from cells of the skin and respiratory passages; collectively, the loss is termed **insensible water loss** because the individual is unaware of its occurrence. Sweating and insensible water loss can increase dramatically in a hot environment, during exercise, or in the presence of fever (Table 35.2).

Although water loss from sweating, defecation, and evaporation from the lungs and skin can vary depending on the environmental conditions or during disease states, loss of water by these routes cannot be regulated. In contrast, renal excretion of water is tightly regulated to maintain water balance. Maintenance of water balance requires that water intake and loss are precisely matched. If intake exceeds loss, **positive water balance** exists. Conversely, when intake is lower than loss, **negative water balance** exists (see Chapter 2 for review of steady-state balance).

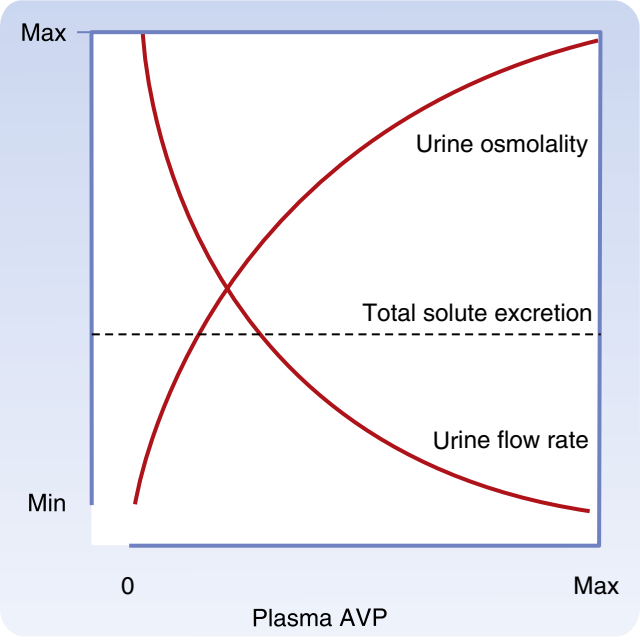
During states of decreased water intake or excessive water losses, the kidneys conserve water by producing low-volume, concentrated urine that is hyperosmotic with respect to plasma. Conversely, when water intake is high, a large volume of hypoosmotic urine is produced. In a healthy individual, urine osmolality (U_{osm}) can vary from approximately 50 to 1200 mOsm/kg H_2O, and the corresponding urine volume can vary from approximately 18 L/day to 0.5 L/day. Importantly the kidneys can regulate excretion of water separately from excretion of total solute (e.g., Na^+, K^+, urea, etc.) (Fig. 35.1). The ability to regulate water excretion separate from excretion of solutes is essential for survival because it allows water balance to be achieved without upsetting other homeostatic functions of the kidneys.

It is important to recognize that disorders of water balance are manifested by alterations in body fluid osmolality, which are usually measured by changes in plasma osmolality (P_{osm}). Because the major determinant of plasma osmolality is Na^+ (with its anions Cl^- and HCO_3^-), these disorders also result in alterations in plasma or serum [Na^+] (Fig. 35.2). One of the most common fluid and electrolyte disorders seen in clinical practice is an alteration in serum [Na^+]. When an abnormal serum [Na^+] is found in an individual, it is tempting to suspect a problem in Na^+ balance. However, the problem most often relates to water balance, not Na^+ balance. As described later, changes in Na^+ balance result in alterations in the ECF volume (ECFV), not its osmolality.

TABLE 35.1 Sources of Water Gain and Loss in Adults at Room Temperature (23°C)

Gain	(mL/day)
Fluid[a]	1200
Food	1000
Metabolically produced from food	300
Total	2500
Loss (mL/day)	
Insensible	700
Sweat	100
Feces	100
Urine	1600
Total	2500

[a]Fluid intake may vary widely for social and cultural reasons.

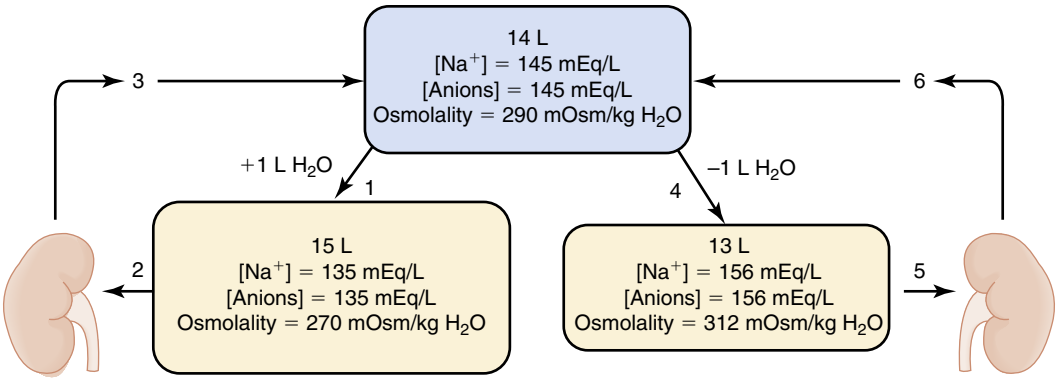


• **Fig. 35.1** Relationships between plasma AVP levels, and urine osmolality, urine flow rate, and total solute excretion. *Max,* Maximum; *Min,* minimum. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)

TABLE 35.2 Effect of Environmental Temperature and Exercise on Water Loss and Intake in Adults

	Normal Temperature	Hot Weather[a]	Prolonged Heavy Exercise[a]
Water Loss			
Insensible loss			
Skin	350	350	350
Lungs	350	250	650
Sweat	100	1400	5000
Feces	100	100	100
Urine[a]	1600	1200	500
TOTAL LOSS	2500	3300	6600

[a]In hot weather and during prolonged heavy exercise, water balance is maintained by increased water ingestion. Decreased excretion of water by the kidneys alone is insufficient to maintain water balance.



• **Fig. 35.2** Response to changes in water balance. Illustrated are the effects of adding or removing 1 L of water from the ECF of a 70-kg individual. **Positive Water Balance:** *(1)* Addition of 1 L of water increases the ECFV and reduces its osmolality. The [Na^+] is also decreased (hyponatremia). *(2)* The normal renal response is to excrete 1 L of water as hypoosmotic urine. *(3)* As a result of the renal excretion of water, the ECFV, osmolality, and [Na^+] are returned to normal. **Negative Water Balance:** *(4)* The loss of 1 L of water from the ECF decreases its volume and increases its osmolality. The [Na^+] is also increased (hypernatremia). *(5)* The renal response is to conserve water by excreting a small volume of hyperosmotic urine. *(6)* With ingestion of water, stimulated by thirst, and conservation of water by the kidneys, the ECF volume, osmolality, and [Na^+] are returned to normal. Size of the boxes indicates relative ECF volume. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)

IN THE CLINIC

In the clinical setting, **hypoosmolality** (a reduction in plasma osmolality) shifts water into cells, and this process results in cell swelling (see Chapter 2). Symptoms associated with hypoosmolality are related primarily to swelling of brain cells. For example, a rapid fall in P_{osm} can alter neurological function and thereby cause nausea, malaise, headache, confusion, lethargy, seizures, and coma. When P_{osm} is increased (i.e., **hyperosmolality**), water is lost from cells. Symptoms of an increase in P_{osm} are also primarily neurological and include lethargy, weakness, seizures, coma, and even death.

Symptoms associated with changes in body fluid osmolality vary depending on how quickly osmolality changes. The rapid osmolality changes (i.e., over hours) are less well tolerated than changes that occur more gradually (i.e., over days to weeks). Indeed, individuals who have developed alterations in their body fluid osmolality over an extended period of time may be entirely asymptomatic. This reflects the compensatory mechanisms in neurons to minimize changes in cell volume over time. For example, cells eliminate intracellular osmoles in response to hypoosmolality while they generate new intracellular osmoles in response to hyperosmolality (see Chapter 2).

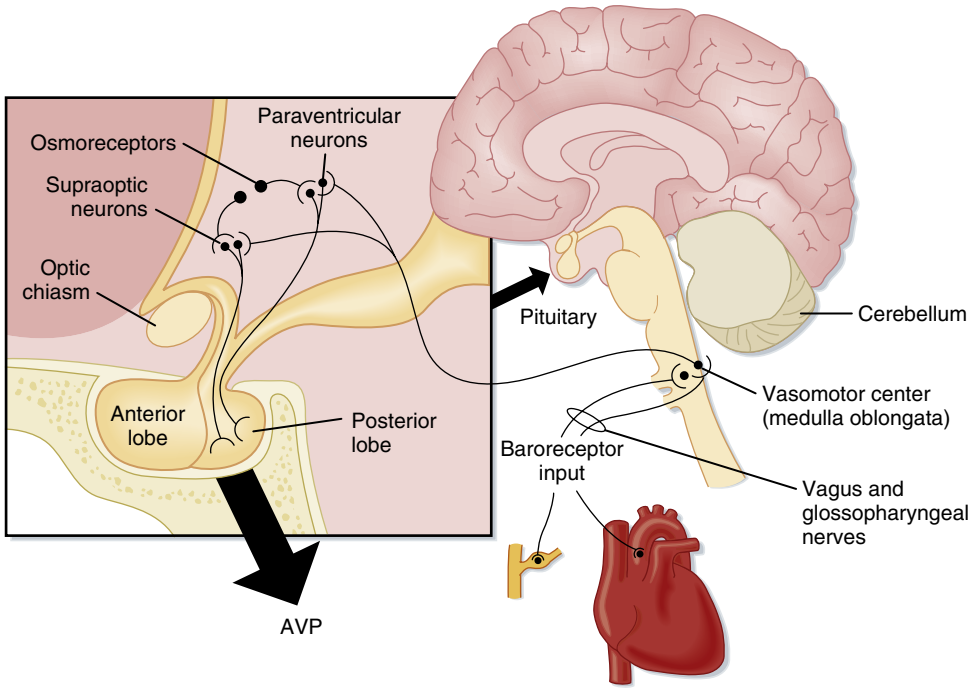
The following sections discuss the mechanisms by which the kidneys excrete either **hypoosmotic (dilute)** or **hyperosmotic (concentrated)** urine. Control of arginine vasopressin secretion and its essential role in regulating water excretion by the kidneys are also explained (see also Chapter 41).

Arginine Vasopressin

Arginine vasopressin (AVP), a nonapeptide, is synthesized in the hypothalamic supraoptic (SON) and paraventricular (PVN) nuclei.[a] AVP acts though vasopressin (V) receptors. Several nephron segments express the type-2 receptor (V_2) that mediates the kidneys' ability to regulate the urine volume and osmolality. When the plasma AVP level is low, a large volume of urine is excreted **(diuretic effect)**, and the urine osmolality is lower than that of plasma (i.e., dilute). When the plasma AVP level is high, a small volume of urine is excreted **(antidiuretic effect)**, and the urine osmolality is greater than that of plasma (i.e., concentrated). Hence, AVP is also known as the **antidiuretic hormone (ADH)**.

Secretion of AVP by the posterior pituitary can be influenced by several factors. Under physiological conditions AVP secretion is controlled by two major mechanisms: osmotic (changes in plasma osmolality) and hemodynamic (changes in blood pressure or volume). Other factors that alter AVP secretion include nausea, acute hypoglycemia, angiotensin II (stimulate), and atrial natriuretic peptide (inhibits). A number of medications and recreational drugs

[a]The SON and PVN synthesize either AVP or oxytocin. AVP-secreting cells predominate in the SON, whereas oxytocin-secreting neurons are primarily found in the PVN. The synthesized hormone is packaged in granules that are transported down the axon of the cell and stored in nerve terminals located in the neurohypophysis (posterior pituitary). The anatomy of the hypothalamus and pituitary gland is shown in Fig. 35.3 (see also Chapter 41).



• **Fig. 35.3** Anatomy of the hypothalamus and pituitary gland (midsagittal section) depicting the pathways for AVP section. Also shown are pathways involved in regulating AVP secretion. Afferent fibers from the baroreceptors are carried in the vagus and glossopharyngeal nerves. The inset box illustrates an expanded view of the hypothalamus and pituitary gland.

AT THE CELLULAR LEVEL

The gene for AVP is located on chromosome 20. It contains approximately 2000 base pairs with three exons and two introns. The gene codes for a preprohormone that consists of a signal polypeptide, the AVP molecule, neurophysin, and a glycopeptide (copeptin). As the cell processes the preprohormone the signal peptide is cleaved off in the rough endoplasmic reticulum. Once packaged in neurosecretory granules, the preprohormone is further cleaved into AVP, neurophysin, and copeptin molecules. The neurosecretory granules are then transported down the axon to the posterior pituitary and stored in the nerve endings until released. When the neurons are stimulated to secrete AVP, the action potential opens Ca^{++} channels in the nerve terminal, which raises the intracellular [Ca^{++}] and causes exocytosis of the neurosecretory granules. All three peptides are secreted in this process. Neurophysin and copeptin do not have an identified physiological function.

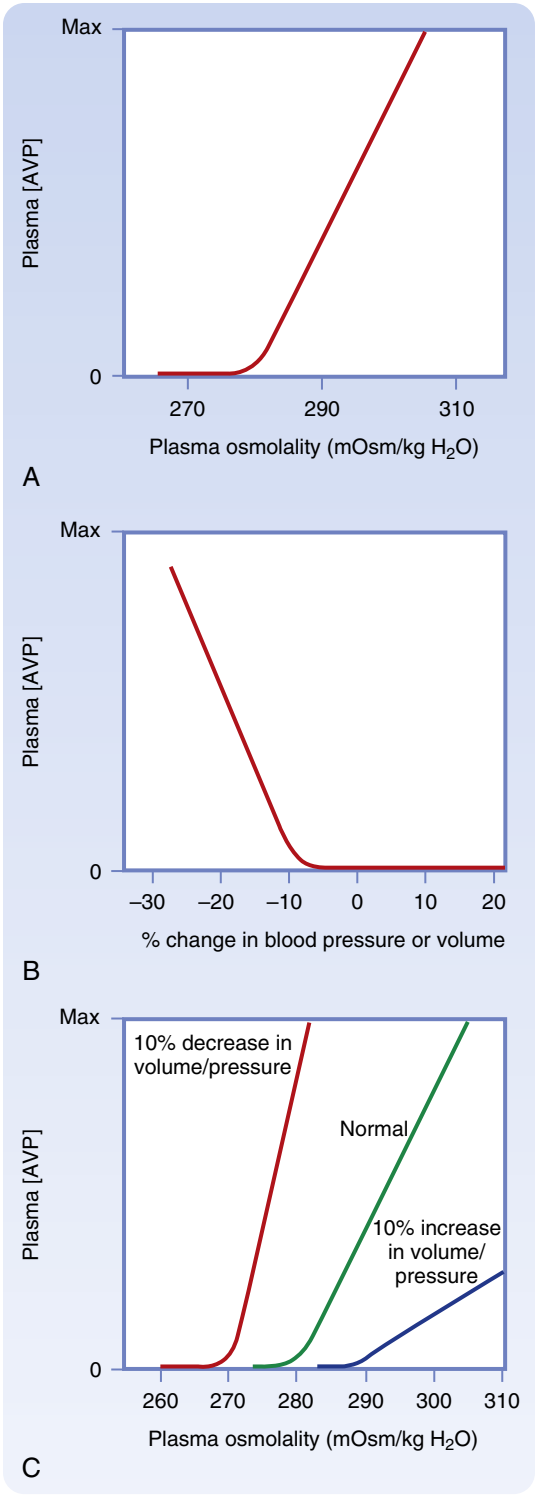
affect AVP secretion. For example, nicotine stimulates secretion, whereas ethanol and anti-emetics inhibit it.

Osmotic Control of AVP Secretion

Changes in the body fluid osmolality play the most important role in regulating AVP secretion. Specialized neurons termed **osmoreceptors**, located in the *organum vasculosum* of the lamina terminalis (OVLT) of the hypothalamus, modulate osmolality changes within a normal range between 275 and 295 mOsm/kg H_2O. The osmoreceptor cells sense changes in body fluid osmolality in response to small changes in the concentration of effective solutes, such as Na^+ and its anions, and are insensitive to ineffective solutes, such as urea and glucose (see Chapter 1).

Effective solutes are those that penetrate cells slowly or not at all, thereby creating an osmotic gradient resulting in efflux of water across the cell membrane. When the effective plasma osmolality (tonicity) increases, osmoreceptor cell shrinkage activates membrane nonselective cationic channels that generate inward current depolarizing the cells. In turn, the osmotically evoked action potential in the OVLT neurons synaptically propagates the electrical activity to downstream effector neurons in the SON and PVN leading to AVP release. Conversely, when the effective plasma osmolality decreases, AVP synthesis and secretion are inhibited. Because AVP is rapidly degraded in the plasma, circulating levels can be reduced to zero within minutes. Recent data demonstrate that cell membrane stretch rather than cell volume determines osmoreceptor activity. The transient receptor potential vanilloid (TRPV) family of cation channels, including TRPV1, TRPV2, and TRPV4, mediate osmotic stimuli in mammals. The channels are activated by cell membrane stretch and mediate inactivation of the osmoreceptors in hypoosmolal states. The mediators of stretch-inactivated cationic channels that respond to cell shrinkage in hyperosmolal states are currently unknown.

The coordinated action of the stimulatory and inhibitor components of the osmoreceptors creates a threshold, or set point. Fig. 35.4A illustrates the effect of changes in plasma osmolality on circulating AVP levels. The slope of



• **Fig. 35.4** Osmotic and hemodynamic (nonosmotic) control of AVP secretion. **A,** Effect of changes in plasma osmolality (constant blood volume and pressure) on plasma AVP levels. **B,** Effect of changes in blood volume or pressure (constant plasma osmolality) on plasma AVP levels. **C,** Interactions between osmolar and blood volume and pressure stimuli on plasma AVP levels.

the relationship is quite steep and accounts for the sensitivity of the system. The set point is the plasma osmolality value at which AVP secretion begins to increase. Below the set point, virtually no AVP is released. The absolute level of the effective plasma osmolality at which minimally and maximally effective levels of plasma AVP occur, varies appreciably from person to person, due to genetic influences on the set and sensitivity of the system. However, the average set point for AVP release corresponds to a plasma osmolality of 280 mOsmol/kg H_2O and levels only 2% to 4% higher normally result in maximum antidiuretic effect. The set point is relatively stable in healthy individuals but can be decreased by pregnancy, menstrual cycle, estrogen, or a significant drop in blood pressure or blood loss. The mechanism responsible for the set point shift during pregnancy is likely due to increased levels of certain hormones (e.g., relaxin and chorionic gonadotropin).

Hemodynamic (Nonosmotic) Control of AVP Secretion

A decrease in blood volume or pressure also stimulates AVP secretion. The receptors responsible for this response are located in both the low-pressure (left atrium and large pulmonary vessels) and the high-pressure (aortic arch and carotid sinus) sides of the circulatory system. Because the low-pressure receptors are located in the high-compliance side of the circulatory system (i.e., venous), and because the majority of blood is on the venous side, these low-pressure receptors can be viewed as responding to the overall vascular volume. The high-pressure receptors respond to arterial pressure. Both groups of receptors are sensitive to stretch of the wall of the structure in which they are located (e.g., cardiac atrial and aortic arch) and are termed **baroreceptors**. Signals from these receptors are carried in afferent fibers of the *vagus* and glossopharyngeal nerves to the brainstem (solitary tract nucleus of the medulla oblongata), which is part of the center that regulates heart rate and blood pressure (see also Chapter 18). Signals are then relayed from the brainstem to the AVP secretory cells of the supraoptic and paraventricular hypothalamic nuclei. The sensitivity of the baroreceptor system is less than that of the central osmoreceptors, and a 5% to 10% decrease in blood volume or pressure is required before AVP secretion is stimulated. This is illustrated in Fig. 35.4B. A number of substances have been shown to alter the secretion of AVP through their effects on blood pressure. These include bradykinin and histamine, which lower pressure and thus stimulate AVP secretion, and norepinephrine, which increases blood pressure and inhibits AVP secretion.

Alterations in blood volume and pressure also affect the response to changes in body fluid osmolality (see Fig. 35.4C). With a decrease in blood volume or pressure, the set point is shifted to lower osmolality values and the slope of the relationship is steeper. In terms of survival of the individual this means that faced with circulatory collapse, the kidneys will continue to conserve water, even though by doing so they reduce the osmolality of the body fluids. With an increase in blood volume or pressure, the opposite occurs. The set point is shifted to higher osmolality values and the slope is decreased.

IN THE CLINIC

Inadequate release of AVP from the posterior pituitary results in excretion of a large volume of dilute urine **(polyuria)**. To compensate for this loss of water the individual must ingest a large volume of water **(polydipsia)** to maintain constant body fluid osmolality. If the individual is deprived of water, body fluid will become hyperosmotic. This condition is called **central (pituitary) diabetes insipidus (CDI)**. It can be inherited, although this is rare. CDI occurs more commonly after head trauma and with brain neoplasms or infections. Individuals with CDI have a urine-concentrating defect that can be corrected by administration of exogenous AVP. The inherited (autosomal dominant) form of CDI is due to mutations in different regions of the *AVP* gene (i.e., AVP, copeptin, and neurophysin). The human placenta produces a cysteine aminopeptidase that degrades AVP. In some women the levels of this vasopressinase result in diabetes insipidus. The associated polyuria can be treated by administration of the synthetic AVP analog **desmopressin (DDAVP)**.

The **syndrome of inappropriate AVP (ADH) secretion (SIADH)** is a relatively common clinical problem characterized by plasma AVP levels that are elevated above what would be expected on the basis of body fluid osmolality, blood volume, or blood pressure—hence the term *inappropriate AVP (ADH) secretion*. The AVP action in the kidney collecting duct causes recruitment of water channels (see below), thus augmenting the effect of AVP to stimulate renal water retention. Individuals with SIADH retain water, and their body fluids become progressively hypoosmotic. In addition, their urine is more hyperosmotic than expected based on the low body-fluid osmolality. SIADH can be caused by drugs, central nervous system infection or tumors, pulmonary diseases, or lung carcinoma. These conditions either stimulate AVP secretion by altering neural input to the AVP secretory cells or secrete AVP (small cell carcinoma). Drug-related SIADH is increasingly common and can be associated with many classes of over the counter and prescription medications, including proton pump inhibitors, nonsteroidal anti-inflammatory, antidepressants, antiseizure, antipsychotic, and antitumor drugs. AVP receptor antagonists bind to V_{1A} and V_2 receptors and induce water diuresis (**aquaresis**) to treat SIADH and other conditions resulting from AVP-dependent water retention by the kidneys (e.g., congestive heart failure and hepatic cirrhosis).

AVP Actions on the Kidneys

The primary action of AVP on the kidneys is to enhance absorption of water from the tubular fluid by increasing the water permeability of the latter portion of the distal tubule and collecting duct. In addition, and importantly, AVP increases the permeability of the medullary portion of the collecting duct to urea. Finally, AVP stimulates NaCl reabsorption by the thick ascending limb of Henle's loop, distal tubule, and collecting duct.

In the absence of AVP, the apical membrane of principal cells (see Chapter 34), located in the latter portion of the distal tubule and along the collecting duct, is relatively impermeable to water. This reflects the fact that in the absence of AVP the apical membrane of these cells contains few water channels (aquaporins), since they are stored inside cells. Thus, in the absence of AVP, little water is reabsorbed by these nephron segments. Binding of AVP to the V_2 receptor located in the basolateral membrane of principal cells results in the recruitment of aquaporin (AQP2) water channels to the apical membrane, allowing water to enter the cell from the tubular lumen. This water then exits the cell across the basolateral membrane, which is always freely permeable to water owing to the presence of AQP3 and AQP4 water channels. Thus in the presence of AVP, water is reabsorbed from the renal tubules.

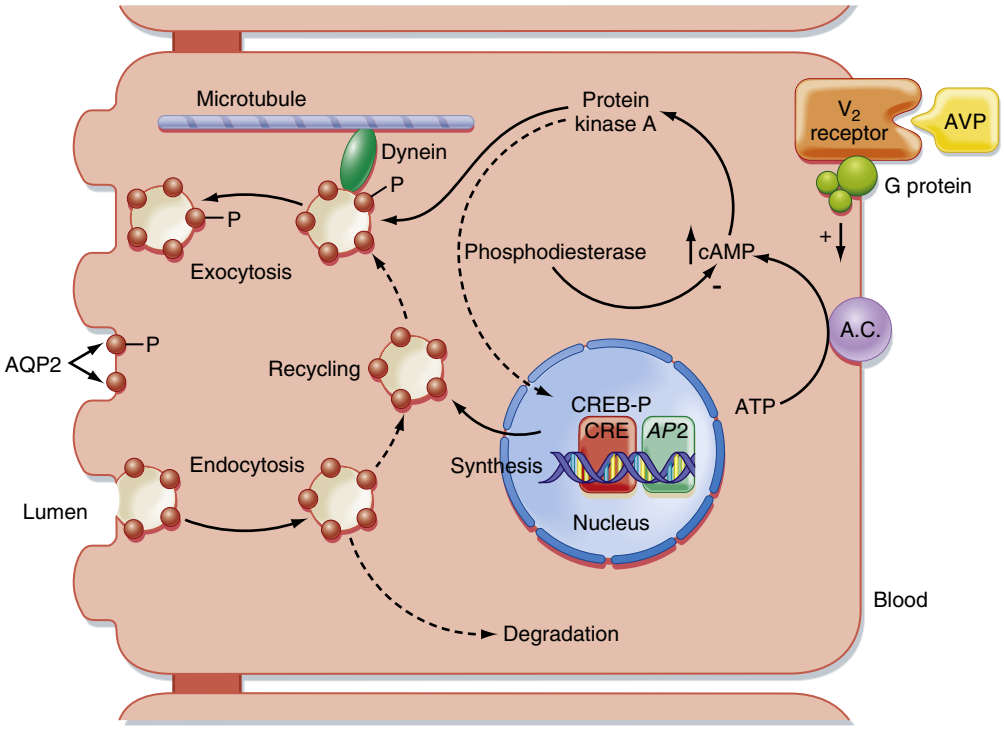
AT THE CELLULAR LEVEL

The gene for the V_2 receptor is located on the X chromosome and codes for a 371–amino acid protein that belongs to the family of receptors with seven membrane spanning domains coupled to heterotrimeric G proteins. As shown in Fig. 35.5, binding of AVP to its receptor on the basolateral membrane activates adenyl cyclase. The increase in intracellular cyclic adenosine monophosphate (cAMP) then activates protein kinase A (PKA), which results in the phosphorylation of AQP2 water channels and increased transcription of the *AQP2* gene via activation of a cAMP-response element (CRE). Intracellular vesicles containing phosphorylated AQP2 move toward the apical membrane along microtubules driven by the molecular motor dynein. Once near the apical membrane, proteins called *SNAREs* interact with the AQP2 containing vesicles and facilitate their fusion with the plasma membrane. Insertion of AQP2 to the membrane allows water to enter the cell driven by the osmotic gradient (lumen osmolality < cell osmolality). The water then exits the cell across the basolateral membrane through AQP3 and AQP4 water channels, which are constitutively present in the basolateral membrane. When the V_2 receptor is not occupied by AVP, the AQP2 water channels are removed from the apical membrane by clathrin-mediated endocytosis, thus rendering the apical membrane impermeable to water. The endocytosed AQP2 molecules may be either stored in intracellular vesicles, ready for reinsertion into the apical membrane when AVP levels in the plasma increase, or degraded.

AVP also regulates long-term expression of AQP2 and AQP3. When large volumes of water are ingested over an extended period of time (e.g., psychogenic polydipsia), the abundance of AQP2 and AQP3 in principal cells is reduced. As a consequence, when water ingestion is restricted, these individuals cannot maximally concentrate urine. Conversely, in states of restricted water ingestion, AQP2 and AQP3 protein expression in principal cells increases, thereby facilitating excretion of maximally concentrated urine.

It is also clear that expression of AQP2 (and in some instances also AQP3) varies in pathological conditions associated with disturbances in urine concentration and dilution. AQP2 expression is reduced in a number of conditions associated with impaired urine-concentrating ability (e.g., hypercalcemia, hypokalemia). By contrast, in conditions associated with water retention (e.g., congestive heart failure, hepatic cirrhosis, pregnancy) AQP2 expression is increased.

AVP also increases the permeability of the terminal portion of the inner medullary collecting duct to urea leading to increased reabsorption of urea and increased osmolality of the medullary interstitial fluid necessary for maximal urine concentration. The cells of the collecting duct express two types of urea transporters (UT), UT-A1 localized to the apical membrane and UT-A3 localized



• **Fig. 35.5** Action of AVP via the V_2 receptor on the principal cell of the late distal tubule and collecting duct. See text for details. *AC,* Adenyl cyclase; *AP2,* aquaporin 2 gene; *AQP2,* aquaporin 2; *cAMP,* cyclic adenosine monophosphate; *CRE,* cAMP response element; *CREB-P,* phosphorylated cAMP response element–binding protein; *P,* phosphorylated proteins. (Adapted from Brown D, Nielsen S. The cell biology of vasopressin action. In: Brenner BM, ed. *The Kidney*. 7th ed. Philadelphia: Saunders; 2004.)

to the basolateral membrane. AVP, acting through the cAMP/PKA cascade, increases expression of UT-A1 and UT-A3. Increasing the osmolality of the interstitial fluid of the renal medulla also increases the permeability of the inner medullary collecting duct to urea. This effect is mediated by the phospholipase C/protein kinase C (PKC) pathway, which increases UT-A1 and UT-A3 expression.

AVP also stimulates reabsorption of NaCl by the thick ascending limb of Henle's loop and by the distal tubule and cortical segment of the collecting duct. This increase in Na^+ reabsorption is associated with increased abundance of three Na^+ transporters: the $Na^+/K^+/2Cl^-$ symporter (thick ascending limb of Henle's loop), the Na^+/Cl^- symporter (distal tubule), and the Na^+ channel ENaC (the latter portion of the distal tubule and collecting duct). Stimulation of thick ascending limb NaCl transport may help maintain the hyperosmotic medullary interstitium necessary for absorption of water from the medullary portion of the collecting duct (see below).

IN THE CLINIC

When the collecting ducts do not respond normally to AVP, urine cannot be maximally concentrated leading to polyuria and polydipsia. This clinical entity is termed **nephrogenic diabetes insipidus (NDI)** to distinguish it from central diabetes insipidus. NDI can result from a number of systemic disorders and rarely can be inherited. Acquired NDI is caused by decreased expression of AQP2 in the collecting duct. Decreased expression of AQP2 impairs the urine-concentrating ability during hypokalemia, lithium ingestion (35% of individuals who take lithium for bipolar disorder develop some degree of NDI), urinary tract obstruction, low-protein diet, and hypercalcemia. Mutations in the AVP V_2 receptor *AVPR2* gene or the *AQP2* gene lead to inherited NDI. Approximately 90% of the hereditary forms result from mutations in the *AVPR2* gene and the remaining 10% result from *AQP2* gene mutations. Since the *AVPR2* gene is located on the X chromosome, its mutations lead to X-linked NDI. The *AQP2* gene is located on chromosome 12, and its mutations can lead to autosomal recessive and very rarely autosomal dominant NDI. The AQP2 channel functions at the cell membrane as homotetramers. Mutations leading to recessive NDI affect the region of *AQP2* gene associated with the formation of the homotetramer water channel pore. Heterozygous carriers produce both normal and defective AQP2 monomers. Since the defective AQP2 monomers are retained in the endoplasmic reticulum, the water channel forms only from normal monomers and the carriers remain asymptomatic. By contrast, mutations leading to the dominant NDI affect the region of *AQP2* gene associated with post-translational modifications, such as AQP2 phosphorylation and not the water channel pore.

Activating (gain-of-function) mutations in the *AVPR2* gene lead to *nephrogenic syndrome of inappropriate antidiuresis (NSIAD)*. In this X-linked disorder, V_2 receptors are constitutively activated. These individuals have laboratory findings similar to those seen in SIADH, including reduced plasma osmolality, hyponatremia (reduced plasma [Na^+]), and urine more concentrated than would be expected from the reduced body fluid osmolality. However, unlike SIADH where circulating levels of AVP are elevated and thus responsible for water retention by the kidneys, these individuals have undetectable levels of AVP in their plasma.

Thirst

The perception of thirst is affected by changes in plasma osmolality, blood volume, or blood pressure. Increased plasma osmolality and reduced blood volume or pressure increase thirst. Of these stimuli, hyperosmolality is more potent and its increase by only 2% to 3% produces a strong desire to drink, whereas loss of blood volume or decrease in blood pressure in the range of 10% to 15% is required to produce the same response in thirst.

As already discussed, there is a genetically determined threshold for AVP secretion (i.e., a body fluid osmolality above which AVP secretion increases). Similarly there is a genetically determined threshold for triggering the sensation of thirst. However, the thirst threshold is higher than the threshold for AVP secretion. On average the threshold for AVP secretion is approximately 280 mOsm/kg H_2O, whereas the thirst threshold is approximately 295 mOsm/kg H_2O. Because of this difference, thirst is stimulated at a body fluid osmolality when AVP secretion is almost maximal.

The center involved in regulating water intake (the thirst center) is located in the same region of the hypothalamus involved with regulating AVP secretion. However, it is not certain whether the same cells serve both functions. Indeed, the thirst response, like the regulation of AVP secretion, only occurs in response to effective solute (e.g., NaCl). Even less is known about the pathways involved in the thirst response to decreased blood volume or pressure, but it is believed that the pathways are the same as those involved in the volume- and pressure-related regulation of AVP secretion. Angiotensin II, acting on cells of the thirst center, also evokes the sensation of thirst. Because angiotensin II levels are increased when blood volume and pressure are reduced, this effect of angiotensin II contributes to the homeostatic response that restores and maintains body fluids at their normal volume.

The sensation of thirst is satisfied by the act of drinking, even before sufficient water is absorbed from the gastrointestinal tract to correct the plasma osmolality. It is interesting to note that cold water is more effective in reducing the thirst sensation. Oropharyngeal and upper gastrointestinal receptors appear to be involved in this response. However, relief of the thirst sensation via these receptors is short lived, and thirst is only completely satisfied when the plasma osmolality or blood volume or pressure is corrected.

It should be apparent that the AVP and thirst systems work in concert to maintain water homeostasis. An increase in plasma osmolality evokes drinking and, via AVP action in the kidneys, conservation of water. Conversely, when plasma osmolality is decreased, thirst is suppressed and, in the absence of AVP, renal water excretion is enhanced. When the fluid intake is dictated by cultural and social determinants rather than thirst, maintaining normal body fluid osmolality relies solely on the ability of the kidneys to excrete water. How the kidneys accomplishes this is discussed in detail in the following sections of this chapter.

IN THE CLINIC

With adequate access to water, the thirst mechanism can prevent development of hyperosmolality. This mechanism is responsible for the polydipsia seen in response to the polyuria of both CDI and NDI. Most individuals ingest water/beverages even in the absence of the thirst sensation. Normally the kidneys are able to excrete this excess water because they can excrete up to 18 L/day of urine. However, in some instances, the volume of water ingested exceeds the kidneys' capacity to excrete water, especially over short periods of time. When this occurs, body fluids become hypoosmotic.

An example of how water intake can exceed the capacity of the kidneys to excrete water is long-distance running. A study of participants in the Boston Marathon found that 13% of the runners developed hyponatremia during the race.[b] This reflected the practice of some runners to ingest water or other hypotonic drinks during the race to remain "well hydrated." In addition, water is produced from the metabolism of glycogen and triglycerides used as fuels by the exercising muscle. Hyponatremia developed because, over the course of the race, the runners achieved a positive water balance resulting from higher ingestion and generation of water compared to its excretion by the kidneys and loss with sweat. In some racers the hyponatremia was severe enough to elicit the neurological symptoms.

The maximum amount of water that can be excreted by the kidneys depends on the amount of solute excreted, which in turn depends on food intake. For example, with maximally dilute urine (U_{osm} = 50 mOsm/kg H_2O), the maximum urine output of 18 L/day will be achieved only if the solute excretion rate is 900 mmol/day:

$$U_{osm} = \text{Solute excretion} / \text{Volume excreted}$$

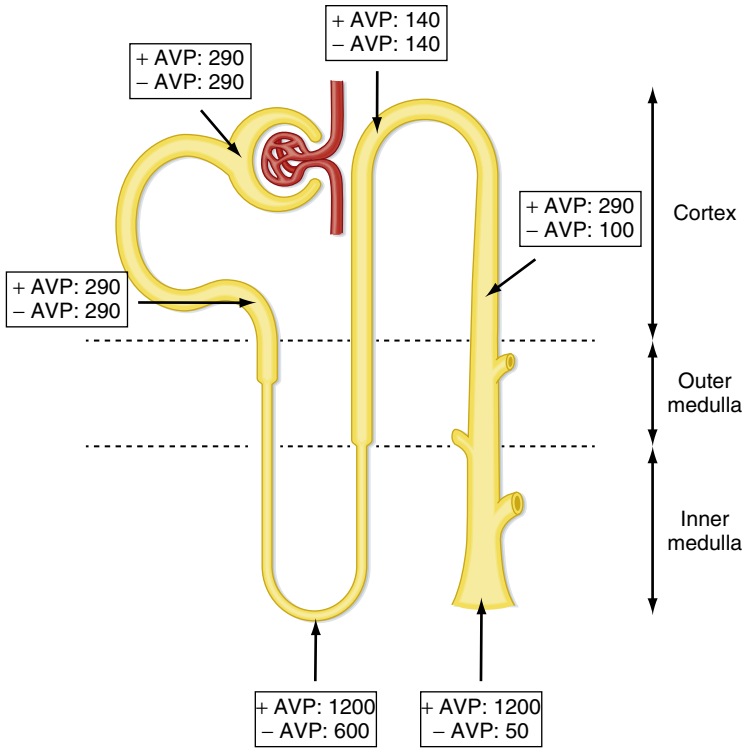
$$50\ \text{mOsm} / \text{kg}H_2O = 900\ \text{mmol} / 18\ \text{L}$$

If solute excretion is reduced, as commonly occurs in the elderly with reduced food intake, the maximum urine output will decrease. For example, if solute excretion is only 400 mmol/day, a maximum urine output (at U_{osm} = 50 mOsm/kg H_2O) of only 8 L/day can be achieved. Thus individuals with reduced food intake have a reduced capacity to excrete water.

[b]Almond CS, et al. Hyponatremia among runners in the Boston Marathon. *N Engl J Med*; 2005;352:1150-1556.

Renal Mechanisms for Dilution and Concentration of Urine

As already noted, water excretion is regulated separately from solute excretion. For this to occur, the kidneys must be able to excrete urine that is either hypoosmotic or hyperosmotic with respect to body fluid. This ability to excrete urine of varying osmolality in turn requires that solute be separated from water at some point along the nephron. As discussed in Chapter 34, reabsorption of solute in the proximal tubule results in reabsorption of a proportional amount of water. Hence solute and water are not separated in this portion of the nephron. Moreover, this proportionality between proximal tubule water and solute reabsorption occurs regardless of whether the kidneys excrete dilute or concentrated urine. Thus, the proximal tubule reabsorbs a large portion of the filtered amount of solute and water, but it does not produce



• **Fig. 35.6** Tubular fluid osmolality along the nephron in the presence (+AVP) and in the absence (–AVP) of arginine vasopressin. See text for details. (Adapted from Sands JM, et al. Urine concentration and dilution. In: Taal MW, et al, eds. Brenner and Rector's *The Kidney.* 9th ed. Philadelphia: Saunders; 2012.)

dilute or concentrated tubular fluid. The loop of Henle, in particular the thick ascending limb, is the major site where solute and water are separated. Thus excretion of both dilute and concentrated urine requires normal function of the Henle's loop.

Excretion of hypoosmotic urine is relatively easy to understand. The nephron must simply reabsorb solute from the tubular fluid and not allow water reabsorption to also occur. As just noted, and as described in greater detail later, reabsorption of solute without concomitant water reabsorption occurs in the ascending limb of Henle's loop. Under appropriate conditions (i.e., in the absence of AVP) the distal tubule and collecting duct also dilute the tubular fluid by reabsorbing solute but not water.

Excretion of hyperosmotic urine (or urinary concentration) is more complex and in essence involves removing water from the tubular fluid without solute. Because water movement is passive, driven by an osmotic gradient, the kidney must generate a hyperosmotic compartment into which water is reabsorbed, without solute, osmotically from the tubular fluid. The hyperosmotic compartment that serves this function is the interstitium of the renal medulla. Henle's loop is critical for generating the hyperosmotic medullary interstitium. Once established, this hyperosmotic compartment drives water reabsorption from the collecting duct and thereby concentrates urine.

Fig. 35.6 summarizes tubular fluid osmolality at several points along the nephron, in both the absence and presence of AVP. Note that tubular fluid entering the loop of Henle from the proximal tubule is isosmotic with respect to plasma and is so regardless of the absence or presence of AVP. Also, tubular fluid leaving the thick ascending limb is hypoosmotic with respect to plasma, in both the absence and presence of AVP. The osmolality of tubular fluid along the collecting duct is hypoosmotic with respect to plasma in the absence of AVP and becomes progressively hyperosmotic (i.e., from the cortex to inner medulla) in the presence of AVP.

Establishment and maintenance of the hyperosmotic medullary interstitium has been a subject of study since the 1940s and the model remains incomplete. While it is generally accepted that the outer medulla contributes to the osmotic gradient by means of an active process termed **countercurrent multiplication**, the source of the gradient in the inner medulla is still incompletely understood. With the caveat that the current model needs refinement, it is presented here because it embodies some fundamental concepts that underlie the process.

Countercurrent multiplication involves reabsorption of solute (principally NaCl) without water from the ascending limb of Henle's loop into the surrounding medullary interstitium. This decreases the osmolality in the tubular fluid and raises the osmolality of the interstitium at this point. The increased osmolality of the interstitium then causes water to be reabsorbed from the descending limb of Henle's loop, thus increasing the tubular fluid osmolality in this segment. Thus at any point along the loop of Henle the fluid in the ascending limb has an osmolality less than

fluid in the adjacent descending limb. This osmotic difference is termed the **single effect**. Because of the countercurrent flow of tubular fluid in the descending limb (fluid flowing into the medulla) and ascending limb (fluid flow out of the medulla), this single effect could be multiplied, resulting in an osmotic gradient within the medullary interstitium, where the tip of the papilla has an osmolality of 1200 mOsm/kg H_2O compared to 300 mOsm/kg H_2O at the corticomedullary junction.

Fig. 35.7 schematically depicts the processes for diluting and concentrating urine. Three key concepts underlie these processes:

1. Urine is concentrated by AVP-dependent reabsorption of water from the collecting duct.
2. Reabsorption of NaCl from the ascending limb of Henle's loop dilutes the tubular fluid and at the same time generates a high [NaCl] in the medullary interstitium (up to 600 mmol/L at the tip of the papilla), which then drives water reabsorption from the collecting duct.
3. Urea accumulates in the medullary interstitium (up to 600 mmol/L), which allows the kidneys to excrete urine with the same high urea concentration. This allows large amounts of urea to be excreted with relatively little water.

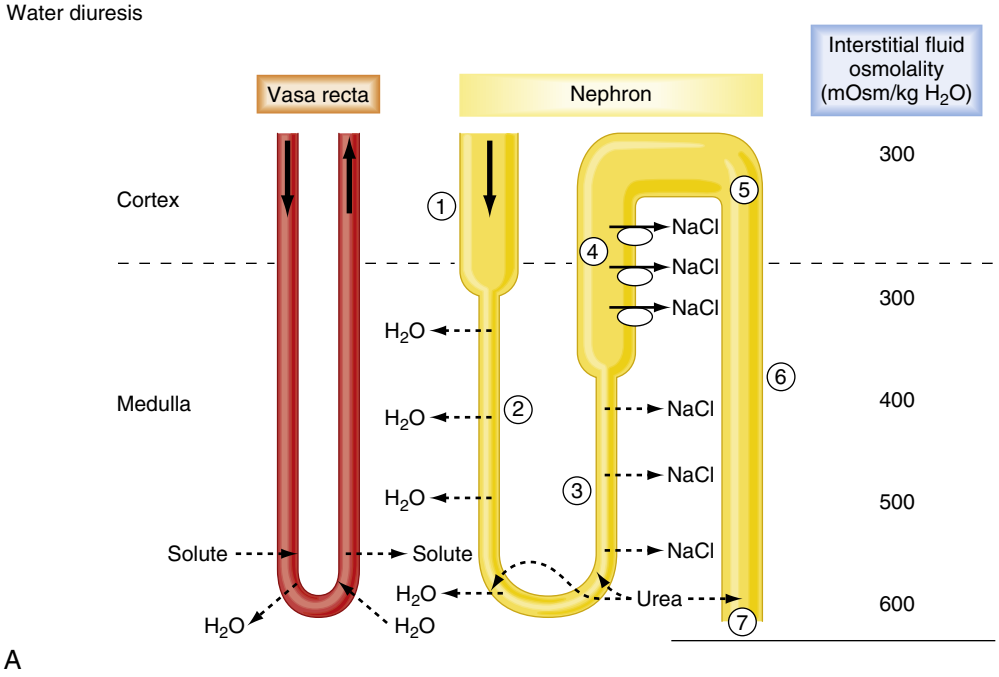
First, how the kidneys excrete dilute urine **(water diuresis or aquaresis)** when AVP levels are low or zero is considered. The following numbers refer to those encircled in Fig. 35.7A:

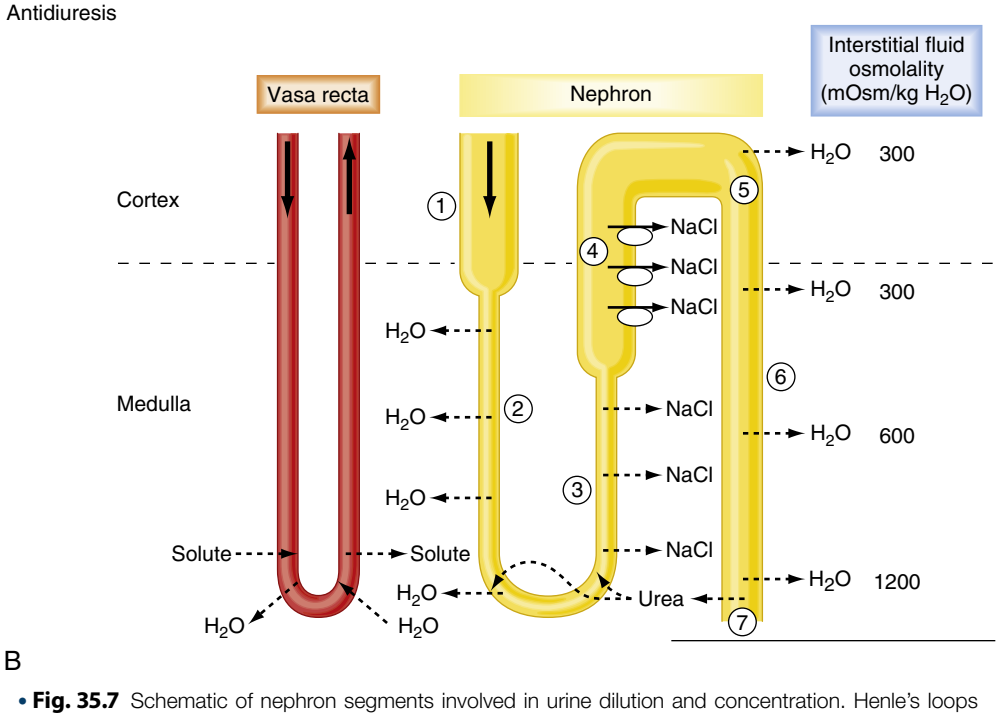
1. Fluid entering the descending thin limb of the loop of Henle from the proximal tubule is isosmotic with respect to plasma. This reflects the essentially isosmotic nature of solute and water reabsorption in the proximal tubule (see Chapter 34). (NOTE: Water is reabsorbed from the segments of the proximal tubule via AQP1.)
2. Water is reabsorbed from the thin descending limb of Henle's loop. Most of this water is reabsorbed in the outer medulla, thereby limiting the amount of water added to the deepest part of the inner medullary interstitial space and thus preserving the hyperosmolality of this region of the medulla. (NOTE: Water is reabsorbed via AQP1.)
3. In the inner medulla the terminal portion of the descending thin limb and all of the thin ascending limb is impermeable to water. (NOTE: AQP1 is *not* expressed.) These same nephron segments express the Cl^- channel CLC-K1, which mediates Cl^- reabsorption, with Na^+ following via the paracellular pathway. This passive reabsorption of NaCl without concomitant water reabsorption begins the process of diluting the tubular fluid.
4. The thick ascending limb of the loop of Henle is also impermeable to water and actively reabsorbs NaCl from the tubular fluid and thereby dilutes it further (see Chapter 34). Dilution occurs to such a degree that this segment is often referred to as the **diluting segment** of the kidney. Fluid leaving the thick ascending limb is hypoosmotic with respect to plasma (see Fig. 35.6).
5. The distal tubule and cortical portion of the collecting duct actively reabsorb NaCl. In the absence of AVP these segments are not permeable to water (i.e., AQP2 is not present in the apical membrane of the cells). Thus, when AVP is absent or present at low levels (i.e., decreased plasma osmolality), the osmolality of tubule fluid in these segments is reduced further because NaCl is reabsorbed without water. Under this condition, fluid leaving the cortical portion of the collecting duct is hypoosmotic with respect to plasma (see Fig. 35.6).
6. The medullary collecting duct actively reabsorbs NaCl. Even in the absence of AVP, this segment is slightly permeable to water and some water is reabsorbed.
7. The urine has an osmolality as low as approximately 50 mOsm/kg H_2O and contains low concentrations of NaCl. The volume of urine excreted can be as much as 18 L/day, or approximately 10% of the glomerular filtration rate (GFR).

Next, how the kidneys excrete concentrated urine **(antidiuresis)** when plasma osmolality and plasma AVP levels are high is considered. The following numbers refer to those encircled in Fig. 35.7B:

1–4. These steps are similar to those for production of dilute urine. An important point in understanding how a concentrated urine is produced is to recognize that while reabsorption of NaCl by the ascending thin and thick limbs of the loop of Henle dilutes the tubular fluid, the reabsorbed NaCl accumulates in the medullary interstitium and raises the osmolality of this compartment. Accumulation of NaCl in the medullary interstitium is crucial for production of urine hyperosmotic to plasma because it provides the osmotic driving force for water reabsorption by the medullary collecting duct. As already noted, AVP stimulates NaCl reabsorption by the thick ascending limb of Henle's loop. This is thought to maintain the medullary interstitial gradient at a time when water is being added to this compartment from the medullary collecting duct, which would tend to dissipate the gradient.

5. Because of NaCl reabsorption by the ascending limb of the loop of Henle, the fluid reaching the collecting duct is hypoosmotic with respect to the surrounding interstitial fluid. Thus an osmotic gradient is established across the collecting duct. In the presence of AVP, which increases the water permeability of the latter portion of the distal tubule and the collecting duct by causing insertion of AQP2 into the luminal membrane of the cells, water diffuses out of the tubule lumen and the tubule fluid osmolality increases. This diffusion of water out of the lumen of the collecting duct begins the process of urine concentration. The maximum osmolality the fluid in the distal tubule and cortical portion of the collecting duct can attain is approximately 290 mOsm/kg H_2O (i.e., the same as plasma), which is the osmolality of the interstitial fluid and plasma within the cortex of the kidney.
6. As the tubular fluid descends deeper into the medulla, water continues to be reabsorbed from the collecting duct, increasing the tubular fluid osmolality to 1200 mOsm/kg H_2O at the tip of the papilla.





• **Fig. 35.7** Schematic of nephron segments involved in urine dilution and concentration. Henle's loops of juxtamedullary nephrons are shown. **A,** Mechanism for excretion of dilute urine (water diuresis). AVP is absent and the collecting duct is essentially impermeable to water. Note also that during a water diuresis the osmolality of the medullary interstitium is reduced as a result of increased vasa recta blood flow and entry of some urea into the medullary collecting duct. **B,** Mechanism for excretion of a concentrated urine (antidiuresis). Plasma AVP levels are maximal and the collecting duct is highly permeable to water. Under this condition the medullary interstitial gradient is maximal. See text for details.

7. The urine produced when AVP levels are elevated has an osmolality of 1200 mOsm/kg H_2O and contains high concentrations of urea and other nonreabsorbed solutes. Urine volume under this condition can be as low as 0.5 L/day.

In comparing the two conditions just described, it should be apparent that a relatively constant volume of dilute tubular fluid is delivered to the AVP-sensitive portions of the nephron (latter portion of the distal tubule and collecting duct). Plasma AVP levels then determine the amount of water reabsorbed by these segments. When AVP levels are low, a relatively small volume of water is reabsorbed by these segments and a large volume of hypoosmotic urine is excreted (up to 10% of the filtered water). When AVP levels are high, a large volume of water is reabsorbed by these same segments and a small volume of hyperosmotic urine is excreted (<1% of filtered water). During antidiuresis, most of the water is reabsorbed in the distal tubule and cortical and outer medullary portions of the collecting duct. Thus, a relatively small volume of fluid reaches the inner medullary collecting duct where it is then reabsorbed. This distribution of water reabsorption along the length of the collecting duct (i.e., cortex > outer medulla > inner medulla) allows for maintenance of a hyperosmotic interstitial environment in the inner medulla by minimizing the amount of water entering this compartment.

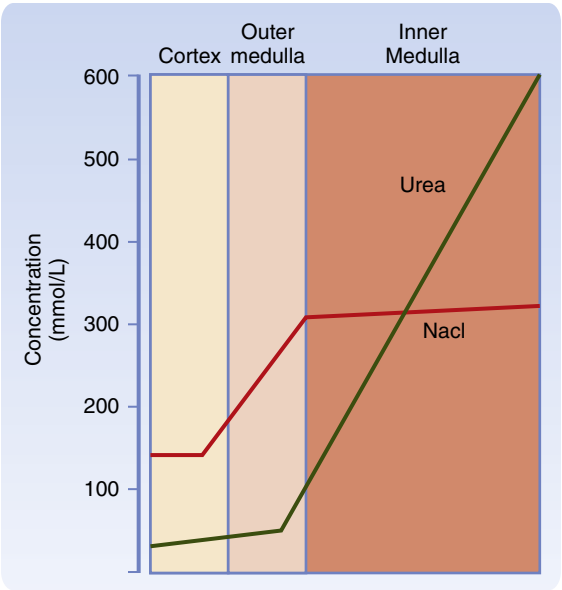
Medullary Interstitium

As noted earlier, the interstitial fluid of the renal medulla is critically important in concentrating urine. The osmotic pressure of the interstitial fluid provides the driving force for reabsorbing water from both the descending thin limb of the loop of Henle and the collecting duct. The principal solutes of the medullary interstitial fluid are NaCl and urea, but the concentration of these solutes is not uniform throughout the medulla (i.e., a gradient exists from cortex to papilla). Other solutes also accumulate in the medullary interstitium (e.g., NH_4^+ and K^+), but the most abundant solutes are NaCl and urea. For simplicity, this discussion assumes that NaCl and urea are the only solutes.

As depicted in Fig. 35.8, NaCl and urea accumulate in the renal medulla, and the interstitial fluid at the tip of the papilla of the inner medulla reaches a maximum osmolality of 1200 mOsm/kg H_2O, with approximately 600 mOsm/kg H_2O attributable to NaCl (300 mmol/L) and 600 mOsm/kg H_2O attributable to urea (600 mmol/L). Establishment of the NaCl gradient is essentially complete at the transition between the outer and inner medulla.

The medullary gradient for NaCl results from accumulation of NaCl reabsorbed by the nephron segments in the medulla during countercurrent multiplication. The most important segment in this regard is the ascending limb of the loop of Henle. Urea accumulation within the medullary interstitium is more complex and occurs most effectively when hyperosmotic urine is excreted (i.e., antidiuresis). When dilute urine is produced, especially over extended periods, the osmolality of the medullary interstitium declines (see Fig. 35.7*A*). This reduced osmolality is almost entirely caused by a decrease in the concentration of urea. This decrease reflects washout by the vasa recta (discussed later) and diffusion of urea from the interstitium into the tubular fluid within the medullary portion of the collecting duct, which is permeable to urea even in the absence of AVP. (NOTE: The cortical and outer medullary portions of the collecting duct have a low permeability to urea, whereas the inner medullary portion has a relatively high permeability because of the presence of the urea transporters UT-A1 and UT-A3, the expression of which is increased by AVP.) Some of this reabsorbed urea is secreted into the thin descending limbs of Henle's loops via the urea transporter UT-A2, and some enters the vasa recta via the UT-B transporter. The urea that is secreted into the descending thin limbs of Henle's loops is then trapped in the nephron until it again reaches the medullary collecting duct, where it can reenter the medullary interstitium. Thus, urea recycles from the interstitium to the nephron and back into the interstitium. This process of urea recycling facilitates accumulation of urea in the medullary interstitium, where it can attain a concentration at the tip of the papilla of 600 mmol/L.

As described, the hyperosmotic medulla is essential for concentrating the tubular fluid within the collecting duct. Because water reabsorption from the collecting duct is driven by the osmotic gradient established in the medullary interstitium, urine can never be more concentrated than that of the interstitial fluid in the papilla. Thus any condition that reduces the medullary interstitial osmolality



• **Fig. 35.8** The medullary interstitial gradient comprises primarily NaCl and urea. The concentrations for NaCl and urea depicted reflect those found in the antidiuretic state (i.e., excretion of hyperosmotic urine). See text for details. (Adapted from Sands JM, et al. Urine concentration and dilution. In: Taal MW, et al, eds. *Brenner and Rector's The Kidney*. 9th ed. Philadelphia: Elsevier; 2012.)

impairs the ability of the kidneys to maximally concentrate urine. Urea within the medullary interstitium contributes to the total osmolality of the urine. However, because the inner medullary collecting duct is highly permeable to urea, especially in the presence of AVP, urea cannot drive water reabsorption across this nephron segment. Instead, urea in the tubular fluid and medullary interstitium equilibrate, and a small volume of urine with a high concentration of urea is excreted.[c] It is the medullary interstitial NaCl concentration that is responsible for reabsorbing water from the medullary collecting duct and thereby concentrating the nonurea solutes (e.g., NH_4^+ salts, K^+ salts, creatinine) in the urine.

Vasa Recta Function

The **vasa recta,** the capillary networks that supply blood to the medulla, are highly permeable to solute and water. As with the loop of Henle, the vasa recta form a parallel set of hairpin loops within the medulla (see Chapter 33). Not only do the vasa recta bring nutrients and oxygen to the medullary nephron segments, but more importantly they also remove the excess water and solute that is continuously added to the medullary interstitium by these nephron segments. The ability of the vasa recta to maintain the medullary interstitial gradient is flow dependent. A substantial increase in vasa recta blood flow dissipates the medullary gradient (i.e., washout of osmoles from the medullary interstitium). Alternatively, reduced blood flow reduces oxygen delivery to the nephron segments within the medulla. Because transport of salt and other solutes requires oxygen and ATP, reduced medullary blood flow decreases salt and solute transport by nephron segments in the medulla. As a result, the medullary interstitial osmotic gradient cannot be maintained.

In summary, the kidneys maintain an osmotic gradient from the corticomedullary junction to the inner medullary tip. The cortical tissue is isotonic to plasma while the medullary tip is hypertonic. This gradient becomes steeper during antidiuresis and decreases in magnitude during diuresis. Recent studies have been focusing on the detailed understanding of the renal functional architecture, including three-dimensional reconstruction and mathematical modeling to develop a more complete understanding how the permeability properties of nephron segments and their three-dimensional arrangements may contribute to the generation and maintenance of osmotic gradient necessary for urinary concentration.[d]

[c]On a typical diet the kidneys must excrete 450 mmol/day of urea. At a maximal urine [urea] of 600 mmol/L this amount of urea can be excreted in less than 1 L of urine. However, if the maximal urine [urea] is reduced because of a decrease in the medullary interstitial fluid [urea], a larger urine volume would be needed to excrete the 450 mmol/day of urea (e.g., 2.25 L of urine would be required if the maximal urine [urea] was only 200 mM).

[d]Nawata, CM, and Pannabecker, TL. Mammalian urine concentration: a review of renal medullary architecture and membrane transporters. *J Comp Physiol B*; 2018;**188**:899–918.

Assessment of Renal Diluting and Concentrating Ability

Assessment of renal water handling includes measurements of urine osmolality and the volume of urine excreted. The range of urine osmolality is from 50 to 1200 mOsm/kg H_2O. The corresponding range in urine volume is 18 L to as little as 0.5 L/day. The ranges are not fixed and vary from individual to individual and can be affected by disease processes.

The ability of the kidneys to dilute or concentrate urine requires the separation of solute and water (i.e., the single effect of the countercurrent multiplication process). This separation of solute and water in essence generates a volume of water that is "free of solute." When urine is dilute, **solute-free water** is excreted from the body. When urine is concentrated, solute-free water is returned to the body (i.e., conserved).

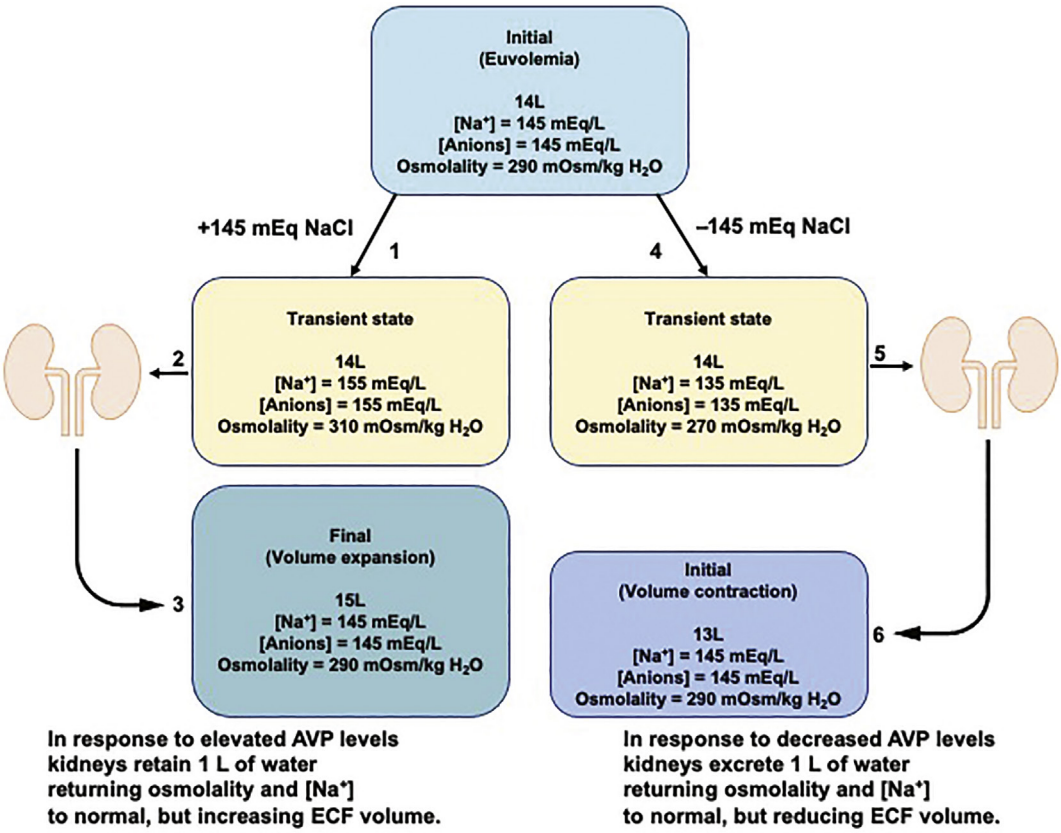
For the kidneys to maximally excrete solute-free water (i.e., 18 L/day) the following conditions must be met:

1. AVP must be absent; without it the collecting duct does not reabsorb a significant amount of water.
2. The tubular structures that separate solute from water (i.e., dilute the tubule fluid) must function normally. In the absence of AVP the following nephron segments can dilute the renal tubular fluid:
   - ascending thin limb of Henle's loop
   - thick ascending limb of Henle's loop
   - distal tubule
   - collecting duct

   Because of its high transport rate, the thick ascending limb is quantitatively the most important nephron segment involved in the separation of solute and water.
3. An adequate amount of tubular fluid must be delivered to the aforementioned nephron sites for maximal separation of solute and water. Factors that reduce delivery (e.g., decreased GFR or enhanced proximal tubule reabsorption) impair the ability to maximally excrete solute-free water.

Similar requirements also apply to conservation of water by the kidneys. For the kidneys to conserve water maximally (6–8 L/day) the following conditions must be met:

1. An adequate amount of tubular fluid must be delivered to those nephron segments that separate solute from water; the most important segment in this regard is the thick ascending limb of Henle's loop. Delivery of tubular fluid to Henle's loop depends on GFR and proximal tubule reabsorption.
2. Reabsorption of NaCl by the nephron segments must be normal; again, the most important segment is the thick ascending limb of Henle's loop.
3. A hyperosmotic medullary interstitium must be present. The interstitial fluid osmolality is maintained by NaCl reabsorption by Henle's loop (conditions 1 and 2) and by effective accumulation of urea. Urea accumulation in turn depends on adequate dietary protein intake.
4. Maximum levels of AVP must be present and the collecting duct must respond normally to AVP.



• **Fig. 35.9** Impact of altered Na^+ balance on ECFV. *(1)* Addition of NaCl (without water) to the ECF increases the $[Na^+]$ and osmolality. *(2)* The increase in ECF osmolality stimulates secretion of AVP from the posterior pituitary, which then acts on the kidneys to conserve water. *(3)* Decreased renal excretion of water together with water ingestion restore plasma osmolality and plasma $[Na^+]$ to normal. However, the ECF volume is now increased by 1 L. *(4)* Removal of NaCl (without water) from the ECF decreases plasma $[Na^+]$ and plasma osmolality. *(5)* Decreased ECF osmolality inhibits AVP secretion. In response to the decrease in plasma AVP the kidneys excrete water. *(6)* Increased renal excretion of water returns the plasma $[Na^+]$ and plasma osmolality to normal. However, ECF volume is now decreased by 1 L. As illustrated, changes in Na^+ balance alter ECFV because of the efficiency of the AVP system to maintain normal body fluid osmolality. (Adapted from Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)

Control of Extracellular Fluid Volume and Regulation of Renal NaCl Excretion

The major solutes of ECF are the salts of Na^+ (see Chapter 2). Of these, NaCl is the most abundant. Because NaCl is also the major determinant of ECF osmolality, alterations in Na^+ balance are commonly assumed to disturb ECF osmolality. However, under normal circumstances this is not the case because the AVP and thirst systems maintain body fluid osmolality within a very narrow range (discussed earlier). As illustrated in Fig. 35.9, adding or removing NaCl from ECF changes its volume and not the $[Na^+]$ (compare initial condition and final conditions). For example, addition of NaCl to ECF (without water) increases the $[Na^+]$ and osmolality of this compartment (ICF osmolality also increases because of osmotic equilibration with ECF.) In response, AVP secretion and thirst are stimulated, and as a result water is ingested and renal water loss is reduced. This restores plasma osmolality (and serum $[Na^+]$) to their initial values, but the volume of ECF is now increased. The opposite occurs when NaCl is lost from ECF. Changes in ECFV can be monitored by measuring body weight, because 1 L of ECF equals 1 kg of body weight.

The kidneys are the major route for excretion of NaCl from the body. Only about 10% of the total daily Na^+ loss occurs by nonrenal routes (e.g., in perspiration and feces). As such, the kidneys are critically important in regulating ECFV. Under normal conditions the kidneys keep ECFV constant (a state termed **euvolemia**) by adjusting the excretion of NaCl to match the amount ingested from food and drink. If ingestion exceeds excretion, ECFV increases above normal **(volume expansion),** whereas the opposite occurs if excretion exceeds ingestion **(volume contraction).**

The typical diet contains approximately 140 mEq/day of Na^+ (8 g of NaCl), and thus Na^+ excretion in urine is also about 140 mEq/day. However, the kidneys can vary excretion of Na^+ over a wide range. Excretion rates as low

as 10 mEq/day can be attained when individuals are placed on a low-salt diet. Conversely, the kidneys can increase their excretion rate to more than 1000 mEq/day when challenged by ingestion of a high-salt diet. These changes in Na^+ excretion can occur with only modest changes in the ECFV and Na^+ content of the body.

The renal response to abrupt changes in NaCl intake typically takes several hours to days, depending on the magnitude of the change. During this transition period the intake and excretion of Na^+ are not matched as in the steady state. Thus the individual experiences either **positive Na^+ balance** (intake > excretion) or **negative Na^+ balance** (intake < excretion). However, by the end of the transition period, a new steady state is established and intake once again equals excretion.

This section focuses on the receptors that control the ECFV and explains various signals that act on the kidneys to regulate NaCl excretion. In addition, responses of the nephron segments to these signals are considered.

Concept of Effective Circulating Volume

As described in Chapter 2, the ECF is subdivided into two compartments: intravascular (plasma) and extravascular (interstitial fluid). Na^+ balance, and thus ECFV, involves a complex system of sensors and effector signals that act primarily on the kidneys to regulate NaCl excretion. Plasma volume determines vascular volume, blood pressure, and cardiac output. Because the primary sensors of this system are located in the large vessels of the vascular system, changes in vascular volume, blood pressure, and cardiac output are the principal factors regulating renal NaCl excretion (discussed later). In a healthy individual, changes in ECFV lead to changes in vascular volume, blood pressure, and cardiac output. A decrease in ECFV results in reduced vascular volume, blood pressure, and cardiac output. Conversely, an increase in ECFV results in increased vascular volume, blood pressure, and cardiac output. The degree to which these cardiovascular parameters change is dependent upon the degree of ECF contraction or expansion and the effectiveness of cardiovascular reflex mechanisms (see Chapters 18 and 19). When a person is in negative Na^+ balance, ECF contracts and renal NaCl excretion decreases. Conversely, with positive Na^+ balance, ECF expands and renal NaCl excretion increases (i.e., **natriuresis**).

However, in some pathological conditions (e.g., congestive heart failure, hepatic cirrhosis), the renal handling of Na^+ does not correlate with the ECFV. Paradoxically, the ECFV increases and renal excretion of NaCl decreases. To explain renal Na^+ handling in these two pathological states, it is necessary to understand the concept of **effective circulating volume (ECV)**. Unlike the ECFV, ECV is *not* a measurable and distinct body fluid compartment. *Effective circulating volume* refers to that portion of the ECF that is contained within the vascular system and is "effectively" perfusing the tissues. More specifically the ECV reflects the activity of volume sensors located in the vascular system (discussed later).

IN THE CLINIC

Patients with congestive heart failure frequently have an increased ECF volume that manifests as increased plasma volume and interstitial fluid accumulating in the lungs **(pulmonary edema)** and peripheral tissues **(generalized edema)**. This excess ECFV is the result of NaCl and water retention by the kidneys. The renal response (i.e., retention of NaCl) is paradoxical because the ECFV is increased. In spite of the increased ECF volume, these patients experience decreased ECV resulting from decreased cardiac output, low blood pressure, or capillary leak of fluid into the interstitial compartment. Therefore, the sensors located in the vascular system respond as they do in ECFV contraction and cause NaCl and water retention by the kidneys.

In healthy individuals, ECV changes directly with ECFV and is determined by the volume of the vascular system (arterial and venous), arterial blood pressure, and cardiac output. However, as noted it is not the case in certain disease states. In the remaining sections of this chapter we examine the relationship between ECFV and renal NaCl excretion in healthy adults.

Volume-Sensing Systems

The volume-sensing sensors are called *vascular volume receptors or baroreceptors*[c] because they respond to pressure-induced stretch of the walls of the structure in which they are located (e.g., blood vessels or the cardiac atria and ventricles).

Volume Sensors in the Low-Pressure Cardiopulmonary Circuit

Baroreceptors located within the walls of the left and right atria, right ventricle, and large pulmonary vessels respond to distention of these structures (see Chapters 18 and 19). Because the low-pressure side of the circulatory system has a high compliance, these sensors respond mainly to the "fullness" of the vascular system. These baroreceptors send signals to the brainstem via afferent fibers in the glossopharyngeal and vagus nerves (cranial nerves IX and X). Activity of the sensors modulates both sympathetic nerve outflow and AVP secretion. For example, a decrease in filling of the pulmonary vessels and cardiac atria increases sympathetic nerve activity and stimulates AVP secretion. Conversely, distention of these structures decreases sympathetic nerve activity. Generally, at least a 5% change in blood volume and pressure is needed to evoke the response.

The cardiac atria possess an additional mechanism related to control of renal NaCl excretion. The myocytes of the atria synthesize and store a peptide hormone, **atrial natriuretic**

[c]The liver and central nervous system also have sensors that respond to changes in blood pressure and [Na^+] and then signal the kidneys to alter NaCl excretion. These systems do not appear to be as important as vascular receptors in monitoring changes in ECFV and effecting changes in renal NaCl excretion and are not considered here.

peptide (ANP). It is released when the atria are distended and, via mechanisms outlined later in this chapter, reduces blood pressure and increases excretion of NaCl and water by the kidneys. The ventricles of the heart also produce a natriuretic peptide, **brain natriuretic peptide (BNP)**, so named because it was first isolated from the brain. Like ANP, BNP is also released from myocytes by distention of the ventricles. Its actions are similar to those of ANP.

Volume Sensors in the High-Pressure Arterial Circuit

Baroreceptors are also present in the arterial side of the circulatory system, located in the wall of the aortic arch, carotid sinus, and the renal afferent arterioles. The aortic arch and carotid baroreceptors send input to the brainstem via afferent fibers in the glossopharyngeal and vagus nerves to alter sympathetic outflow and AVP secretion. Decreased blood pressure increases sympathetic nerve activity and AVP secretion while increased pressure tends to reduce sympathetic nerve activity (and activates parasympathetic nerve activity). The sensitivity of the high-pressure baroreceptors is similar to that in the low-pressure side of the vascular system.

The **juxtaglomerular apparatus (JGA)** of the kidneys (see Chapter 33), particularly the afferent arteriole, responds directly to changes in pressure. If perfusion pressure in the afferent arteriole is reduced, renin is released from the juxtaglomerular cells. By contrast, renin secretion is suppressed when perfusion pressure is increased. As described later in this chapter, renin determines blood levels of angiotensin II and aldosterone, both of which reduce renal NaCl excretion.

IN THE CLINIC

Constriction of a renal artery (e.g., by an atherosclerotic plaque) reduces renal perfusion pressure, which stimulates renin secretion by the afferent arteriole of the JGA. Renin increases the production of the potent vasoconstrictor angiotensin II that affects arterioles throughout the vascular system and increases systemic blood pressure. Increased blood pressure is sensed by the JGA of the contralateral kidney (i.e., the kidney without stenosis of its renal artery), and renin secretion from that kidney is suppressed. In addition, increased angiotensin II levels also inhibit renin secretion by the contralateral kidney (negative feedback). Treatment strategies for patients with stenotic renal arteries include administration of angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, or surgical repair of renal arterial stenosis.

Volume Sensor Signals

When the vascular volume sensors have detected a change in ECFV, they send signals to the kidneys to adjust NaCl and water excretion. Accordingly, when ECF expands, renal NaCl and water excretion increase. Conversely, when ECF contracts, renal NaCl and water excretion decrease. The signals involved in coupling the volume sensors to the kidneys are neural and hormonal and are summarized in Box 35.1.

• BOX 35.1 Signals Involved in Control of Renal NaCl and Water Excretion

Renal Sympathetic Nerves (↑Activity: ↓NaCl Excretion)

↓GFR
↑Renin secretion
↑Na^+ reabsorption along the nephron

Renin-Angiotensin-Aldosterone (↑Secretion: ↓NaCl Excretion)

↑Angiotensin II stimulates Na^+ reabsorption along the nephron
↑Aldosterone stimulates Na^+ reabsorption in the distal tubule and collecting duct and to a lesser degree in the thick ascending limb of Henle's loop
↑Angiotensin II stimulates AVP secretion

Natriuretic Peptides: ANP, BNP & Urodilatin (↑Secretion: ↑NaCl Excretion)

↑GFR
↓Renin secretion
↓Aldosterone secretion (indirect via ↓angiotensin II and direct on adrenal gland)
↓NaCl and water reabsorption by the collecting duct
↓AVP secretion and inhibition of AVP action on the distal tubule and collecting duct

AVP (↑Secretion: ↓H_2O Excretion)

↑H_2O reabsorption by the distal tubule and collecting duct

Renal Sympathetic Nerves

As described in Chapter 33, sympathetic nerve fibers innervate the glomerular afferent and efferent arterioles as well as the nephron cells. ECF contraction activates the low- and high-pressure vascular baroreceptors leading to stimulation of sympathetic nerve activity, including fibers innervating the kidneys. The stimulation has the following effects:

1. Constriction of the afferent and efferent arterioles (mediated by α-adrenergic receptors). This vasoconstriction is greater on the afferent arteriole and decreases the hydrostatic pressure within the glomerular capillary lumen, which decreases GFR. Reduction of GFR decreases Na^+ filtration.
2. Stimulation of renin secretion by juxtaglomerular cells (mediated by β-adrenergic receptors). As described later, renin ultimately increases the circulating levels of angiotensin II and aldosterone, both of which stimulate Na^+ reabsorption by the nephron.
3. Direct stimulation of NaCl reabsorption along the nephron (mediated by α-adrenergic receptors). Because of the large amount of Na^+ reabsorbed by the proximal tubule, the effect of increased sympathetic nerve activity is quantitatively most important for this segment.

As a result, increased renal sympathetic nerve activity decreases NaCl excretion, an adaptive response that works

to restore ECFV to normal. With ECF expansion, renal sympathetic nerve activity decreases. This generally reverses the effects just described.

Renin-Angiotensin-Aldosterone System

Renin is an aspartyl protease that initiates a cascade leading to the production of angiotensin II, a potent vasoconstrictor that increases blood pressures and ECFV. Renin-expressing cells localize to the walls of the afferent arterioles at the entrance to the glomeruli and thus are termed juxtaglomerular (JG) cells. Renin synthesis and secretion are stimulated by renal baroreceptors, β-adrenergic receptors, and the macula densa.

1. *Renal baroreceptors.* The afferent arteriole behaves as a high-pressure baroreceptor. When perfusion pressure to the kidneys is reduced, renin secretion is stimulated. Conversely, an increase in perfusion pressure inhibits renin release.
2. β-*Adrenergic receptors.* The sympathetic nerve fibers from the main renal nerve densely innervate the afferent arterioles. Activation of β-adrenergic receptors stimulates renin secretion.
3. *Macula densa.* Delivery of NaCl to the macula densa regulates GFR by a process termed **tubuloglomerular feedback** (see Chapter 33). In addition, the macula densa plays a role in renin secretion. When NaCl delivery to the macula densa decreases, renin secretion is enhanced. Conversely, an increase in NaCl delivery inhibits renin secretion. It is likely that macula densa–mediated renin secretion helps maintain systemic arterial pressure under conditions of a reduced vascular volume. For example, when vascular volume is reduced, tissue perfusion (including the kidneys) decreases. This in turn decreases GFR and the filtered amount of NaCl. The reduced delivery of NaCl to the macula densa stimulates renin secretion, which acts through angiotensin II (a potent vasoconstrictor) to increase blood pressure and thereby maintain tissue perfusion.

AT THE CELLULAR LEVEL

The adult kidney contains only a small number of JG cells producing sufficient amounts of renin to maintain the blood pressure and fluid and electrolyte balance during homeostasis. By contrast, situations that threaten homeostasis such as hypotension, dehydration, or sodium depletion require much higher renin levels to restore blood pressure as well as fluid and electrolyte balance. The higher demand for renin is met by recruitment of additional cells along the renal arterioles to produce renin. Recruitment occurs from the renin progenitors that differentiated after completion of renal morphogenesis to become arteriolar smooth muscle cells. The recruited smooth muscle cells dedifferentiate to become renin-producing again. Renin synthesis and secretion is stimulated by a *decrease* in intracellular [Ca^{++}], a response opposite that of most secretory cells, where secretion is stimulated by an increase in intracellular [Ca^{++}]. Conversely, signals that increase intracellular [Ca^{++}] inhibit renin secretion. Renin secretion and release is mainly controlled by the cAMP pathway. β-Adrenergic receptors linked to G-protein subunit alpha and JG cell–specific adenylyl cyclase V and VI are essential in cAMP generation in JG cells. cAMP availability is the net result of positive adenylyl cyclase activity and competing degradative activity of calcium calmodulin-activated phosphodiesterase 1C. Acutely increasing intracellular [Ca^{++}] decreases net cAMP generation by dampening adenylyl cyclase and enhancing phosphodiesterase activities. Extracellular [Ca^{++}] affects intracellular [Ca^{++}] via Ca^{++}-sensing receptor (CaSR). Acute stimulation of CaSR results in a marked decrease in cAMP levels and inhibition of renin release. By contrast, chronic CaSR stimulation leads to elevated renin levels. The specific subcellular mechanisms of these effects are an area of intense study.

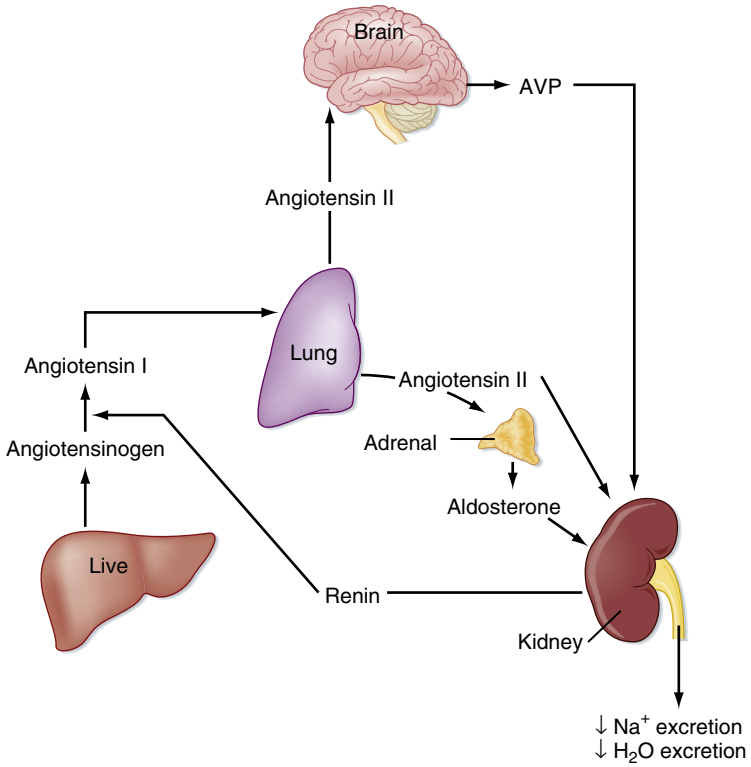
Stretch of the afferent arteriole, angiotensin-II, and endothelin increase intracellular [Ca^{++}] and thus inhibit renin secretion. The stimulatory effect of sympathetic nerve activity on renin secretion is mediated by norepinephrine, which increases intracellular cAMP via β-adrenergic receptors. Prostaglandin E_2 also increases JG cell cAMP levels and therefore stimulates renin secretion. Natriuretic peptides and nitric oxide (NO) inhibit renin secretion by increasing intracellular cyclic guanosine monophosphate (cGMP).

Control of renin secretion by the macula densa is complex and appears to involve several paracrine factors, including ATP, adenosine, and prostaglandin E_2 (see Chapter 33).

Fig. 35.10 summarizes the essential components of the renin-angiotensin-aldosterone system (RAAS). Renin alone does not have a physiological function; it functions solely as a proteolytic enzyme. Its substrate is a circulating protein, **angiotensinogen**, which is produced by the liver. Angiotensinogen is cleaved by renin to yield a 10–amino acid peptide, **angiotensin I**. Angiotensin I also has no known physiological function, and it is cleaved to an 8–amino acid peptide, **angiotensin II**, by **angiotensin-converting enzyme (ACE)** found on the surface of vascular endothelial cells. Lung and renal endothelial cells are important sites for the conversion of angiotensin I to angiotensin II. ACE also degrades bradykinin, a potent vasodilator. Angiotensin II has several important physiological functions:

1. Stimulation of aldosterone secretion by the adrenal cortex.
2. Vasoconstriction of arterioles, which increases blood pressure.
3. Stimulation of AVP secretion and thirst.
4. Increasing NaCl reabsorption by the proximal tubule, thick ascending limb of Henle's loop, distal tubule, and collecting duct. Quantitatively, the proximal tubule effect is the largest.

Angiotensin II is an important secretagogue for **aldosterone**, a major mineralocorticoid produced by the



• **Fig. 35.10** Schematic representation of the essential components of the renin-angiotensin-aldosterone system (RAAS). Activation of RAAS decreases renal Na^+ and water excretion. NOTE: Angiotensin I is converted to angiotensin II by an angiotensin-converting enzyme that is present on all vascular endothelial cells. As shown, the endothelial cells within the lungs play a significant role in this conversion process. See text for details.

glomerulosa cells of the adrenal cortex. Aldosterone sensitivity is conferred by the expression of mineralocorticoid receptor and an enzyme **11β-hydroxysteroid dehydrogenase 2** in the latter portion of the distal tubule and collecting duct and to a lesser extent in the thick ascending limb of Henle's loop and early portion of the distal tubule. Aldosterone binds to the mineralocorticoid receptor while the enzyme increases aldosterone specificity by metabolizing another class of hormones named glucocorticoids and thus prevents them from occupying the mineralocorticoid receptor.

Aldosterone has many effects in the kidneys (see also Chapters 34, 36, and 37). With regard to regulation of the ECFV, aldosterone stimulates NaCl reabsorption. It stimulates Na^+ entry by increasing the abundance and activity of ENaC in the apical membrane of principal cells. Extrusion of Na^+ from cells across the basolateral membrane occurs by Na^+,K^+-ATPase, the abundance of which is also increased by aldosterone. Thus, aldosterone increases reabsorption of NaCl from the tubular fluid in the distal nephron, whereas reduced levels of aldosterone decrease the amount of NaCl reabsorbed.

As summarized in Box 35.1, RAAS activation occurs during ECFV contraction and leads to decreased renal excretion of NaCl. RAAS suppression results from ECFV expansion and leads to increased renal NaCl excretion.

IN THE CLINIC

Diseases of the adrenal cortex can alter aldosterone levels and thereby impair the ability of the kidneys to maintain Na^+ balance and euvolemia. With decreased secretion of aldosterone **(hypoaldosteronism)**, the reabsorption of NaCl, mainly by the aldosterone-sensitive distal nephron, is reduced and NaCl is lost in the urine. When urinary NaCl loss exceeds the dietary NaCl intake, negative Na^+ balance ensues and ECFV decreases. In response to ECF contraction, sympathetic tone increases leading to elevated levels of renin, angiotensin II, and AVP. The opposite effects result from increased aldosterone secretion **(hyperaldosteronism)**; NaCl reabsorption by the aldosterone-sensitive distal nephron increases and excretion of NaCl falls, leading to increased ECFV. These effects lead to reduction of the sympathetic tone and levels of renin, angiotensin II, and AVP. As described later, ANP and BNP levels are elevated in this setting.

Natriuretic Peptides

A number of endogenous substances act on the kidneys to increase NaCl excretion (see Chapter 34). The natriuretic peptides produced by the heart and kidneys are best understood and will be the focus of the following discussion.

The heart produces two natriuretic peptides. Atrial natriuretic peptide (ANP) is produced and stored in atrial

myocytes while brain natriuretic peptide (BNP) is produced and stored in ventricular myocytes. Both peptides are secreted when the heart dilates in states of volume expansion or heart failure. BNP and ANP relax vascular smooth muscle tone and promote renal NaCl and water excretion. **Urodilatin** is a natriuretic peptide produced by the kidneys and promotes renal NaCl excretion. The natriuretic peptides antagonize the effects of RAAS on renal NaCl and water excretion by the following mechanisms:

1. Increase of GFR and the filtered amount of NaCl by vasodilation of the afferent and constriction of the efferent glomerular arterioles.
2. Inhibition of renin secretion by the afferent arterioles.
3. Inhibition of aldosterone secretion: (a) indirectly by decreasing renin secretion, thereby reducing angiotensin II–induced aldosterone levels; and (b) directly by inhibiting aldosterone secretion from the glomerulosa cells of the adrenal cortex.
4. Inhibition of NaCl reabsorption from the collecting duct, which is also caused in part by reduced levels of aldosterone. However, natriuretic peptides increase cGMP, which inhibits cation channels in the apical membrane of cells in the medullary collecting duct cells and thereby decreases NaCl reabsorption.
5. Inhibition of AVP secretion by the posterior pituitary and AVP action on the collecting duct. These effects decrease water reabsorption by the collecting duct and thus increase excretion of water in the urine.

The net effect of natriuretic peptides is to increase excretion of NaCl and water by the kidneys.

Arginine Vasopressin

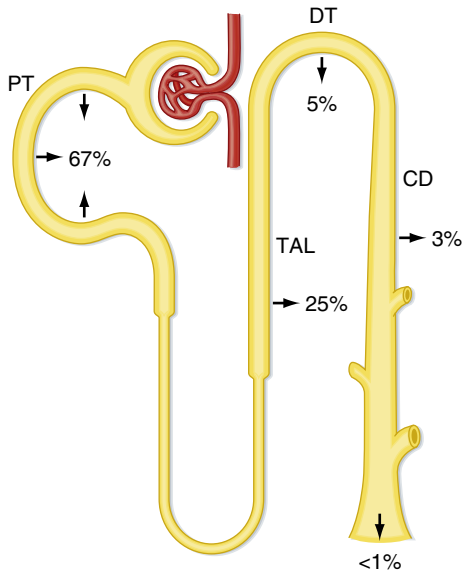
As discussed previously, ECF contraction stimulates AVP secretion by the posterior pituitary. Elevated AVP levels decrease renal water excretion, and reestablishes euvolemia.

Control of NaCl Excretion During Euvolemia

Maintenance of Na^+ balance and therefore euvolemia requires precise balance between the amount ingested and excreted. As already noted, kidneys are the major route for Na^+ excretion. Accordingly, in a euvolemic individual we can equate daily urine Na^+ excretion with Na^+ intake.

Under conditions of salt restriction (i.e., low-salt diet), virtually no Na^+ appears in the urine. Conversely, in individuals who ingest large salt quantities, renal Na^+ excretion can exceed 1000 mEq/day. The time course for adjustment of renal Na^+ excretion varies (hours to days) and depends on the magnitude of the change in salt intake. Acclimation to large changes in salt intake requires a longer time than acclimation to small changes in intake.

The general features of Na^+ transport along the nephron are illustrated in Fig. 35.11. Most (67%) of the Na^+ filtered by the glomerulus is reabsorbed by the proximal tubule. An additional 25% is reabsorbed by the thick ascending limb of the loop of Henle, and the remainder by the distal tubule and collecting duct.



• **Fig. 35.11** Segmental Na^+ reabsorption. The percentage of the filtered load of Na^+ reabsorbed by each nephron segment is indicated. *CD,* Cortical collecting duct; *DT,* distal tubule; *PT,* proximal tubule; *TAL,* thick ascending limb.

In a normal adult the filtered amount (load) of Na^+ is approximately 25,000 mEq/day:

Equation 35.1

$$\begin{aligned}\text{Filtered load of } Na^+ &= (\text{GFR}) \times (\text{Plasma } [Na^+]) \\ &= (180 \text{ L / day}) \times (140 \text{ mEq / L}) \\ &= 25{,}200 \text{ mEq / day}\end{aligned}$$

With a typical diet, less than 1% of this filtered load is excreted in urine (≈140 mEq/day).[f] Because of the large filtered load of Na^+, small changes in its reabsorption by the nephron can profoundly affect Na^+ balance and thus ECFV. For example, an increase in Na^+ excretion from 1% to 3% of the filtered load represents an additional loss of approximately 500 mEq/day of Na^+. Because the ECF $[Na^+]$ is 140 mEq/L, such Na^+ loss would decrease the ECFV by more than 3 L (i.e., water excretion would parallel the loss of Na^+ to maintain body fluid osmolality constant: 500 mEq/day ÷ 140 mEq/L = 3.6 L/day of fluid loss). Such fluid loss in a 70-kg individual would represent a 26% decrease in ECFV.

In euvolemic individuals the nephron segments distal to the loop of Henle (distal tubule and collecting duct) are the main nephron segments where Na^+ reabsorption is adjusted to maintain excretion at a level appropriate for dietary intake. However, this does not mean that other portions of the nephron are not involved in this process. Because the reabsorptive capacity of the distal tubule and collecting duct

[f]The percentage of the filtered load excreted in urine is termed **fractional excretion.** In this example the fractional excretion of Na^+ is 140 mEq/day ÷ 25,200 mEq/day = 0.005, or 0.5%.

is limited, these other nephron segments (i.e., proximal tubule and loop of Henle) must reabsorb the bulk of the filtered Na^+ load. During euvolemia, Na^+ handling by the nephron occurs in two sequential events:

1. Na^+ handling by the proximal tubule and loop of Henle delivers a relatively constant portion of the filtered Na^+ load to the distal tubule. The combined action of these nephron segments reabsorbs approximately 92% of the filtered Na^+ and delivers 8% to the distal tubule.
2. Na^+ handling by the distal tubule and collecting duct leads to urinary excretion of Na^+ that is equivalent to the amount of Na^+ that is ingested in the diet.

Mechanisms for Maintaining Constant Delivery of NaCl to the Distal Tubule

A number of mechanisms maintain a constant delivery of Na^+ to the beginning of the distal tubule. These processes are autoregulation of the GFR (and thus the filtered Na^+ load) glomerulotubular balance, and load dependency of Na^+ reabsorption by the loop of Henle.

Autoregulation of the GFR (see Chapter 33) allows maintenance of a relatively constant filtration rate over a wide range of perfusion pressures. Because the filtration rate is constant, the filtered Na^+ load is also constant.

Despite the autoregulatory control of GFR, small variations occur. If changes were not compensated by adjusting Na^+ reabsorption from the nephron, Na^+ excretion would change markedly. Fortunately, Na^+ reabsorption in the euvolemic state, especially by the proximal tubule, changes in parallel with changes in GFR. This phenomenon is termed **glomerulotubular balance**. Thus if GFR increases, the amount of Na^+ reabsorbed by the proximal tubule also increases. The opposite occurs if GFR decreases (see Chapter 34 for more details).

The final mechanism that helps maintain constant delivery of Na^+ to the distal tubule and collecting duct involves the ability of the loop of Henle to increase its reabsorptive rate in response to increased delivery of Na^+.

Regulation of Distal Tubule and Collecting Duct NaCl Reabsorption

When delivery of Na^+ is constant, small adjustments in Na^+ reabsorption, primarily by the aldosterone-sensitive distal nephron, are sufficient to balance excretion with intake. Aldosterone is the primary regulator of Na^+ reabsorption and thus of NaCl excretion. When aldosterone levels are elevated, Na^+ reabsorption by these segments is increased (Na^+ excretion is decreased). When aldosterone levels are decreased, Na^+ reabsorption is decreased (NaCl excretion is increased). Other factors have been shown to alter Na^+ reabsorption (e.g., angiotensin II, natriuretic peptides), but their role during euvolemia is unclear.

As long as variations in dietary salt intake are minor, the described mechanisms can maintain euvolemia. However, these mechanisms cannot effectively handle significant changes in, Na^+ intake, leading to ECFV expansion or contraction. In extreme situations, additional factors act on the kidneys to adjust Na^+ excretion and thereby reestablish the euvolemic state.

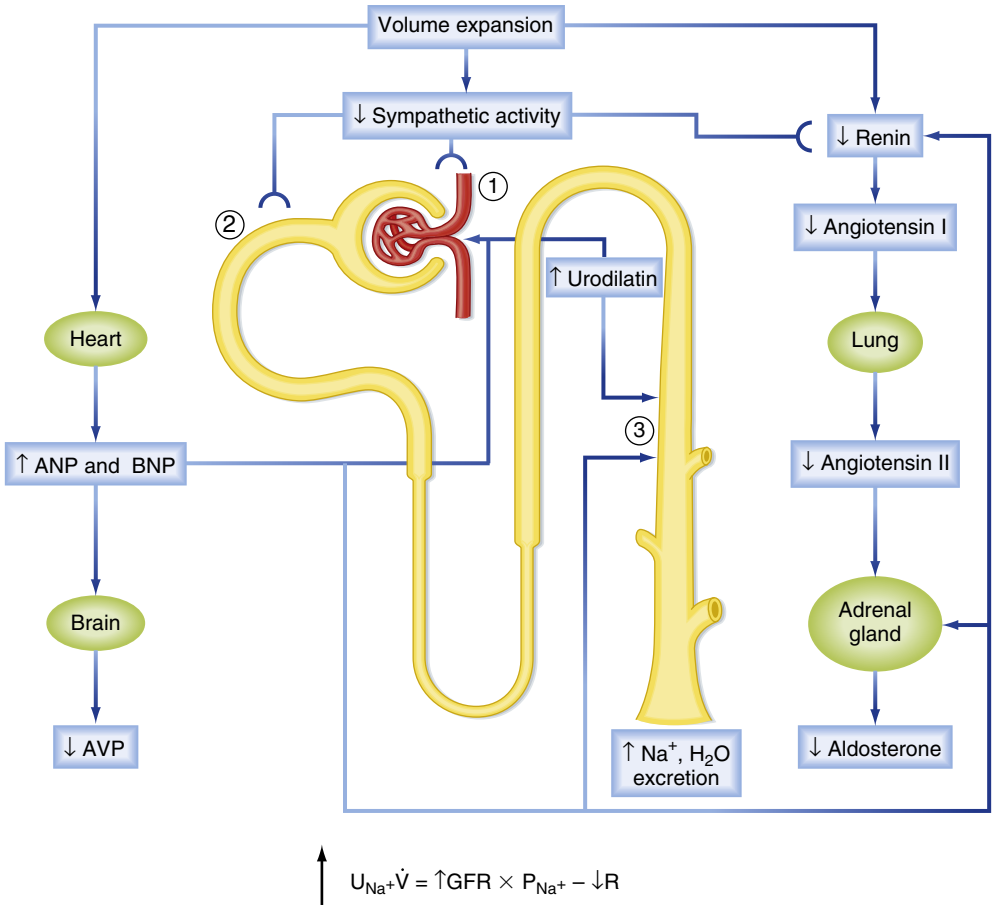
Control of NaCl Excretion During Volume Expansion

During ECFV expansion, the high-pressure and low-pressure vascular volume sensors send signals to the kidneys to increase excretion of NaCl and water. The signals include:

1. Decreased activity of renal sympathetic nerves.
2. Decreased release of ANP and BNP from the heart and urodilatin from the kidneys.
3. Inhibition of AVP secretion from the posterior pituitary and its action on the collecting duct.
4. Decreased renin secretion and thus decreased production of angiotensin II.
5. Decreased aldosterone secretion as a result of reduced angiotensin II levels, and elevated natriuretic peptide levels.

The integrated response of the nephron to the signals is illustrated in Fig. 35.12. Three general responses to ECFV expansion occur (the numbers match those encircled in Fig. 35.12):

1. *GFR increases.* GFR increases mainly as a result of decreased sympathetic nerve activity. Sympathetic fibers innervate the afferent and efferent arterioles of the glomerulus and control their diameter. Decreased sympathetic nerve activity leads to arteriolar dilation and elevation of renal plasma flow (RPF). Because the effect appears to be greater on the afferent arterioles, the hydrostatic pressure within the glomerular capillary increases, thereby increasing the GFR. Because RPF increases to a greater degree than GFR, the filtration fraction (GFR/RPF) decreases. Natriuretic peptides also increase GFR by dilating the afferent arterioles and constricting the efferent arterioles. Thus increased natriuretic peptide levels present during ECFV expansion contribute to this response. With the increase in GFR, the filtered load of Na^+ increases.
2. *The reabsorption of Na^+ decreases in the proximal tubule and loop of Henle.* Several mechanisms reduce Na^+ reabsorption by the proximal tubule. Because activation of the sympathetic nerve fibers that innervate this nephron segment stimulates proximal tubule Na^+ reabsorption, the decreased sympathetic nerve activity that results from ECF expansion decreases Na^+ reabsorption. In addition, angiotensin II directly stimulates Na^+ reabsorption by the proximal tubule. Because angiotensin II levels are also reduced under this condition, proximal tubule Na^+ reabsorption decreases as a result. Starling forces across the proximal tubule also change. The elevated hydrostatic pressure within the glomerular capillaries also tends to increase the hydrostatic pressure within the peritubular capillaries. In addition, decreased filtration fraction reduces the peritubular oncotic pressure. These alterations in the capillary Starling forces (i.e., hydrostatic and



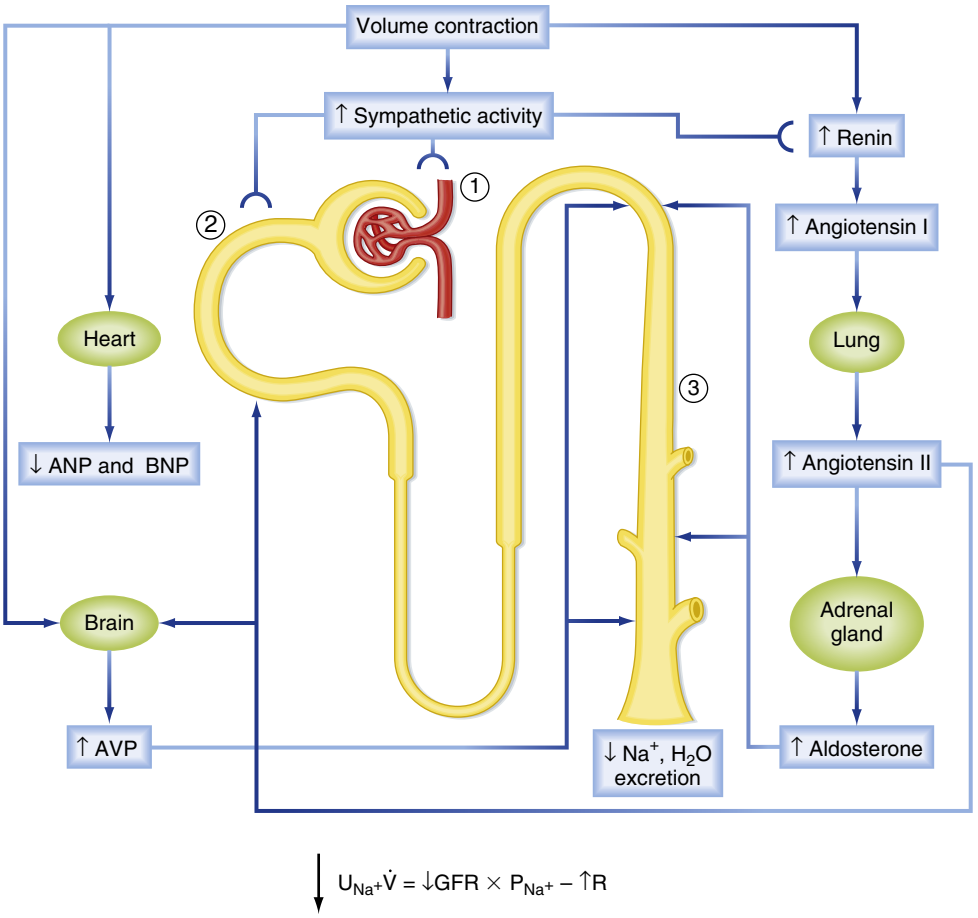
• **Fig. 35.12** Integrated response to ECF expansion. *Numbers* refer to the description of the response in the text. *ANP,* Atrial natriuretic peptide; *BNP,* brain natriuretic peptide; *GFR,* glomerular filtration rate; P_{Na+}, plasma [Na^+]; *R,* tubular reabsorption of Na^+; $U_{Na+}\dot{V}$, Na^+ excretion rate.

oncotic) reduce the absorption of solute (e.g., NaCl) and water from the lateral intercellular space and thus reduce tubular reabsorption of NaCl (see Chapter 34 for a complete description of this mechanism). Increased filtered load and decreased NaCl reabsorption by the proximal tubule result in delivery of more NaCl to the loop of Henle. Because activation of sympathetic nerves and angiotensin II and aldosterone stimulate NaCl reabsorption by the thick ascending limb of the loop of Henle, the reduced nerve activity and low angiotensin II and aldosterone levels that occur with ECF expansion reduce NaCl reabsorption by the thick ascending limb. Thus the fraction of the filtered load delivered to the distal tubule increases.

3. *Na^+ reabsorption decreases in the distal tubule and collecting duct.* As noted, the amount of Na^+ delivered to the distal tubule exceeds that observed in the euvolemic state (i.e., the amount of Na^+ delivered to the distal tubule varies in proportion to the degree of ECF expansion). The increased Na^+ load overwhelms the reabsorptive capacity of the distal tubule and collecting duct. NaCl reabsorption is also impaired due to reduced levels of angiotensin II and aldosterone, as well as increased levels of natriuretic peptides.

The final component in the response to ECFV expansion is increased excretion of water. As Na^+ excretion increases, plasma osmolality begins to fall. This decreases secretion of AVP. Its secretion is also inhibited in response to elevated natriuretic peptide levels. In addition, natriuretic peptides inhibit the action of AVP on the collecting duct. Together, these effects decrease water reabsorption by the collecting duct and thereby increase renal water excretion. Excretion of Na^+ and water occurs in concert; euvolemia can be restored and body fluid osmolality return to normal. The time course of the response (hours to days) depends on the magnitude of the ECFV expansion and the ongoing Na^+ and water intake. If the degree of ECFV expansion is small, the mechanisms generally restore euvolemia within 24 hours. With large degrees of ECFV expansion, the response may take days.

In summary, renal response to ECFV expansion involves an integrated action of the entire nephron: (1) the amount of filtered Na^+ is increased; (2) Na^+ reabsorption by the proximal tubule and loop of Henle is reduced (glomerulotubular balance does not occur under this condition); (3) reabsorption of Na^+ by the distal tubule and collecting duct is decreased secondary to reduced aldosterone levels;



• **Fig. 35.13** Integrated response to ECFV contraction. *Numbers* refer to the description of the response in the text. *ANP,* Atrial natriuretic peptide; *BNP,* brain natriuretic peptide; *GFR,* glomerular filtration rate; P_{Na+}, plasma [Na^+]; *R,* tubular reabsorption of Na^+; $U_{Na+}\dot{V}$, Na^+ excretion rate.

and (4) excretion of a larger fraction of filtered Na^+ restores euvolemia.

Control of NaCl Excretion During Volume Contraction

During ECFV contraction, the high- and low-pressure vascular volume sensors signal to the kidneys to reduce NaCl and water excretion and thereby restore euvolemia. The signals include:

1. Increased renal sympathetic nerve activity.
2. Increased renin secretion, which increases angiotensin II and aldosterone levels.
3. Inhibition of ANP and BNP secretion by the heart and urodilatin secretion by the kidneys.
4. Stimulation of AVP secretion by the posterior pituitary.

The integrated response of the nephron to the signals is described next and illustrated in Fig. 35.13. The numbers below correlate with those in the figure:

1. *GFR decreases.* Afferent and efferent arteriolar constriction occurs as a result of increased renal sympathetic nerve activity. Because the effect is greater on the afferent arteriole, the hydrostatic pressure in the glomerular capillaries falls, which decreases GFR. Because RPF decreases more than GFR, filtration fraction increases. The decrease in GFR reduces the filtered amount of Na^+.
2. *Na^+ reabsorption by the proximal tubule and loop of Henle is increased.* Several mechanisms augment Na^+ reabsorption in the proximal tubule. For example, increased sympathetic nerve activity and angiotensin II levels directly stimulate Na^+ reabsorption. Decreased hydrostatic pressure within the glomerular capillaries also reduces the hydrostatic pressure within the peritubular capillaries. In addition, as just noted, the increased filtration fraction results in an increase in the peritubular oncotic pressure. These alterations in the capillary Starling forces facilitate movement of fluid from the lateral intercellular space into the capillary and thereby stimulate reabsorption of NaCl and water by the proximal tubule (see Chapter 34 for a complete description of this mechanism). Increased sympathetic nerve activity as well as elevated levels of angiotensin II and aldosterone stimulate Na^+ reabsorption by the thick ascending limb.
3. *Na^+ reabsorption by the distal tubule and collecting duct is enhanced.* The small amount of Na^+ that is delivered to the aldosterone-sensitive distal nephron, owing to decreased filtration and increased reabsorption by the

proximal tubule and loop of Henle, is almost completely reabsorbed. Stimulation of Na^+ reabsorption from this segment is enhanced by increased aldosterone levels, although increased sympathetic nerve activity and increased angiotensin II levels may also contribute to this response.

Finally, water reabsorption by the latter portion of the distal tubule and the collecting duct is enhanced by AVP, the levels of which are elevated through activation of the low- and high-pressure vascular volume sensors as well as angiotensin II. As a result, water excretion is reduced. Because both water and Na^+ are retained by the kidneys in equal proportions, euvolemia is reestablished and body fluid osmolality returns to normal. The time course (hours to days) and the degree to which euvolemia can be restored depend on the magnitude of ECF contraction as well as the Na^+ and water intake (enteral or parenteral) and ongoing Na^+ and water losses (sensible and insensible).

In brief, the nephron's response to ECFV contraction involves the integrated action of all its segments: (1) the filtered amount of Na^+ is decreased; (2) Na^+ reabsorption by the proximal tubule and loop of Henle is enhanced (GFR is decreased, whereas proximal reabsorption is increased, and thus glomerulotubular balance does not occur under this condition); (3) delivery of Na^+ to the aldosterone-sensitive distal nephron is reduced in addition to enhanced Na^+ and water reabsorption from this segment, virtually eliminating urinary Na^+ and water excretion.

Key Concepts

1. Regulation of body fluid osmolality (i.e., steady-state balance) requires that the amount of water added to the body exactly matches the amount lost. Water is lost from the body by sensible and insensible mechanisms. Excretion of water by the kidney is regulated by AVP secreted from the posterior pituitary. When AVP levels are high, urine volume decreases and it becomes hyperosmotic. When AVP levels are low, urine volume increases and its osmolality falls.
2. Disorders of water balance alter body fluid osmolality. Because Na^+ with its anions is the major determinant of ECF osmolality, disorders of water balance manifest as changes in ECF $[Na^+]$. Positive water balance (intake > excretion) leads to hyponatremia and decreases body fluid osmolality. Negative water balance (intake < excretion) leads to hypernatremia and increase body fluid osmolality.
3. The ECFV is determined by the amount of Na^+ in the compartment. To maintain normal ECFV (i.e., euvolemia) Na^+ excretion must match Na^+ intake. The kidneys are the major site for regulating excretion of NaCl from the body. Volume sensors located primarily in the vascular system monitor volume and pressure. When ECFV expansion occurs, neural and hormonal signals increase renal excretion of NaCl and water and thereby restore euvolemia. When ECFV contraction occurs, neural and hormonal signals decrease renal Na^+ and water excretion and euvolemia can be restored. The sympathetic nervous system, RAAS, and natriuretic peptides are important components of the system that maintain steady-state Na^+ balance.