Regulation of Urine Concentration and Volume

A solution's **osmolality** (oz″mo-lal′ĭ-te) is the number of solute particles dissolved in one liter (1000 g) of water and reflects the solution's ability to cause osmosis. For any solution interfacing with a semipermeable membrane, this ability, called *osmotic activity*, is determined only by the number of nonpenetrating solute particles (solute particles unable to pass through the membrane) and is independent

of their type. Ten sodium ions have the same osmotic activity as ten glucose molecules or ten amino acids in the same volume of water. Because the *osmol* (equivalent to 1 mole of a nonionizing substance in 1 L of water) is a fairly large unit, the **milliosmol (mOsm)** (mil"e-oz'mōl), equal to 0.001 osmol, is used to describe the solute concentration of body fluids.

One crucial renal function is to keep the solute load of body fluids constant at about 300 mOsm, the osmotic concentration of blood plasma, by regulating urine concentration and volume. The kidneys accomplish this feat by a **countercurrent mechanism.** The term *countercurrent* means that something flows in opposite directions through adjacent channels. In the kidneys the countercurrent mechanism involves the interaction between the flow of filtrate through the long loops of Henle of juxtamedullary nephrons (the *countercurrent multiplier*), and the flow of blood through the adjacent vasa recta blood vessels (the *countercurrent exchanger*). The countercurrent mechanism establishes an osmotic gradient extending from the cortex through the depths of the medulla that allows the kidneys to vary urine concentration dramatically.

The osmolality of the filtrate entering the PCT is identical to that of plasma, about 300 mOsm. As described earlier, because of PCT reabsorption of water *and* solutes, the filtrate is still isosmotic with plasma by the time the descending limb of the loop of Henle is reached. However, its osmolality increases from 300 to about 1200 mOsm in the deepest part of the medulla (Figure 25.13). How does this increase in concentration occur? The answer lies in the unique workings of the long loop of Henle of the juxtamedullary nephrons, and the vasa recta. Notice in Figure 25.13 that in each case the fluids involved—filtrate in the loop of Henle and blood in the vasa recta—first descend and then ascend through parallel limbs.

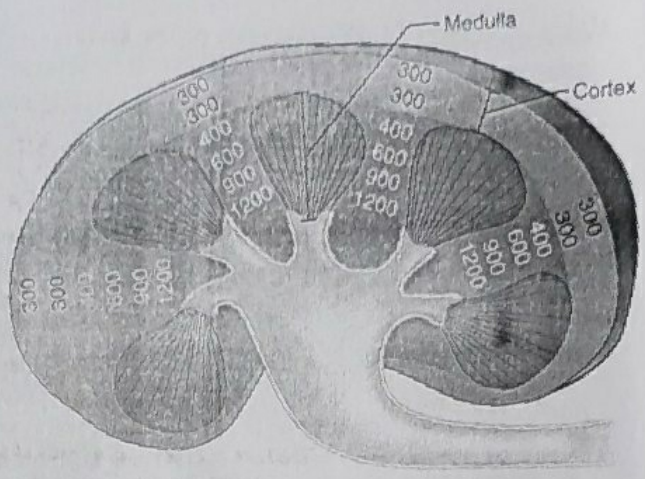

FIGURE 25.13 **Osmotic gradient in the renal medulla.** The osmolality of the interstitial fluid in the renal cortex is isotonic at 300 mOsm/L, but the osmolality of the interstitial fluid in the renal medulla increases progressively from 300 mOsm/L at the boundary with the corticomedullary junction to 1200 mOsm/L at the medullary-pelvis junction.

The Countercurrent Multiplier

First, we will follow filtrate processing through the loop of Henle, as portrayed in Figure 25.14a, to see how the loop functions as a **countercurrent multiplier** to establish the osmotic gradient. The countercurrent multiplier functions because of three factors:

1. The descending limb of the loop of Henle is relatively impermeable to solutes and freely permeable to water. Because the osmolality of the medullary interstitial fluid increases all along the descending limb (the mechanism of this increase is explained shortly), water passes osmotically out of the filtrate all along this course. Thus, the filtrate osmolality reaches its highest point (1200 mOsm) at the "elbow" of the loop.

2. The ascending limb is permeable to solutes, but not to water. As the filtrate rounds the corner into the ascending limb, the tubule permeability changes, becoming impermeable to water and selectively permeable to salt. The Na^+ and Cl^- concentration in the filtrate entering the ascending limb is very high (and interstitial fluid concentrations of these two ions are lower). Although the thin segment of the ascending limb of the loop of Henle also contributes to Na^+ and Cl^- reabsorption, most of the NaCl reabsorption takes place in the thick segment via its Na^+-K^+-$2Cl^-$ cotransporter. As Na^+ and Cl^- are extruded from the filtrate into the medullary interstitial fluid, they contribute to the high osmolality there. Because it loses salt but not water, the filtrate in the ascending limb becomes increasingly dilute until, at 100 mOsm at the DCT, it is hypoosmotic, or hypotonic, to blood plasma and cortical fluids.

Notice in Figure 25.14 that there is a constant difference in filtrate concentration between the two limbs of the loop of Henle. Because the ascending limb is relatively more permeable to Na^+ and Cl^-, some salt diffuses back into the filtrate in that portion of the tubule, even as NaCl is being actively reabsorbed. Consequently, the solute content in the ascending limb filtrate is always about 200 mOsm lower than the filtrate concentration in the descending limb and in the surrounding medullary interstitial fluid. However, because of countercurrent flow, the loop of Henle is able to "multiply" these small changes in solute concentration into a gradient change along the vertical length of the loop (both

? What portion of the nephron acts as the countercurrent multiplier? As the countercurrent exchanger?

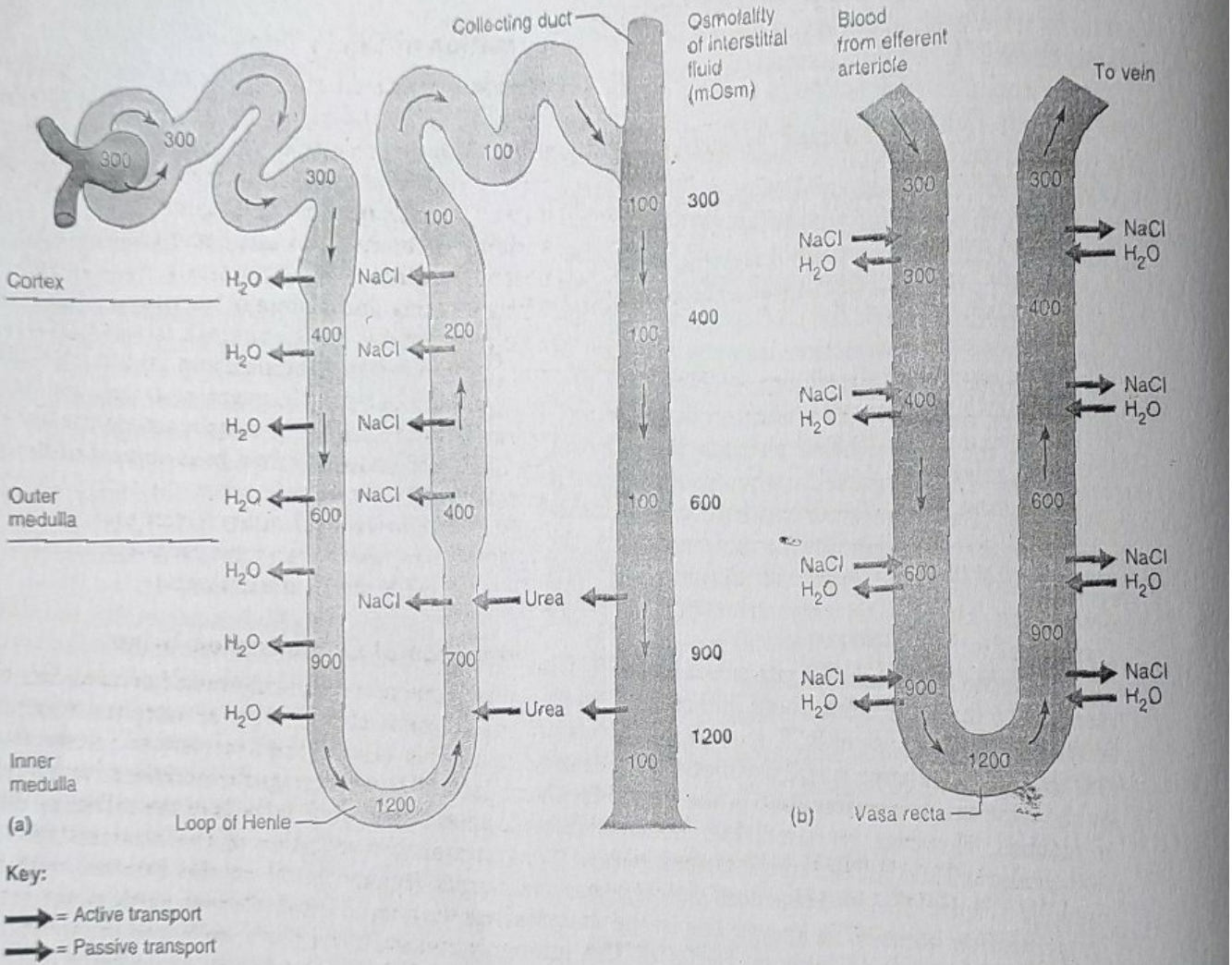

FIGURE 25.14 Countercurrent mechanism for establishing and maintaining the medullary osmotic gradient. (a) Filtrate entering the descending limb of the loop of Henle is isosmotic to both blood plasma and cortical interstitial fluid. As the filtrate flows from the cortex to the medulla in the descending limb, water leaves the tubule by osmosis and the filtrate osmolality increases from 300 to 1200 mOsm. As the filtrate flows into the ascending limb, the permeability of the tubule epithelium changes from being permeable to water and impermeable to salt to the opposite condition: water impermeable, salt permeable. Consequently, NaCl leaves the ascending limb, diluting the filtrate as it approaches the cortex. Thus the descending limb produces increasingly salty filtrate, while the ascending limb uses this high salt concentration to establish the high osmolality of the interstitial fluid in the medulla and the medullary osmotic gradient. Diffusion of urea from the lower portion of the collecting duct also contributes to the high osmolality in the medulla. (b) Dissipation of the medullary osmotic gradient is prevented because the blood in the vasa recta continuously becomes isosmotic to the interstitial fluid—becoming more concentrated as it follows the descending limb of the loop of Henle and less concentrated as it approaches the cortical region. This occurs because of the high porosity and sluggish blood flow in the vasa recta.

The countercurrent multiplier is the loop of Henle of juxtamedullary nephrons; The countercurrent exchanger is the vasa recta. ■

inside and outside) that is closer to 900 mOsm (1200 mOsm – 300 mOsm).

Although the two limbs of the loop of Henle are not in direct contact with each other, they are close enough to influence each other's exchanges with the interstitial fluid they share. Hence, water diffusing out of the descending limb produces the increasingly "salty" filtrate that the ascending limb uses to raise the osmolality of the medullary interstitial fluid. Furthermore, the more NaCl the ascending limb extrudes, the more water diffuses out of the descending limb and the saltier the filtrate in the descending limb becomes. This establishes a positive feedback mechanism that produces the high osmolality of the fluids in the descending limb and the interstitial fluid.

3. The collecting ducts in the deep medullary regions are permeable to urea. The amount of urea in the filtrate remains high because most nephron segments beyond the PCT are impermeable to it. However, as urine passes through the collecting duct in the deep medullary region where the duct is highly permeable to urea, urea diffuses out of the duct into the medullary interstitial fluid, where it contributes to the high osmolality in that region. Urea continues to move out of the duct passively until its concentration inside and outside the duct is equal. Even though the ascending limb of the loop of Henle is poorly permeable to urea, when urea concentration in the medullary interstitial space is high, some urea does enter the limb. However, it is recycled back to the collecting duct, where it diffuses out again. Unlike the active reabsorption of NaCl in the thick part of the ascending limb, which is a crucial element of the countercurrent multiplier system, urea's cycling simply equalizes its concentration inside and outside the renal tubules.

The Countercurrent Exchanger

As shown in Figure 25.14b, the vasa recta function as a **countercurrent exchanger,** maintaining the osmotic gradient established by the cycling of salt while delivering blood to cells in the area. Because these vessels receive only about 10% of the renal blood supply, blood flow through the vasa recta is sluggish. Moreover, they are freely permeable to water and NaCl, allowing blood to make passive exchanges with the surrounding interstitial fluid and achieve equilibrium. Consequently, as the blood flows into the medullary depths, it loses water and gains salt (becomes hypertonic). Then, as it emerges from the medulla into the cortex, the process is reversed: It picks up water and loses salt. Because blood leaving and reentering the cortex via the vasa recta has the same solute concentration, the vessels of the vasa recta act as a countercurrent exchanger. This system does not create the medullary gradient, but it protects it by preventing rapid removal of salt from the medullary interstitial space.

Formation of Dilute Urine

Because tubular filtrate is diluted as it travels through the ascending limb of the loop of Henle, all the kidney needs to do to secrete dilute (hypoosmotic) urine is allow the filtrate to continue on its way into the renal pelvis (Figure 25.15a). When antidiuretic hormone is not being released by the posterior pituitary, that is exactly what happens. The collecting ducts remain essentially impermeable to water due to the absence of aquaporins at the luminal cell membranes, and no further water reabsorption occurs. Moreover, as noted, Na^+ and selected other ions can be removed from the filtrate by DCT and collecting duct cells so that urine becomes even more dilute before entering the renal pelvis. The osmolality of urine can plunge as low as 50 mOsm, about one-sixth the concentration of glomerular filtrate or blood plasma.

Formation of Concentrated Urine

As its name reveals, **antidiuretic hormone** inhibits *diuresis* (di"u-re'sis), or urine output. It accomplishes this via a second-messenger system using cyclic AMP that increases the number of water-filled channels in the principal cells of the collecting ducts by stimulating shuttling of the channels' protein subunits (aquaporin 2) to the luminal surfaces, where they are inserted. Consequently water passes easily into and through the cells into the interstitial space, and the osmolality of the filtrate becomes equal to that of the interstitial fluid.

In the distal tubules, which are in the cortex, the filtrate osmolality is approximately 100 mOsm, but as the filtrate flows through the collecting ducts and is subjected to the hyperosmolar conditions in the medulla, water, followed by urea, rapidly leaves the filtrate (Figures 25.15b and 25.16e). Depending on the amount of ADH released (which is keyed to the level of body hydration), urine concentration may rise as high as 1200 mOsm, the concentration of interstitial fluid in the deepest part of the medulla. With maximal ADH secretion, up to 99% of the water in the filtrate is reabsorbed and returned to the blood, and less than 1 L/day (about 1 ml/min) of highly concentrated urine is excreted. The ability of our kidneys to produce such concentrated urine is critically tied to our ability to survive without water. Water reabsorption that depends on the presence of ADH is called **facultative water reabsorption.**

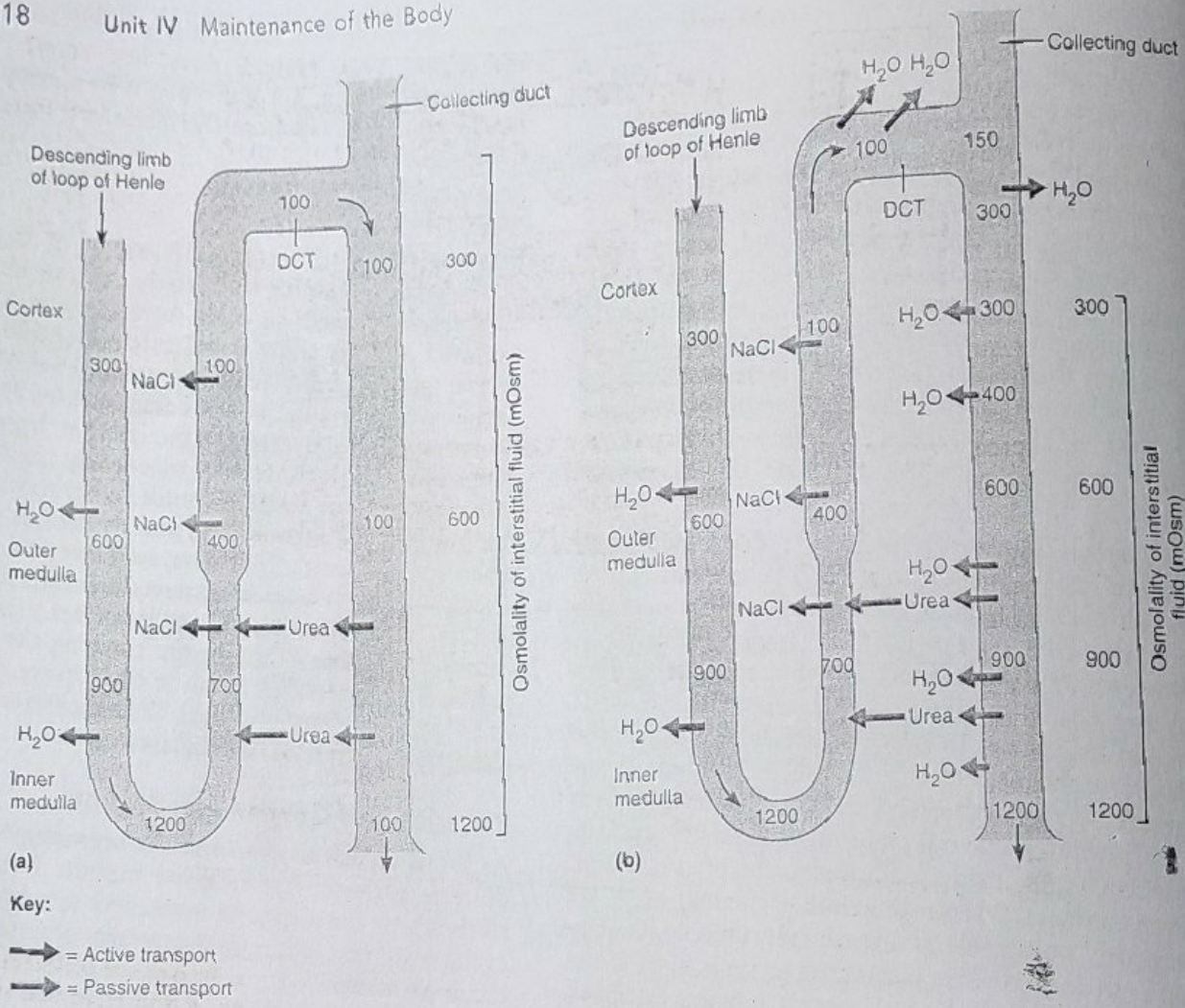

FIGURE 25.15 **Mechanisms for forming dilute and concentrated urine.** **(a)** Because the filtrate is diluted by the workings of the countercurrent mechanism, all that is needed to secrete dilute urine is to allow the filtrate reaching the DCT to be excreted. **(b)** Concentrated urine is excreted in the presence of ADH. ADH causes insertion of aquaporins in luminal membranes of principal cells of the late DCT and collecting duct. Consequently water rapidly leaves the filtrate in the collecting duct.

ADH is released more or less continuously unless the blood solute concentration drops too low. Release of ADH is enhanced by any event that raises plasma osmolality above 300 mOsm/L, such as sweating or diarrhea, or reduced blood volume or blood pressure (See Chapter 26). Although release of ADH is the "signal" to produce concentrated urine that opens the door (pores) for water reabsorption, the kidneys' ability to respond to this signal depends on the high medullary osmotic gradient.

ADH. Other diuretics increase urine flow by inhibiting Na^+ reabsorption and the obligatory water reabsorption that normally follows. Examples include caffeine (found in coffee, tea, and colas) and many drugs prescribed for hypertension or the edema of congestive heart failure. Common diuretics, like Lasix and Diuril, inhibit Na^+-associated symporters in the ascending loop of Henle or the DCT.

Renal Cl