7.5 Mechanism of Concentration and Dilution of Urine

Learning Objectives

- Describe how the proximal tubule reabsorbs an isosmotic fluid
- Summarize the transport characteristics of the various parts of the loop of Henle and the distal tubule, focusing on its treatment of salt, water, and urea
- Describe how ADH varies the permeability of the distal nephron to water and urea
- Explain what is meant by countercurrent multiplier
- Explain how these transport characteristics produce an osmotic gradient from low in the cortex to high in the inner medulla
- Draw on a graph the relative contributions of NaCl and urea to the osmotic gradient in cortex and medulla
- Explain the function of the vasa recta as countercurrent exchangers
- Predict the concentration and urine flow in low and high ADH states
- Explain the origin of osmotic diuresis in diabetes mellitus, for example

LIFE ON DRY LAND STRUGGLES AGAINST DESICCATION

The end product of protein metabolism is urea. The end product of purine metabolism is uric acid. These and other materials must be excreted every day. The total obligatory excretion depends on the dietary intake of protein and electrolytes, but typically the body must excrete about 600 mOsmol of solutes every day through urine. If we can excrete urine that is only isosmotic with plasma, about 300 mOsM, the obligatory solute excretion of 600 mOsmol would require about 2 L of water. In fact, the kidney can excrete urine that is about 4 times as concentrated as plasma or 1200 mOsM. The obligatory solute load could then be excreted in 0.5 L of water, saving us the trouble of having to find and drink 1.5 L of water every day. This may not seem like a big deal to people who obtain their water from a tap, but it is a big deal to primitive people who drank from streams or ponds and had no other source of water and no way to carry it. Our kidneys evolved to handle the natural environment, not the modern, artificial one. The natural environment on land is generally an arid one in which the kidneys must conserve water and excrete excess water when necessary. Water is conserved by using as little as possible to excrete the obligatory solute load in a small volume of concentrated urine. Excess water is eliminated by excreting a large volume of dilute urine. The subject of this chapter is how the kidneys achieve this feat.

CONTROL OF URINE CONCENTRATION USES AN OSMOTIC GRADIENT AND REGULATED WATER PERMEABILITY

Here, we consider the overall plan of controlling urine concentration. We consider two extreme cases: (1) the kidney maximally concentrates the urine and (2) the kidney maximally dilutes the urine. The ability of the kidney to concentrate the urine is controlled by a hormone, antidiuretic hormone (ADH) also called arginine vasopressin (AVP). This hormone has this name because it decreases the volume of urine. Thus it has an antidiuretic effect. This hormone also causes vasoconstriction; hence its other name, vasopressin. The overall mechanism for concentrating or diluting the urine is shown diagrammatically in Figure 7.5.1.

In the first case, where the kidneys maximally concentrate urine, the aggregate activity of the nephrons with their associated vasculature establishes an osmotic gradient running from about 300 mOsM in the cortex to about 1200 mOsM in the inner medulla. It takes energy to establish this osmotic gradient, and the energy is derived from kidney metabolism. The gradient is established by pumping NaCl out of the tubule into the interstitial fluid and by the countercurrent arrangement of the loop of Henle. How this happens is described in detail later. Because the ascending limb of the loop of Henle pumps out NaCl, the fluid presented to the distal tubule is hypoosmotic. In the presence of ADH, the late distal tubule is permeable to water. When the tubule fluid enters the collecting duct it has equilibrated with the osmotic pressure of the cortex, about 300 mOsM. ADH increases the water permeability of the outer and inner medullary collecting ducts, so that when the fluid travels along the collecting duct from cortex to outer medulla to inner medulla, through areas of increasing osmotic pressure, water moves from the tubule into the interstitium. Thus water is removed from the tubular fluid and the tubular fluid becomes increasingly concentrated. In this case, the kidneys excrete a small volume of concentrated urine.

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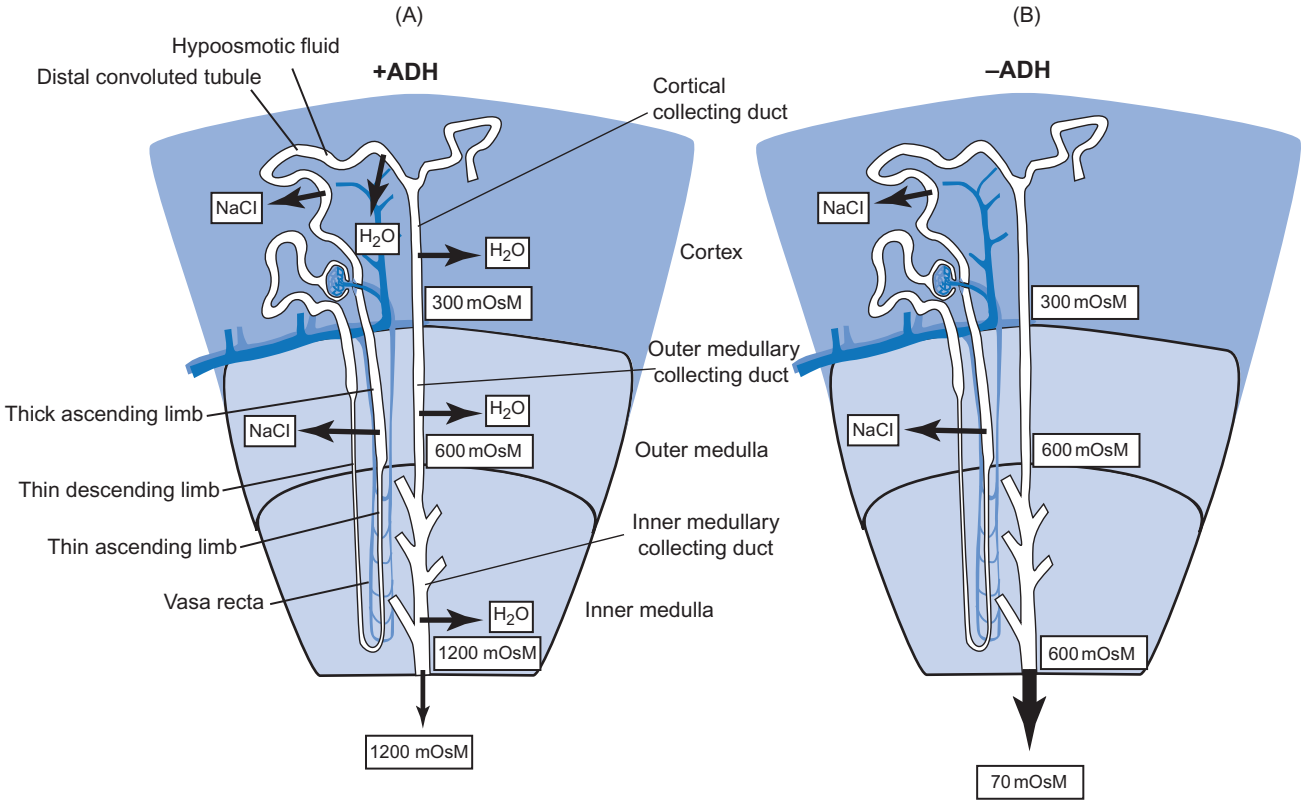

FIGURE 7.5.1 Overview of concentration and dilution of urine. In the presence of ADH (also known as AVP), the distal nephron (late distal tubule and collecting duct) is permeable to water (A). Therefore, the osmotic pressure of the tubule fluid equilibrates with the osmotic pressure within the kidney interstitium. This runs from 300 mOsM in the cortex to about 1200 mOsM in the inner medulla. Water moves from the hypoosmotic tubule contents to the hyperosmotic interstitium. As a result, water is reabsorbed and tubular fluid becomes concentrated. In the absence of ADH (B), the distal nephron remains impermeable to water. The tubular fluid flowing from cortex to inner medulla cannot equilibrate its osmotic pressure with the hyperosmolar interstitium. As a result, the kidneys excrete a large volume of dilute urine.

In the second case, the kidneys maximally dilute the urine. As before, the fluid presented to the distal tubule is hypoosmotic to plasma because the thick ascending limb of the loop of Henle pumps out NaCl but it is impermeable to water. Now, however, the distal tubule and collecting ducts remain impermeable to water because ADH secretion is low. The consequence is that the tubular fluid cannot equilibrate its osmotic pressure with the surrounding interstitium because water movement is slow. The result is that water is not reabsorbed in the collecting duct and the final urine has a large volume and a low osmolarity. The low ADH levels also alter the osmotic gradient in the interstitium. The increased osmolarity seen in the inner medulla disappears in the absence of ADH.

The above description provides an overview of how the kidney produces concentrated or dilute urine. How does the kidney establish the osmotic gradient in the first place?

TUBULAR TRANSPORT MECHANISMS DIFFER ALONG THE LENGTH OF THE NEPHRON

THE PROXIMAL TUBULE REABSORBS AN ISOSMOTIC SOLUTION

The reabsorption of nutrients, water, and salt from the proximal tubule was described in Chapter 7.4 and is summarized again in Figure 7.5.2. The Na^+, K^+-ATPase provides the motive force for all of the cotransport processes by establishing a favorable electrochemical gradient for Na^+ entry into the cell at the apical membrane. This favorable gradient powers the movement of a large number of solutes including glucose, amino acids, phosphate, lactate, sulfate, and indirectly through Na^+–H^+ exchange, HCO_3^-. Water and urea reabsorption passively follow the movement of osmotically active solutes so that the fluid that remains at the end of the proximal tubule is isosmotic with plasma. At this point, all of the nutrients are reabsorbed but the concentration of some secreted materials is higher. This fluid is presented to the loop of Henle.

THE DESCENDING LIMB OF THE LOOP OF HENLE IS PERMEABLE TO WATER AND UREA

The descending limb of the loop of Henle is permeable to both water and urea. This is due to the presence of **aquaporin** channels (**AQP1**) and **urea transporters** (**UT-A2**). As we shall see later, the effect of these is to allow osmotic equilibration between the tubular fluid and the kidney interstitium (see Figure 7.5.3).

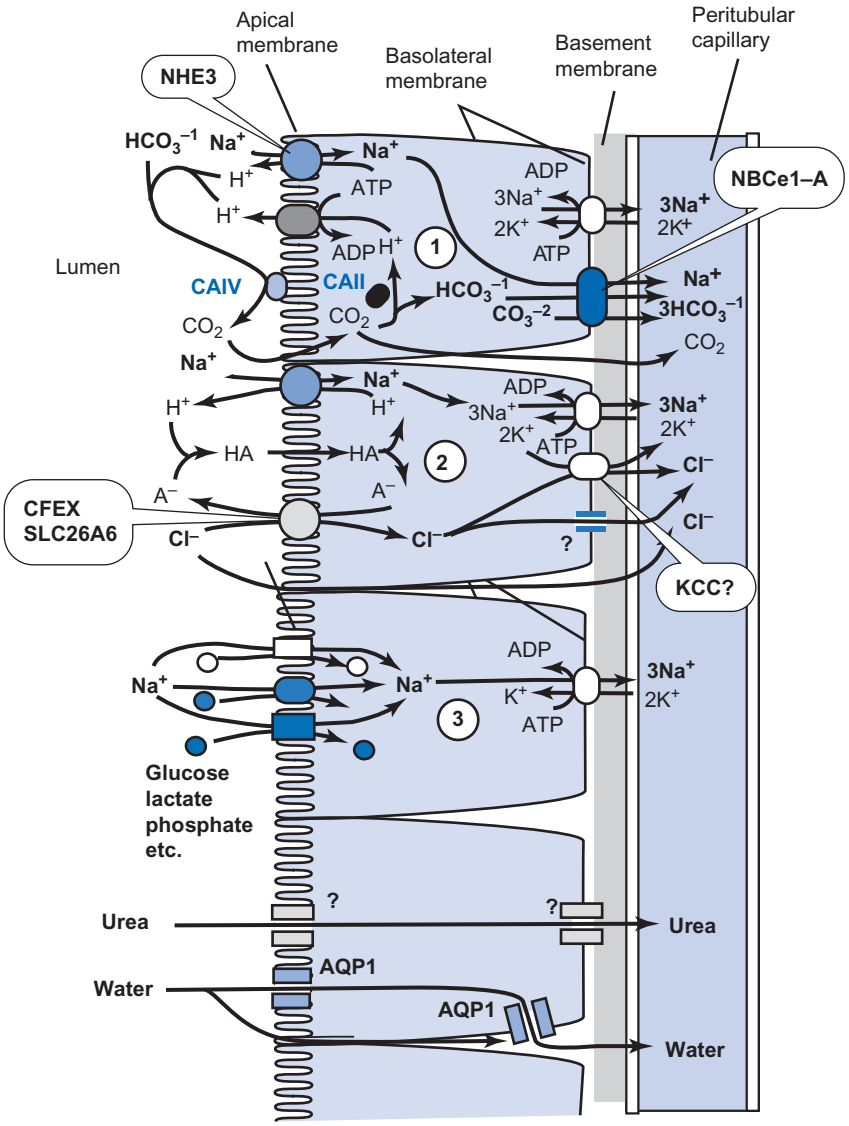

FIGURE 7.5.2 Synopsis of the mechanism of water, urea, Na, Cl, K, and HCO_3^- reabsorption in the proximal convoluted tubule. Na^+ reabsorption occurs in three ways: (1) by entry into the cell by the Na–H exchanger (NHE3) that is coupled to the reabsorption of HCO_3^- on the basolateral membrane by the Na–bicarbonate exchanger, electrogenic (NBCe1-A); (2) by entry into the cell by the NHE3 again that is pumped out of the cell by the Na,K-ATPase on the basolateral membrane, accompanied by Cl^- that is mostly reabsorbed passively and paracellularly, but also enters the cell over the chloride-organic exchanger (CFEX) and exits the cell by the K-Chloride channel (KCC1, KCC3 and KCC4 are expressed in the kidney) or possibly by a chloride channel; (3) Na^+ entry into the cell by secondary active transport mechanisms that couple Na^+ entry to entry of other substrates such as glucose, amino acids or anionic acids such as phosphate, citrate or lactate, followed by pumping out across the basolateral membrane. The anions carried by the CFEX can be HCO_3^-, formic acid, or oxalic acid, with oxalic acid being most important. Water and urea are passively reabsorbed through aquaporins and unidentified pathways for urea.

THE THIN ASCENDING LIMB OF THE LOOP OF HENLE IS PERMEABLE TO NaCl BUT NOT WATER

The thin ascending limb of the loop of Henle brings tubular fluid around from the descending limb to the thick ascending limb. It is impermeable to water and urea but may be permeable to Cl. The basolateral membrane of the thin ascending limb cells has a chloride channel, **ClC-Ka**, that functions only when associated with an accessory protein called **barttin**. Deletion of ClC-Ka homologue in rats causes diabetes insipidus—an inability to concentrate the urine, and in humans defects in **ClC-Kb** are linked to **Bartter syndrome**, characterized by impaired ability to concentrate the urine. ClC-Kb is found in the thick ascending limb of the Loop of Henle (see Figures 7.5.4 and 7.5.5).

THE THICK ASCENDING LIMB PUMPS OUT SALT BUT IS IMPERMEABLE TO WATER

The mechanism of NaCl transport in the cells of the thick ascending limb of the loop of Henle is shown schematically in Figure 7.5.5. These cells possess very active basolateral Na^+,K^+-ATPase activity that powers the overall transport. Transported ions enter the apical membrane by a **Na:K:2Cl cotransporter (NKCC2 = SLC12A2)**. This carrier is inhibited by the "loop diuretics," **furosemide** and **bumetanide**. The apical membrane contains a K^+ channel (renal outer medullary K = ROMK1) that recycles K^+ across the apical membrane. Cells of the thick ascending limb also have chloride channels (ClC-Kb) and a K-Cl electroneutral cotransporter (KCC4) on the basolateral membrane.

THE DISTAL TUBULE CAN PUMP OUT SALT

The distal tubule consists of two functionally distinct regions. The early distal tubule is impermeable to water and urea and its permeability is not regulated by ADH. The late distal tubule has water channels and its permeability is regulated by ADH. The late distal tubule is also called the **connecting duct** because it connects the rest of the nephron to the collecting duct. As in most parts of the nephron, the Na^+,K^+-ATPase powers Na^+ reabsorption in the early distal tubule. Na^+ enters the cell

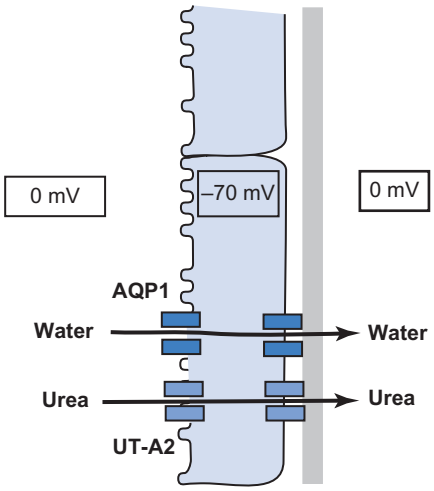

FIGURE 7.5.3 Transport mechanisms in cells of the thin descending limb of Henle in long loops of Henle. Short loops of Henle, originating from the cortical nephrons, have no AQP1.

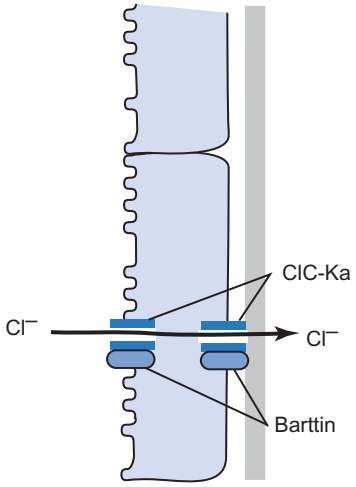

FIGURE 7.5.4 Transport mechanisms in cells of the thin ascending limb of the loop of Henle. Chloride channels on the basolateral membrane here and in the thick ascending limb of the loop of Henle are necessary for the ability to concentrate the urine. The ClC-Ka and ClC-Kb channels both require an accessory protein, barttin

by a Na^+-Cl^- cotransporter on the apical membrane, and the cotransported Cl^- leaves the cell passively through a chloride channel on the basolateral membrane. The apical Na^+-Cl^- cotransporter is inhibited by a class of diuretics called **thiazides**. Thus the early distal tubule can reabsorb NaCl, whereas water and urea are not reabsorbed. The transport processes in the early distal tubule are shown diagrammatically in Figure 7.5.6.

ADH REGULATES THE WATER PERMEABILITY OF THE LATE DISTAL TUBULE AND COLLECTING DUCT

The late distal tubule and collecting duct are heterogeneous, containing several cell types. The main types are the **principal cells** and the **intercalated cells**. The principal cells are responsible for regulating ion and water transport, whereas the intercalated cells are involved in excretion of acid; they are discussed in Chapter 7.7. The principal cells contain aquaporins on both the apical and the basolateral membranes. AQP2 is located on the apical membrane, whereas AQP3 and AQP4 are on the basolateral membrane. The number of AQP2 molecules on the apical membrane is influenced by ADH. Thus the permeability of the entire distal nephron is controlled by ADH (see Chapter 7.6). These cells also can reabsorb NaCl. Here, Na^+ enters the cell through **EnaC**, the epithelial Na channel. This channel is blocked by **amiloride**. Once again, the Na^+,K^+-ATPase provides the gradient for passive Na^+ entry at the apical membrane. The principal cells also play an important role in the regulation of K^+ excretion, as will be discussed in Chapter 7.6. The transport mechanisms of the principal cells of the late distal tubule (also known as the connecting tubule) and collecting duct are shown in Figure 7.5.7.

ADH REGULATES UREA TRANSPORT IN THE INNER MEDULLARY COLLECTING DUCT

The inner medullary collecting duct differs from the outer medullary and cortical collecting ducts in that it is permeable to urea when stimulated by ADH. The UT-A1 type of urea transporter is on the apical membrane of the principal cells of the inner medullary collecting duct and the UT-A3 is on the basolateral membrane (see Figure 7.5.8).

THE NEPHRON PRODUCES AN OSMOTIC GRADIENT WITHIN THE KIDNEY INTERSTITIUM

Experimental results for the concentrations of urea and NaCl in slices of kidneys from water-deprived dogs are shown in Figure 7.5.9. These results show that the osmotic gradient in the outer medulla is produced by NaCl, and then the NaCl gradient levels off. In the inner medulla, the osmotic gradient rises because the urea concentration rises. The explanation for these contributions rests with the countercurrent arrangement of the loop of Henle and in the transport mechanisms present in the different segments of the nephron. First, we will consider the contribution of NaCl.

The characteristics of the loop of Henle dealing with NaCl and water transport are as follows:

- The thin descending limb of the loop of Henle is permeable to water but not NaCl.
- The thin ascending limb is impermeable to water but is permeable to NaCl.
- The thick ascending limb actively pumps out NaCl but is impermeable to water (see Figure 7.5.3).
- The descending limb and ascending limb are arranged with countercurrent flow.

These characteristics allow the formation of an osmotic gradient. The descending limb and ascending limb are closely apposed, with a small intervening interstitial volume, so that flow down into the medulla within the descending limb is opposite to the flow up and out

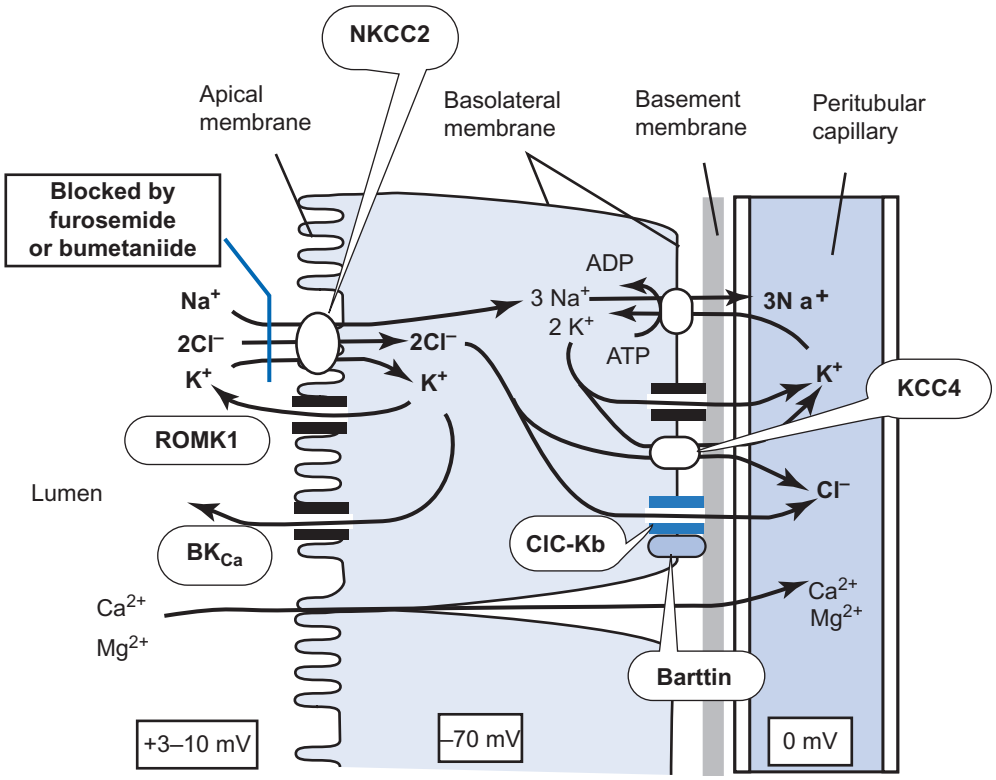

FIGURE 7.5.5 Mechanism of transport in cells of the thick ascending limb of the loop of Henle. Na^+, K^+, and Cl^- all enter the cell at the apical membrane through the operation of a Na:K:2Cl cotransporter. The protein is referred to as NKCC2 and its gene is referred to as SLC12A2. The K^+ that enters is recycled through an apical K^+ channel, ROMK1. Na^+ and Cl^- that enter are removed from the cell by the operation of the Na^+,K^+-ATPase and by two efflux routes for Cl^-: a K:Cl symport (or cotransporter, KCC4) and by a chloride channel (ClC-Kb). K^+ that exits the cell through the K:Cl symport and through a basolateral K^+ channel is recycled back into the cell through the Na^+,K^+-ATPase. Na^+ can also be absorbed through the paracellular route in these cells.

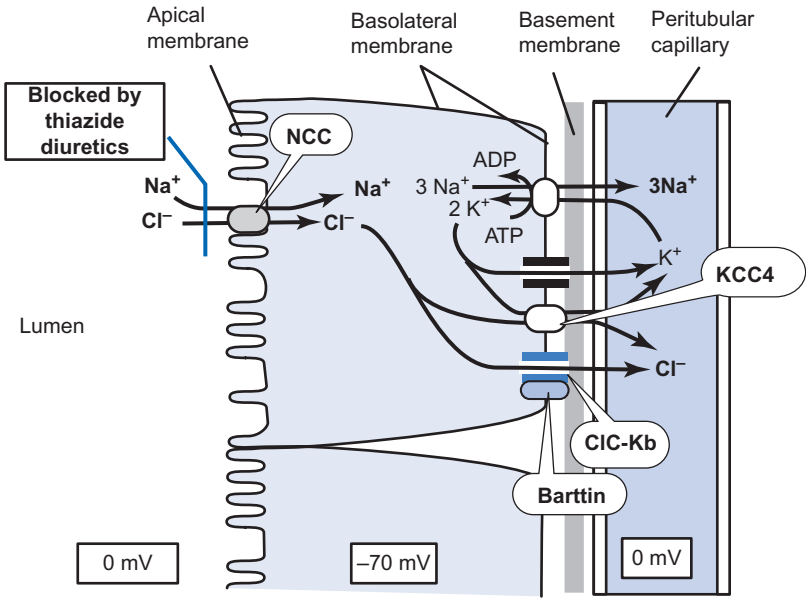

FIGURE 7.5.6 Mechanisms of transport in the early distal tubule. The early distal tubule is impermeable to both water and urea but it can pump modest amounts of NaCl. It does this by electroneutral uptake of Na^+ and Cl^- on the apical membrane through the Na−Chloride cotransporter (NCC). The Na,K-ATPase pumps the Na^+ out of the cell on the basolateral membrane whereas Cl^- exits the cell over the K-Cl channel (KCC4) and a chloride channel (ClC-Kb). K^+ that exits the cell over KCC4 is recycled into the cell by the Na,K-ATPase. The distal nephron epithelium is "tight," whereas the proximal tubule epithelium is "leaky." Thus the distal nephron can support large differences in concentrations of ions between tubular fluid and interstitium, whereas the proximal tubule cannot.

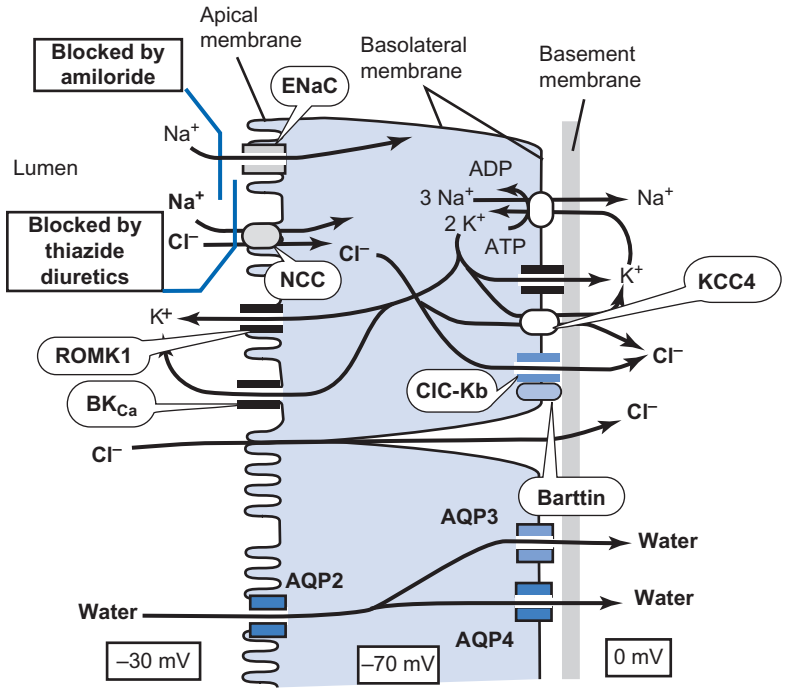

FIGURE 7.5.7 Transport mechanisms in the principal cells of the cortical and outer medullary collecting ducts. These cells alone among the kidney tubule possess an amiloride-sensitive Na^+ entry mechanism, mediated by **ENaC**, the epithelial Na^+ channel, which is inhibited by amiloride. These cells can reabsorb NaCl. These cells are also important in K^+ secretion. They have water channels whose insertion into the apical membrane is controlled by circulating levels of ADH, also known as AVP.

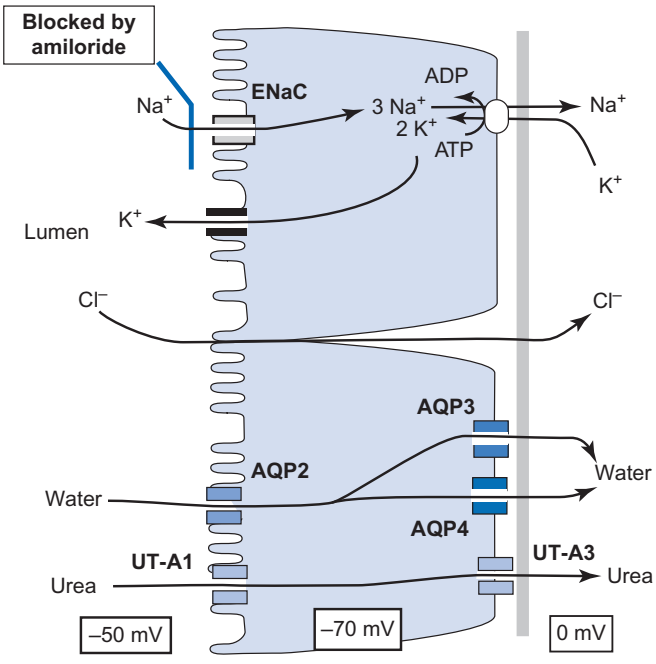

FIGURE 7.5.8 Major transport pathways in inner medullary collecting duct principal cells. The apical membrane has urea transporter UT-A1 and aquaporin 2 (AQP2); the basolateral membrane has UT-A3 and AQP3 and AQP4. These cells remain capable of absorbing NaCl mediated by ENaC on the apical membrane and the Na,K-ATPase on the basolateral membrane.

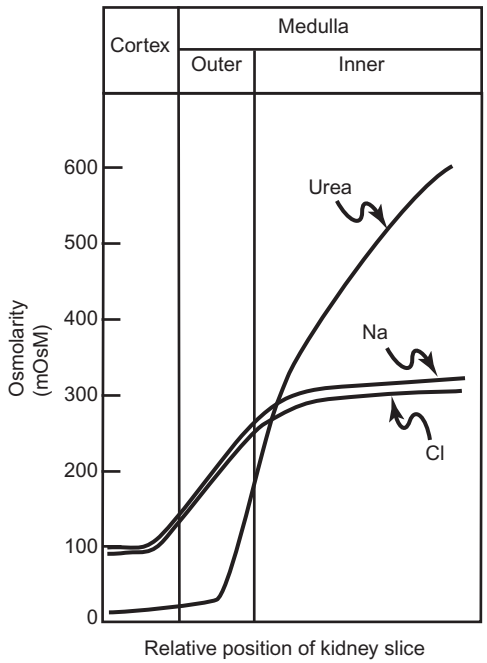

FIGURE 7.5.9 Contributions of Na, Cl, and urea to the interstitial osmotic gradient that runs from the kidney cortex to the inner medulla. In the cortex, the osmotic pressure is about 300 mOsM with about half contributed by Na and half contributed by Cl, with little contribution by urea. In the outer medulla, the interstitial osmolarity climbs to about 700 mOsM at the border of the inner and outer medulla, with about 100 mOsM contributed by urea and 600 mOsM by NaCl. In the inner medulla, the osmotic pressure gradually increases with distance to reach a maximum of about 1200 mOsM, with about 600 mOsM due to NaCl and another 600 mOsM due to urea. These contributions are due to the spatial separation of transporters within the nephron and its countercurrent flow.

of the medulla within the ascending limb. Suppose that the thick ascending limb is capable of creating a transepithelial concentration gradient of NaCl, called the **single effect**, which corresponds to the difference between the osmolarity of the interstitial fluid and the tubular fluid in the thick ascending limb. Since the thick ascending limb pumps out NaCl but is impermeable to water, the interstitial fluid becomes hyperosmotic. Because the thin descending limb is permeable to water, water leaves the descending limb and equilibrates with the interstitial fluid. Thus the fluid in the descending limb is also concentrated because water leaves the tubule without accompanying NaCl. This more highly concentrated fluid then flows around the bend in the loop of Henle and presents itself to the thick ascending limb. So now the thick ascending limb has a higher starting concentration of NaCl. When it produces its single effect, it does so from a higher starting concentration. Repetition of the concentration, equilibration, and countercurrent flow produces a standing gradient running from 300 mOsM at the juncture of cortex and medulla to 600 mOsM at the juncture of the inner and outer medulla. The loop of Henle is described as a **countercurrent multiplier** because its single effect is **multiplied by the countercurrent flow**.

THE VASA RECTA *ARE* COUNTERCURRENT EXCHANGERS

The experimental observation is that the fluid presented to the distal tubule is hypoosmotic to plasma. The active pumping of NaCl out of the thick ascending limb, and the inability of water to follow the NaCl, partially explains this observation. However, the **vasa recta** are necessary to carry off the water reabsorbed from the descending limb and to carry off the extra NaCl reabsorbed from the thick ascending limb.

Unlike the thick ascending limb, the vasa recta passively exchange salts and water along their course from the cortex down into the medulla and back again to the cortex. Equilibration of osmotic pressure, however, lags behind the osmotic gradient because the vasa recta blood is flowing. The consequence is that residual salt and water remain in the vasa recta from its course through the medulla, so that vasa recta blood returns from the medulla with more salt than water, and hence it is hypertonic. Without this return flow, the thick ascending limb could not dilute its tubular contents.

UREA CONTRIBUTES TO THE OSMOTIC GRADIENT IN THE INNER MEDULLA

Figure 7.5.9 shows that urea makes the major contribution to the osmotic gradient in the inner medulla. This is also a consequence of the spatial separation of transport characteristics of the loop of Henle and the collecting duct. Urea transporters are located in the descending limb of the loop of Henle (UT-A2), in the inner medullary collecting duct (UT-A1 and UT-A3) and in the descending vasa recta (UT-B1). We consider the case where ADH secretion is high so that the water permeability of the distal nephron is high. The tubular fluid entering the late distal tubule has some urea, and it is hypoosmotic due to active pumping out of NaCl in the thick ascending limb of the loop of Henle. Water is reabsorbed in the late distal tubule so when the fluid reaches the collecting duct it is isosmotic once again. This water reabsorption occurs without urea reabsorption, so urea becomes slightly concentrated in the late distal tubule. As the fluid moves down the cortical and outer medullary collecting ducts, water continues to be reabsorbed but the nephron remains impermeable to urea. Thus the urea becomes progressively more concentrated. When the fluid enters the inner medulla, urea permeability is high so that urea passively leaves the collecting duct and equilibrates with the inner medullary interstitial fluid. The descending limb of the loop of Henle possesses UT-A2 urea transporters, so that the fluid in the inner medullary loop of Henle also equilibrates with this high urea concentration. This tubular fluid moves up to the thick ascending limb, now carrying more urea. But here the urea permeability is low: all of this urea survives to the distal tubule, where once again it is concentrated by removal of water. In this way, urea produces a cycle that establishes its contribution to the inner medullary osmotic gradient. Urea concentration in the urine is set by its highest concentration in the kidney interstitium.

Figure 7.5.10 illustrates the role of NaCl, urea, and various nephron segments in the establishment of the osmotic gradient within the kidney interstitium.

TRANSPORT BY THE VASA RECTA IS ESSENTIAL TO THE OPERATION OF THE LOOP OF HENLE

In the absence of the vasa recta, all of the NaCl pumped into the interstitial fluid by the thick ascending limb would eventually have to return to the cortex through the kidney tubule. Likewise, in the absence of the vasa recta, all of the water reabsorbed into the kidney interstitial fluid would also have to return to the cortex through the kidney tubule. Thus the loop of Henle could produce a concentration gradient, but the fluid leaving the tubule at the top of the thick ascending limb would have the same constituents at steady state as what entered the tubule at the end of the proximal tubule. In short, nothing could be accomplished by the loop of Henle in the absence of the vasa recta. The vasa recta carries away all of the water and salt reabsorbed by the loop. It does this by passive exchange, but the magnitude of the flow with respect to the vasa recta's permeability is crucial: the vasa recta blood does not completely equilibrate with the interstitial fluid because its flow is too fast relative to its permeability. The result is that the vasa recta blood contains more reabsorbed salt than reabsorbed water, and it is hypertonic. The numbers in boxes in Figure 7.5.10 indicate the approximate flows and osmolarities of either vasa recta blood or tubular fluid at various points along the nephron.

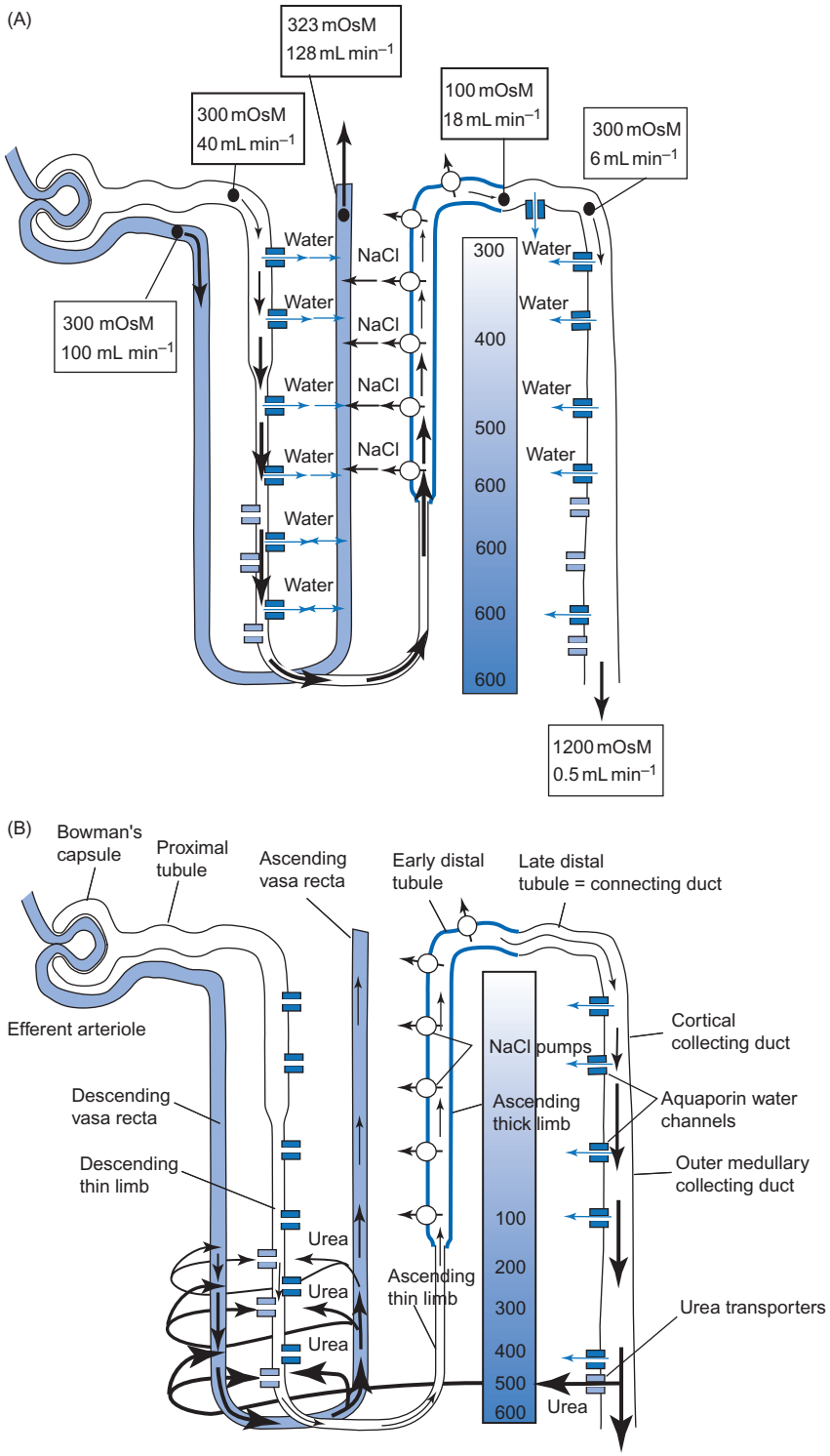

FIGURE 7.5.10 Contribution of NaCl (A) and urea (B) to the osmotic gradient in the kidney interstitium. The thick ascending limb can actively transport NaCl out of the tubule and into the interstitial fluid, but it is impermeable to water. Therefore, the thick ascending limb concentrates the interstitial fluid and dilutes the tubular fluid. The increased osmotic pressure draws water out of the descending thin limb, which is permeable to water but not NaCl. The result is that the fluid in the descending limb becomes as concentrated as the interstitial fluid. This fluid then flows around the bend in the loop of Henle, providing yet more salt for the thick ascending limb. As a result, NaCl builds up in the interstitial fluid and a gradient of osmotic pressure is set up in the outer medulla. The increase in osmolarity of the inner medulla is caused by urea recycling, as shown in (B). The thin ascending limb, thick ascending limb, and distal nephron up to the inner medulla collecting duct are impermeable to urea. The inner medulla, however, has urea transporters. The urea in the collecting duct is progressively concentrated when water leaves the duct in response to the progressively higher interstitial osmotic pressure. In the inner medulla, the high urea concentration favors massive urea movement into the interstitial fluid, which then enters both the descending thin limb and the descending vasa recta. This urea is then recycled in two ways: in the vasa recta and in the tubule. The descending vasa recta turns and becomes the ascending vasa recta. Although the ascending vasa recta has no urea transporters, it is highly fenestrated and urea probably leaves the ascending vasa recta as it flows up toward the cortex. This produces a gradient in urea concentration, high nearest the innermost medulla and progressively dilute going from the inner to outer medulla. Urea that enters the descending limb of the loop of Henle cannot escape anywhere along the ascending thin or thick limb, distal nephron, or cortical and outer medullary collecting duct. All of the urea present in the tubular fluid at the tip of the loop of Henle will come around again to be concentrated by water removal and then recycled again. In this way, the urea concentration builds up in the interstitial fluid. About one-half of the 1200 mOsM osmolarity at the tip of the renal pyramid is due to urea (see Figure 7.5.9).

At steady state, there must be material balance for the entire medulla. The mass balance equation is given as

$$\text{Input} = \text{output}$$
$$Q_{\text{vr in}} + Q_{\text{pct out}} + Q_{\text{dt out}} = Q_{\text{vr out}} + Q_{\text{tal out}} + Q_{\text{urine out}}$$
$$M_{\text{vr in}} + M_{\text{pct out}} + M_{\text{dt out}} = M_{\text{vr out}} + M_{\text{tal out}} + M_{\text{urine out}}$$

[7.5.1]

where Q is the flow, in mL min^{-1}, and M is the moles of osmotically active solutes, in OsMoles. The subscript "vr" means "vasa recta," "pct" means "proximal convoluted tubule," "dt" means "distal tubule," "tal" means "thick ascending limb," and "urine" refers to the final fluid that exits the collecting duct. The vasa recta input of fluid and osmoles respectively in Figure 7.5.10 is 100 mL min^{-1} and 100 mL $min^{-1} \times 300$ mOsM = 30.0 mOsmol min^{-1}. Similarly, the output of the proximal tubule (input to the medulla) is 40 mL min^{-1} and 12.0 mOsmol min^{-1}. The flow of fluid and osmoles at the end of the distal tubule is 6 mL min^{-1} and 1.8 mOsmol min^{-1}, respectively. Thus the sum of the fluids inputs is $100 + 40 + 6 = 146$ mL min^{-1} and osmole inputs sum as $30.0 + 12.0 + 1.8 = 43.8$ mOsmol min^{-1}. On the output side, the vasa recta output is 128 mL min^{-1} and 128 mL $min^{-1} \times 323 = 41.3$ mOsmol min^{-1}. The output of the thick ascending limb is 18 mL min^{-1} and 1.8 mOsmol min^{-1}, and urinary output is 0.5 mL min^{-1} and 0.6 mOsmol min^{-1}. The sums of the outputs are $128 + 18 + 0.5 = 146$ mL min^{-1}, and $41.3 + 1.8 + 0.6 = 43.7$ mOsmol min^{-1}, which match the inputs for fluid and for total osmoles. This exercise should make it clear that, without the vasa recta removing reabsorbed water and salt, the composition of the fluid leaving the thick ascending limb would of necessity be the same as the fluid leaving the proximal tubule. Although the thick ascending limb does all the work of reabsorption, all parts of the loop of Henle are involved, including the vasa recta.

INCREASED SOLUTE LOADS IN THE DISTAL NEPHRON PRODUCE AN OSMOTIC DIURESIS

The proximal convoluted tubule avidly reabsorbs filtered glucose into the peritubular capillaries so that it is all reabsorbed by the end of the proximal tubule. The mechanism for glucose reabsorption was described in Chapter 7.4. The proximal tubule is the only site for glucose reabsorption. If the filtered load of glucose overwhelms the proximal tubule transport mechanisms, glucose escapes to the loop of Henle. There is no reabsorption of glucose beyond the proximal tubule, and the glucose becomes progressively more concentrated as the nephron reabsorbs water and salt. The glucose exerts an osmotic pressure and produces an **osmotic diuresis**, the severity being directly proportional to the amount of excreted glucose. This is the origin of the **polyuria** of persons with uncontrolled diabetes mellitus in which the plasma concentration of glucose exceeds its renal threshold. Any osmotically active material in the distal nephron will have this effect. Mannitol is freely filtered by the kidney but neither secreted nor reabsorbed. Injection of mannitol will produce an osmotic diuresis that is directly proportional to the amount of mannitol injected.

ADH CONTROLS DISTAL NEPHRON PERMEABILITY

ADH increases the water permeability of the late distal tubule (or connecting duct) and all parts of the collecting duct. It also increases the urea permeability of the inner medullary collecting duct. When the distal nephron permeability to water and urea is high, all of the mechanisms for concentrating the urine operate, and the kidneys excrete a small volume of highly concentrated urine. In the absence of ADH, the distal nephron is not permeable to either water or urea. Fluid that enters the distal tubule is hypoosmotic, about 100 mOsM. Low water permeability prevents water from leaving the hypoosmotic fluid to equilibrate with the interstitial fluid. Thus the tubular fluid stays hypoosmotic all the way through the collecting duct. Because the late distal tubule and collecting duct can pump out some Na^+, the final concentration of the urine is actually lower than 100 mOsM. The kidneys can maximally dilute urine to about 70 mOsM. The low urea permeability in the absence of ADH shuts off the urea recycling, so that the concentration profile in the kidney interstitium is changed. Figure 7.5.11 shows approximate values for tubular fluid concentration along the nephron in the presence and absence of ADH.

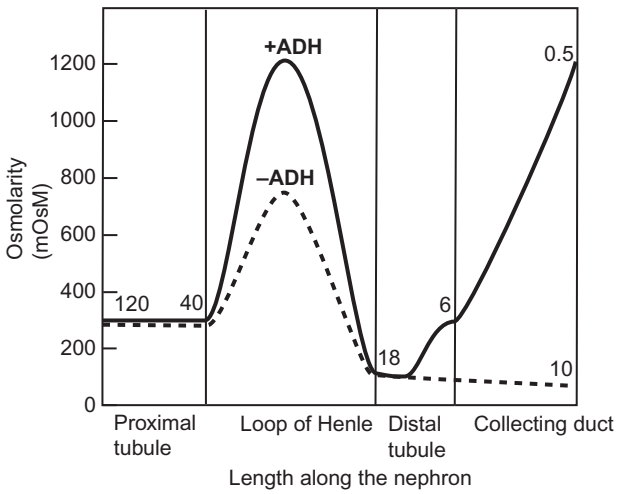

FIGURE 7.5.11 Concentration profile of the tubular fluid along the nephron ± ADH. In either the presence or absence of ADH, the glomerulus filters an isosmotic solution that is reabsorbed in the proximal tubule as an isosmotic solution. Fluid traveling down into the medulla is progressively concentrated as water leaves the fluid through aquaporin channels to equilibrate with the hyperosmolar interstitial fluid. This occurs in either the presence or the absence of ADH, but the interstitial osmotic pressure gradient is maximal when the kidney is stimulated by ADH, and minimal when ADH is absent. This is due to the removal of the component of osmolarity contributed by urea when ADH is absent, because urea recycling is broken. In the absence of ADH, the urine reaches its minimum concentration due to continued ion pumping in the distal nephron and low water and urea permeability in the distal nephron.

Clinical Applications: Diabetes Insipidus and SIADH

"Diabetes insipidus" derives its name from "diabetes," meaning "to siphon off" and "insipidus," meaning "tasteless." This describes the urinary output from persons afflicted with the condition: they excrete a large volume of highly dilute, and hence tasteless, urine. The urine production can be enormous. This symptom can be caused by any of four separate defects:

1. Hypothalamic diabetes insipidus—inability to synthesize or secrete ADH.
2. Nephrogenic diabetes insipidus—inability of the kidney to respond to normal ADH.
3. Transient diabetes insipidus of pregnancy—accelerated metabolism of ADH.
4. Primary polydipsia—excess ingestion of fluids rather than decreased ADH.

Hypothalamic diabetes insipidus can be caused by:

- hereditary defects,
- tumors,
- head trauma or surgery.

People with hereditary defects in ADH often do not present with symptoms at birth, but develop them in childhood. This contrasts with babies with congenital nephrogenic diabetes insipidus, who have the disease during the first weeks of life. Most hereditary diabetes insipidus involves defects in neurophysin. A working hypothesis is that the neurophysin somehow folds badly and progressively gums up ADH synthesis or secretion.

Hereditary nephrogenic diabetes insipidus involves genetic defects either in the V2 receptor or in its target, AQP2. More than 90% of persons afflicted with nephrogenic diabetes insipidus are males whose X chromosome has one of over 100 different types of defective V2 receptors. A female with nephrogenic diabetes insipidus most likely has a defect in AQP2. Acquired nephrogenic diabetes insipidus can be caused by chronic kidney disease.

In pregnant women, the placenta produces an enzyme called **cysteine aminopeptidase** that is released into the plasma and degrades both oxytocin and ADH. This accelerates degradation of ADH, decreases concentrations of circulating ADH, and temporarily produces large volumes of dilute urine.

The syndrome of **inappropriate antidiuretic hormone secretion**, or **SIADH**, occurs when plasma ADH levels are high when ordinarily they would be low. The inappropriate ADH secretion retains water even when plasma osmolarity is low. Thus the hallmark of SIADH is plasma hypoosmolarity. Because Na^+ is the major extracellular cation, plasma hypoosmolarity almost always means hyponatremia, low blood [Na^+]. Although SIADH has a number of causes, its most common is an ADH-secreting tumor.

SUMMARY

One of the chief jobs of the renal system is excreting an obligatory solute load while simultaneously either retaining water or getting rid of excess water. Thus it is designed to excrete a concentrated urine under conditions of water deprivation or a dilute urine under conditions of water excess. This is regulated through ADH.

The transport characteristics of the loop of Henle and vasa recta, together with their spatial arrangement as parallel hair-pin loops, allow the loop of Henle to establish an osmotic gradient within the kidney interstitium, running from low osmolarity in the cortex to high osmolarity within the inner medulla. Once this gradient is established, production of a concentrated urine consists of allowing the incipient urine to equilibrate with this hyperosmotic interstitium. The gradient is most concentrated in the presence of ADH, when the gradient reaches a high of about 1200 mOsM. About half of this is due to NaCl concentrated by the thick ascending limb of the loop of Henle, whereas the remaining half is due to recirculation of urea. In the absence of ADH, the contribution of urea to the osmotic gradient is washed out.

The establishment of the osmotic gradient is a complicated business which has not yet been thoroughly understood. In principle, the loop of Henle functions as a countercurrent multiplier. It produces a single effect, the creation of an osmotic gradient across its epithelium, and this effect is multiplied by the countercurrent arrangement of flow. Both descending and ascending limbs of the loop of Henle, plus the vasa recta, are required components. The fluid presented to the distal tubule is hypoosmotic, and this can be sustained only if the vasa recta contains hyperosmotic fluid. The vasa recta functions as countercurrent exchangers. About half of the final osmotic gradient is produced by urea recycling within the kidney inner medulla. This is produced by the fact that urea is permeable only to the inner medullary collecting duct.

REVIEW QUESTIONS

1. How are filtered fluid and solutes reabsorbed in the proximal tubule? What is the main transport mechanism in the thick ascending limb of Henle? How is fluid and salt absorbed in the early distal tubule? Late distal tubule?
2. How does NaCl contribute to the osmolarity of the medullary interstitium? What transport features of the nephron allow this to happen?
3. How does urea contribute to the osmolarity of the medullary interstitium? What transport features of the nephron allow this to happen?
4. What hormone controls the final dilution and concentration of urine?
5. What is the limit of concentration of human urine? What limits it?
6. What is the limit of dilution of human urine? What limits it?
7. What is the role of the vasa recta in concentration or dilution of urine?