cortical collecting duct contains *high-resistance epithelia* with two cell types. Principal cells are the main water, Na^+-reabsorbing, and K^+-secreting cells, and the site of action of aldosterone, K^+-sparing diuretics, and mineralocorticoid receptor antagonists such as spironolactone. The other cells are type A and B intercalated cells. Type A intercalated cells mediate acid secretion and bicarbonate reabsorption also under the influence of aldosterone. Type B intercalated cells mediate bicarbonate secretion and acid reabsorption.

Virtually all transport is mediated through the cellular pathway for both principal cells and intercalated cells. In principal cells, passive apical Na^+ entry occurs through the amiloride-sensitive, epithelial Na^+ channel (ENaC) with basolateral exit via the Na^+/K^+-ATPase (Fig. 332e-3E). This Na^+ reabsorptive process is tightly regulated by aldosterone and is physiologically activated by a variety of proteolytic enzymes that cleave extracellular domains of ENaC; plasmin in the tubular fluid of nephrotic patients, for example, activates ENaC, leading to sodium retention. Aldosterone enters the cell across the basolateral membrane, binds to a cytoplasmic mineralocorticoid receptor, and then translocates into the nucleus, where it modulates gene transcription, resulting in increased Na^+ reabsorption and K^+ secretion. Activating mutations in ENaC increase Na^+ reclamation and produce hypokalemia, hypertension, and metabolic alkalosis (Liddle's syndrome). The potassium-sparing diuretics amiloride and triamterene block ENaC, causing reduced Na^+ reabsorption.

Principal cells secrete K^+ through an apical membrane potassium channel. Several forces govern the secretion of K^+. Most importantly, the high intracellular K^+ concentration generated by Na^+/K^+-ATPase creates a favorable concentration gradient for K^+ secretion into tubular fluid. With reabsorption of Na^+ without an accompanying anion, the tubular lumen becomes negative relative to the cell interior, creating a favorable electrical gradient for secretion of potassium. When Na^+ reabsorption is blocked, the electrical component of the driving force for K^+ secretion is blunted, and this explains lack of excess urinary K^+ loss during treatment with potassium-sparing diuretics or mineralocorticoid receptor antagonists. K^+ secretion is also promoted by aldosterone actions that increase regional Na^+ transport favoring more electronegativity and by increasing the number and activity of potassium channels. Fast tubular fluid flow rates that occur during volume expansion or diuretics acting "upstream" of the cortical collecting duct also increase K^+ secretion, as does the presence of relatively nonreabsorbable anions (including bicarbonate and semisynthetic penicillins) that contribute to the lumen-negative potential. Off-target effects of certain antibiotics, such as trimethoprim and pentamidine, block ENaCs and predispose to hyperkalemia, especially when renal K^+ handling is impaired for other reasons. Principal cells, as described below, also participate in water reabsorption by increased water permeability in response to vasopressin.

Intercalated cells do not participate in Na^+ reabsorption but, instead, mediate acid-base secretion. These cells perform two types of transport: active H^+ transport mediated by H^+-ATPase (proton pump), and Cl^-/HCO_3^- exchange. Intercalated cells arrange the two transport mechanisms on opposite membranes to enable either acid or base secretion. Type A intercalated cells have an apical proton pump that mediates acid secretion and a basolateral Cl^-/HCO_3^- anion exchanger for bicarbonate reabsorption (Fig. 332e-3*E*); aldosterone increases the number of H^+-ATPase pumps, sometimes contributing to the development of metabolic alkalosis. Secreted H^+ is buffered by NH_3 that has diffused into the collecting duct lumen from the surrounding interstitium. By contrast, type B intercalated cells have the anion exchanger on the apical membrane to mediate bicarbonate secretion while the proton pump resides on the basolateral membrane to enable acid reabsorption. Under conditions of acidemia, the kidney preferentially uses type A intercalated cells to secrete the excess H^+ and generate more HCO_3^-. The opposite is true in states of bicarbonate excess with alkalemia where the type B intercalated cells predominate. An extracellular protein called *hensin* mediates this adaptation.

Inner medullary collecting duct cells share many similarities with principal cells of the cortical collecting duct. They have apical Na^+ and K^+ channels that mediate Na^+ reabsorption and K^+ secretion, respectively (Fig. 332e-3*F*). Inner medullary collecting duct cells also have vasopressin-regulated water channels (aquaporin-2 on the apical membrane, aquaporin-3 and -4 on the basolateral membrane). The antidiuretic hormone vasopressin binds to the V2 receptor on the basolateral membrane and triggers an intracellular signaling cascade through G-protein-mediated activation of adenylyl cyclase, resulting in an increase in the cellular levels of cyclic AMP. This signaling cascade stimulates the insertion of water channels into the apical membrane of the inner medullary collecting duct cells to promote increased water permeability. This increase in permeability enables water reabsorption and production of concentrated urine. In the absence of vasopressin, inner medullary collecting duct cells are water impermeable, and urine remains dilute.

Sodium reabsorption by inner medullary collecting duct cells is also inhibited by the natriuretic peptides called *atrial natriuretic peptide* or *renal natriuretic peptide* (urodilatin); the same gene encodes both peptides but uses different posttranslational processing of a common preprohormone to generate different proteins. Atrial natriuretic peptides are secreted by atrial myocytes in response to volume expansion, whereas urodilatin is secreted by renal tubular epithelia. Natriuretic peptides interact with either apical (urodilatin) or basolateral (atrial natriuretic peptides) receptors on inner medullary collecting duct cells to stimulate guanylyl cyclase and increase levels of cytoplasmic cGMP. This effect in turn reduces the activity of the apical Na^+ channel in these cells and attenuates net Na^+ reabsorption, producing natriuresis.

The inner medullary collecting duct transports urea out of the lumen, returning urea to the interstitium, where it contributes to the hypertonicity of the medullary interstitium. Urea is recycled by diffusing from the interstitium into the descending and ascending limbs of the loop of Henle.

HORMONAL REGULATION OF SODIUM AND WATER BALANCE

The balance of solute and water in the body is determined by the amounts ingested, distributed to various fluid compartments, and excreted by skin, bowel, and kidneys. *Tonicity*, the osmolar state determining the volume behavior of cells in a solution, is regulated by water balance **(Fig. 332e-4*A*)**, and *extracellular blood volume* is regulated by Na^+ balance **(Fig. 332e-4*B*)**. The kidney is a critical modulator of both physiologic processes.

WATER BALANCE

Tonicity depends on the variable concentration of *effective osmoles* inside and outside the cell causing water to move in either direction across its membrane. Classic effective osmoles, like Na^+, K^+, and their anions, are solutes trapped on either side of a cell membrane, where they collectively partition and obligate water to move and find equilibrium in proportion to retained solute; Na^+/K^+-ATPase keeps most K^+ inside cells and most Na^+ outside. Normal tonicity (~280 mosmol/L) is rigorously defended by osmoregulatory mechanisms that control water balance to protect tissues from inadvertent *dehydration* (cell shrinkage) or *water intoxication* (cell swelling), both of which are deleterious to cell function (Fig. 332e-4*A*).

The mechanisms that control osmoregulation are distinct from those governing extracellular volume, although there is some shared physiology in both processes. While cellular concentrations of K^+ have a determinant role in any level of tonicity, the routine surrogate marker for assessing clinical tonicity is the concentration of serum Na^+. Any reduction in total body water, which raises the Na^+ concentration, triggers a brisk sense of thirst and conservation of water by decreasing renal water excretion mediated by release of vasopressin from the posterior pituitary. Conversely, a decrease in plasma Na^+ concentration triggers an increase in renal water excretion by suppressing the secretion of vasopressin. Whereas all cells expressing mechanosensitive TRPV1, 2, or 4 channels, among potentially other sensors, respond to changes in tonicity by altering their volume and Ca^{2+} concentration, only $TRPV^+$ neuronal cells connected to the organum vasculosum of the lamina terminalis are *osmoreceptive*. Only these cells, because of their neural