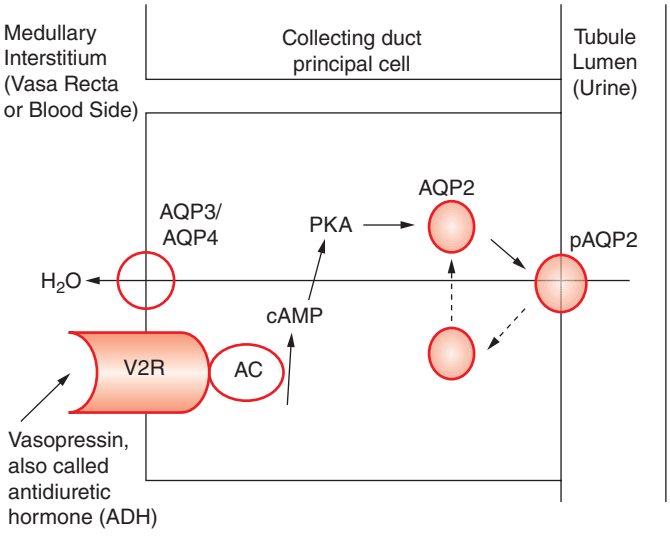

FIGURE 63-3 Vasopressin and the regulation of water permeability in the renal collecting duct. Vasopressin binds to the type 2 vasopressin receptor (V2R) on the basolateral membrane of principal cells, activates adenylyl cyclase (AC), increases intracellular cyclic adenosine monophosphatase (cAMP), and stimulates protein kinase A (PKA) activity. Cytoplasmic vesicles carrying aquaporin-2 (AQP) water channel proteins are inserted into the luminal membrane in response to vasopressin, thereby increasing the water permeability of this membrane. When vasopressin stimulation ends, water channels are retrieved by an endocytic process and water permeability returns to its low basal rate. The AQP3 and AQP4 water channels are expressed on the basolateral membrane and complete the transcellular pathway for water reabsorption. pAQP2, phosphorylated aquaporin-2. *(From JM Sands, DG Bichet: Nephrogenic diabetes insipidus. Ann Intern Med 144:186, 2006, with permission.)*

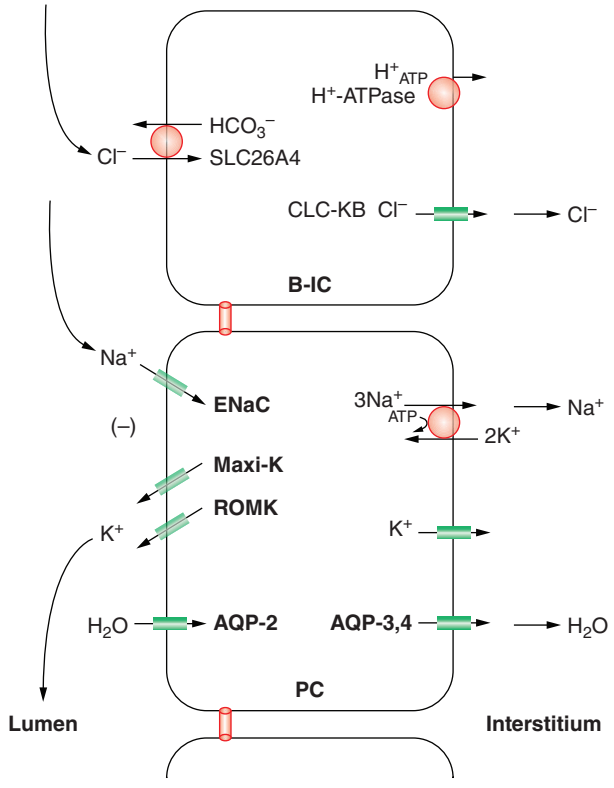

FIGURE 63-4 Sodium, water, and potassium transport in principal cells (PC) and adjacent β-intercalated cells (B-IC). The absorption of Na^+ via the amiloride-sensitive epithelial sodium channel (ENaC) generates a lumen-negative potential difference, which drives K^+ excretion through the apical secretory K^+ channel ROMK (renal outer medullary K^+ channel) and/or the flow-dependent BK channel. Transepithelial Cl^- transport occurs in adjacent β-intercalated cells, via apical Cl^--HCO_3^- and Cl^--OH^- exchange (SLC26A4 anion exchanger, also known as pendrin) basolateral CLC chloride channels. Water is absorbed down the osmotic gradient by principal cells, through the apical aquaporin-2 (AQP-2) and basolateral aquaporin-3 and aquaporin-4 (Fig. 63-3).

renin-angiotensin-aldosterone axis, and increased circulating AVP) that synergistically increases renal Na^+-Cl^- reabsorption, vascular resistance, and renal water reabsorption. This occurs in the context of decreased cardiac output, as occurs in hypovolemic states, low-output cardiac failure, decreased oncotic pressure, and/or increased capillary permeability. Alternatively, excessive arterial vasodilation results in *relative* arterial underfilling, leading to neurohumoral activation in the defense of tissue perfusion. These physiologic responses play important roles in many of the disorders discussed in this chapter. In particular, it is important to appreciate that AVP functions in the defense of circulatory integrity, inducing vasoconstriction, increasing sympathetic nervous system tone, increasing renal retention of both water and Na^+-Cl^-, and modulating the arterial baroreceptor reflex. Most of these responses involve activation of systemic V_{1A} AVP receptors, but concomitant activation of V_2 receptors in the kidney can result in renal water retention and hyponatremia.

HYPOVOLEMIA

Etiology True volume depletion, or hypovolemia, generally refers to a state of combined salt and water loss, leading to contraction of the ECFV. The loss of salt and water may be renal or nonrenal in origin.

RENAL CAUSES Excessive urinary Na^+-Cl^- and water loss is a feature of several conditions. A high filtered load of endogenous solutes, such as glucose and urea, can impair tubular reabsorption of Na^+-Cl^- and water, leading to an osmotic diuresis. Exogenous mannitol, often used to decrease intracerebral pressure, is filtered by glomeruli but not reabsorbed by the proximal tubule, thus causing an osmotic diuresis. Pharmacologic diuretics selectively impair Na^+-Cl^- reabsorption at specific sites along the nephron, leading to increased urinary Na^+-Cl^- excretion. Other drugs can induce natriuresis as a side effect. For example, acetazolamide can inhibit proximal tubular Na^+-Cl^- absorption via its inhibition of carbonic anhydrase; other drugs, such as the antibiotics trimethoprim and pentamidine, inhibit distal tubular Na^+ reabsorption through the amiloride-sensitive ENaC channel, leading to urinary Na^+-Cl^- loss. Hereditary defects in renal transport proteins are also associated with reduced reabsorption of filtered Na^+-Cl^- and/or water. Alternatively, mineralocorticoid deficiency, mineralocorticoid resistance, or inhibition of the mineralocorticoid receptor (MLR) can reduce Na^+-Cl^- reabsorption by the aldosterone-sensitive distal nephron. Finally, tubulointerstitial injury, as occurs in interstitial nephritis, acute tubular injury, or obstructive uropathy, can reduce distal tubular Na^+-Cl^- and/or water absorption.

Excessive excretion of free water, i.e., water without electrolytes, can also lead to hypovolemia. However, the effect on ECFV is usually less marked, given that two-thirds of the water volume is lost from the ICF. Excessive renal water excretion occurs in the setting of decreased circulating AVP or renal resistance to AVP (central and nephrogenic diabetes insipidus, respectively).

EXTRARENAL CAUSES Nonrenal causes of hypovolemia include fluid loss from the gastrointestinal tract, skin, and respiratory system. Accumulations of fluid within specific tissue compartments, typically the interstitium, peritoneum, or gastrointestinal tract, can also cause hypovolemia.

Approximately 9 L of fluid enter the gastrointestinal tract daily, 2 L by ingestion and 7 L by secretion; almost 98% of this volume is absorbed, such that daily fecal fluid loss is only 100–200 mL. Impaired gastrointestinal reabsorption or enhanced secretion of fluid can cause hypovolemia. Because gastric secretions have a low pH (high H^+