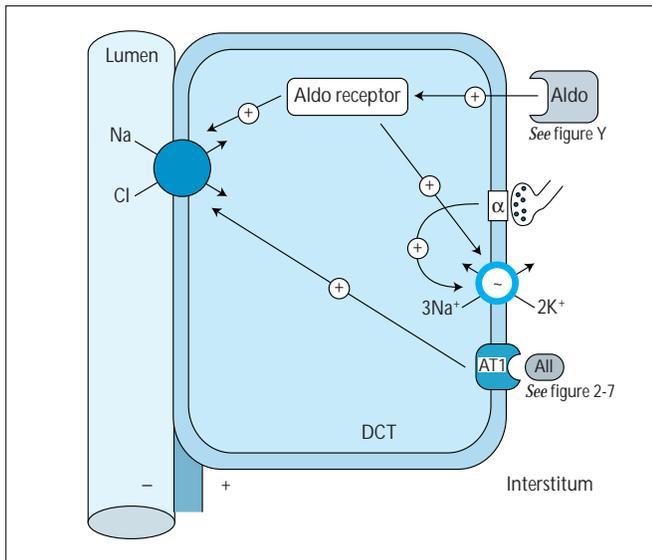
**FIGURE 2-16**

Cellular mechanisms and regulation of sodium (Na) and chloride (Cl) transport by thick ascending limb (TAL) cells. Na, Cl, and potassium (K) enter cells by way of the bumetanide-sensitive Na-K-2Cl cotransporter (NKCC2) at the apical membrane. K recycles back through apical membrane K channels (ROMK) to permit continued operation of the transporter. In this nephron segment, the asymmetric operations of the luminal K channel and the basolateral chloride channel generate a transepithelial voltage, oriented with the lumen positive. This voltage drives paracellular Na absorption. Although arginine vasopressin (AVP) is known to stimulate Na reabsorption by TAL cells in some species, data from studies in human subjects suggest AVP has minimal or no effect [31,32]. The effect of AVP is mediated by way of production of cyclic adenosine monophosphate (cAMP). Prostaglandin E_2 (PGE_2) and cytochrome P450 (c-P450) metabolites of arachidonic acid (20-HETE [hydroxy-eicosatetraenoic acid] and 20-COOH-AA) inhibit transepithelial NaCl transport, at least in part by inhibiting the Na-K-2Cl cotransporter [33–35]. PGE_2 also inhibits vasopressin-stimulated Na transport, in part by activating G_i and inhibiting adenylyl cyclase [36]. Increases in medullary NaCl concentration may activate transepithelial Na transport by increasing production of PGE_2 . **Inset A.** Regulation of NKCC2 by chronic Na delivery. Animals were treated with 0.16 mol NaCl or water as drinking fluid for 2 weeks. The Western blot shows upregulation of NKCC2 in the group treated with saline [37]. G_i —inhibitory G protein; PR—prostaglandin receptor; V_2 —AVP receptors. (Modified from Ecelbarger [37].)

**FIGURE 2-17**

Mechanisms and regulation of sodium (Na) and chloride (Cl) transport by the distal nephron. As in other nephron segments, intracellular Na concentration is maintained low by the action of the Na-K ATPase (sodium-potassium adenosine triphosphatase) pump at the basolateral cell membrane. Na enters distal convoluted tubule (DCT) cells across the luminal membrane coupled directly to chloride by way of the thiazide-sensitive Na-Cl cotransporter. Activity of the Na-Cl cotransporter appears to be stimulated by both aldosterone and angiotensin II (AII) [38–40]. Transepithelial Na transport in this segment is also stimulated by sympathetic nerves acting by way of α receptors [41,42]. The DCT is impermeable to water.

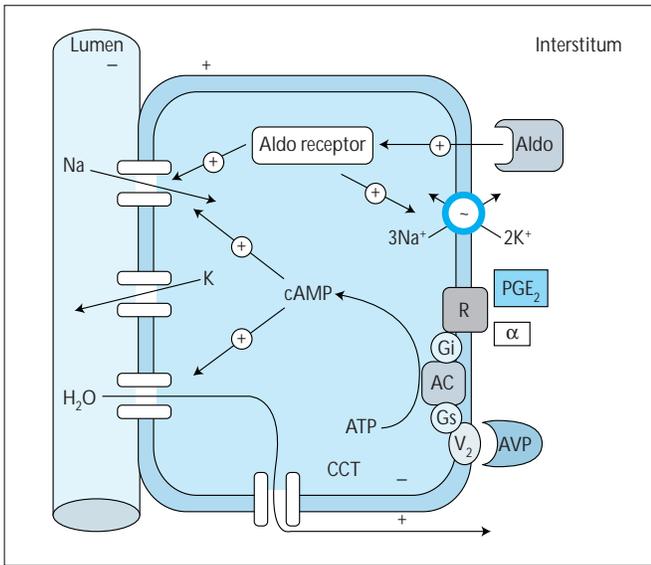


FIGURE 2-18

Principal cortical collecting tubule (CCT) cells. In these cells, sodium (Na) enters across the luminal membrane through Na channels (ENaC). The movement of cationic Na from lumen to cell depolarizes the luminal membrane, generating a transepithelial electrical gradient oriented with the lumen negative with respect to interstitium. This electrical gradient permits cationic potassium (K) to diffuse preferentially from cell to lumen through K channels (ROMK). Na transport is stimulated when aldosterone interacts with its intracellular receptor [43]. This effect involves both increases in the number of Na channels at the luminal membrane and increases in the number of Na-K ATPase (Sodium-potassium adenosine triphosphatase) pumps at the basolateral cell membrane. Arginine vasopressin (AVP) stimulates both Na absorption (by interacting with V_2 receptors and, perhaps, V_1 receptors) and water transport (by interacting with V_2 receptors) [44–46]. V_2 receptor stimulation leads to insertion of water channels (aquaporin 2) into the luminal membrane [47]. V_2 receptor stimulation is modified by PGE_2 and α_2 agonists that interact with a receptor that stimulates G_i [48]. AC—adenylyl cyclase; ATP—adenosine triphosphate; cAMP—cyclic adenosine monophosphate; CCT—cortical collecting tubule; G_i —inhibitory G protein; G_s —stimulatory G protein; R— R_i receptor.

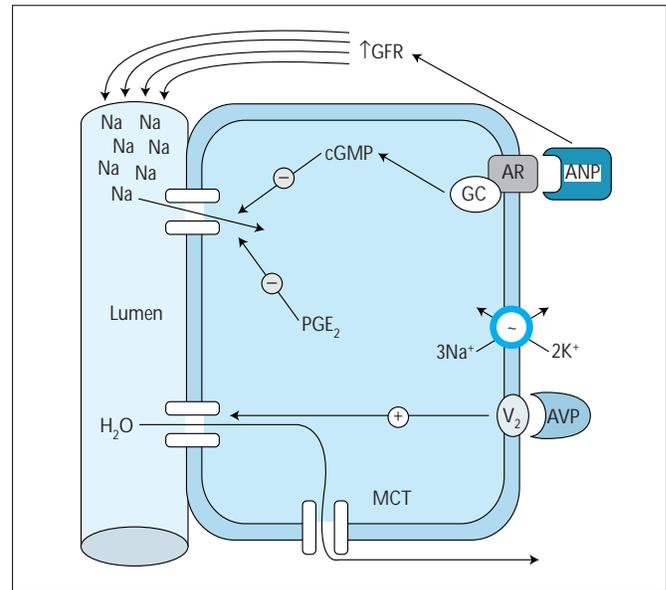


FIGURE 2-19

Cellular mechanism of the medullary collecting tubule (MCT). Sodium (Na) and water are reabsorbed along the MCT. Atrial natriuretic peptide (ANP) is the best-characterized hormone that affects Na absorption along this segment [22]. Data on the effects of arginine vasopressin (AVP) and aldosterone are not as consistent [46,49]. Prostaglandin E_2 (PGE_2) inhibits Na transport by inner medullary collecting duct cells and may be an important intracellular mediator for the actions of endothelin and interleukin-1 [50,51]. ANP inhibits medullary Na transport by interacting with a G-protein-coupled receptor that generates cyclic guanosine monophosphate (cGMP). This second messenger inhibits a luminal Na channel that is distinct from the Na channel expressed by the principal cells of the cortical collecting tubule, as shown in Figure 2-18 [52,53]. Under normal circumstances, ANP also increases the glomerular filtration rate (GFR) and inhibits Na transport by way of the effects on the renin-angiotensin-aldosterone axis, as shown in Figures 2-7 to 2-10. These effects increase Na delivery to the MCT. The combination of increased distal Na delivery and inhibited distal reabsorption leads to natriuresis. In patients with congestive heart failure, distal Na delivery remains depressed despite high levels of circulating ANP. Thus, inhibition of apical Na entry does not lead to natriuresis, despite high levels of MCT cGMP. AR—ANP receptor; GC—guanylyl cyclase; K—potassium; V_2 —receptors.

Causes, Signs, and Symptoms of Extracellular Fluid Volume Expansion and Contraction

CAUSES OF VOLUME EXPANSION

Primary renal sodium retention (with hypertension but without edema)

- Hyperaldosteronism (Conn's syndrome)
- Cushing's syndrome
- Inherited hypertension (Liddle's syndrome, glucocorticoid remediable hyperaldosteronism, pseudohypoaldosteronism Type II, others)
- Renal failure
- Nephrotic syndrome (mixed disorder)

Secondary renal sodium retention

- Hypoproteinemia
- Nephrotic syndrome
- Protein-losing enteropathy
- Cirrhosis with ascites

Low cardiac output

- Hemodynamically significant pericardial effusion
- Constrictive pericarditis
- Valvular heart disease with congestive heart failure
- Severe pulmonary disease
- Cardiomyopathies

Peripheral vasodilation

- Pregnancy
- Gram-negative sepsis
- Anaphylaxis
- Arteriovenous fistula
- Trauma
- Cirrhosis
- Idiopathic edema (?)
- Drugs: minoxidil, diazoxide, calcium channel blockers (?)

Increased capillary permeability

- Idiopathic edema (?)
- Burns
- Allergic reactions, including certain forms of angioedema
- Adult respiratory distress syndrome
- Interleukin-2 therapy
- Malignant ascites

Sequestration of fluid ("3rd spacing," urine sodium concentration low)

- Peritonitis
- Pancreatitis
- Small bowel obstruction
- Rhabdomyolysis, crush injury
- Bleeding into tissues
- Venous occlusion

FIGURE 2-20

In volume expansion, total body sodium (Na) content is increased. In primary renal Na retention, volume expansion is modest and edema does not develop because blood pressure increases until Na excretion matches intake. In secondary Na retention, blood pressure may not increase sufficiently to increase urinary Na excretion until edema develops.

CAUSES OF VOLUME DEPLETION

Extrarenal losses (urine sodium concentration low)

- Gastrointestinal salt losses
 - Vomiting
 - Diarrhea
 - Nasogastric or small bowel aspiration
 - Intestinal fistulae or ostomies
 - Gastrointestinal bleeding
- Skin and respiratory tract losses
 - Burns
 - Heat exposure
 - Adrenal insufficiency
 - Extensive dermatologic lesions
 - Cystic fibrosis
 - Pulmonary bronchorrhea
 - Drainage of large pleural effusion

Renal losses (urine sodium concentration normal or elevated)

- Extrinsic
 - Solute diuresis (glucose, bicarbonate, urea, mannitol, dextran, contrast dye)
 - Diuretic agents
 - Adrenal insufficiency
 - Selective aldosterone deficiency
- Intrinsic
 - Diuretic phase of oliguric acute renal failure
 - Postobstructive diuresis
 - Nonoliguric acute renal failure
 - Salt-wasting nephropathy
 - Medullary cystic disease
 - Tubulointerstitial disease
 - Nephrocalcinosis

FIGURE 2-21

In volume depletion, total body sodium is decreased.