36

Potassium, Calcium, and Phosphate Homeostasis

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. How does the body maintain K^+ homeostasis?
2. What is the distribution of K^+ within the body compartments? Why is this distribution important?
3. What are the hormones and factors that regulate plasma K^+ levels? Why is this regulation important?
4. How do the various nephron segments transport K^+ and what mechanisms determine how much K^+ is excreted in the urine?
5. Why is the distal tubule and collecting duct important in regulating K^+ excretion?
6. How do plasma K^+ levels, aldosterone, vasopressin, tubular fluid flow rate, and acid-base balance influence K^+ excretion?
7. What is the physiological importance of calcium (Ca^{++}) and inorganic phosphate (P_i)?
8. How does the body maintain Ca^{++} and P_i homeostasis?
9. What are the roles of kidneys, gastrointestinal tract, and bone in maintaining plasma Ca^{++} and P_i levels?
10. What hormones and factors regulate plasma Ca^{++} and P_i levels?
11. What are the cellular mechanisms responsible for Ca^{++} and P_i reabsorption along the nephron?
12. What hormones regulate renal Ca^{++} and P_i excretion by the kidneys?
13. What is the role of the calcium-sensing receptor?
14. What are the common clinical disorders of Ca^{++} and P_i homeostasis?
15. What is the role of the kidneys in the vitamin D metabolism?
16. What effects do loop and thiazide diuretics have on Ca^{++} excretion?
17. What is the effect of chronic dietary potassium deficiency on blood pressure?
18. What are the effects of chronic total body K^+ depletion on kidney function?

K^+ Homeostasis

Potassium (K^+) is the most abundant cation in the body. The vast majority of total body K^+ is located intracellularly (98%) where the $[K^+]$ is 150 mEq/L. Only 2% of total body K^+ exists in the ECF at a concentration of approximately 4 mEq/L. The large $[K^+]$ difference across cell membranes (≈146 mEq/L) is maintained by the Na^+,K^+-ATPase. The $[K^+]$ gradient is important in maintaining the potential difference across cell membranes and is critical for the excitability of nerve and muscle cells, as well as for the contractility of cardiac, skeletal, and smooth muscle cells (Fig. 36.1). Skeletal muscles contain the largest single pool of K^+ in the body. In an adult, the skeletal muscles contain approximately 225 times more K+ than all extracellular compartments in the body. Moreover, due to the large number of Na^+,K^+-ATPase pumps and K^+ channels, skeletal muscles possess a huge capacity for K^+ exchange. Despite wide fluctuations of the dietary K^+ load, $[K^+]$ remains remarkably constant in the intracellular fluid (ICF) and extracellular fluid (ECF). A $[K^+]$ in ECF that exceeds 5.0 mEq/L constitutes **hyperkalemia.** Conversely, a $[K^+]$ in ECF of less than 3.5 mEq/L constitutes **hypokalemia.** During hypokalemia, skeletal muscle cells release K^+ to preserve $[K^+]$ in the ECF leading to total body K^+ depletion.

IN THE CLINIC

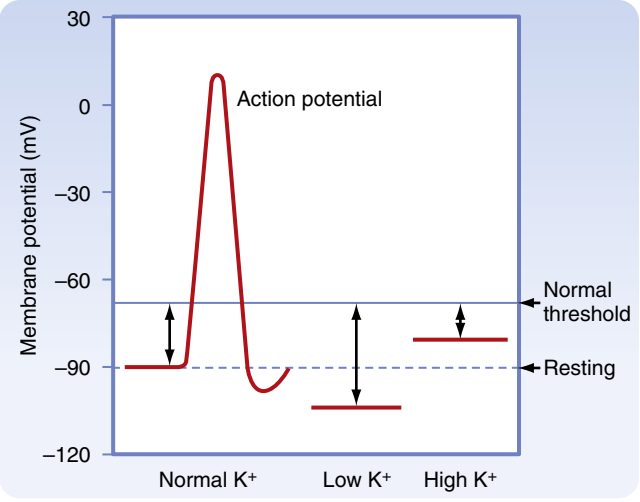
The K^+ level is usually determined from a venous blood sample. K^+ levels were traditionally measured in serum from coagulated blood, but are now more frequently measured in plasma from heparinized blood. Serum levels may generally be 0.2 to 0.4 mEq/L higher than plasma levels. Inappropriate blood sampling technique may affect the results. K^+ levels rise in the ECF after physical activity (see later). Thus blood sampling to measure K^+ should be done after several minutes of rest. **Hemolysis** of red blood cells during or after phlebotomy will release K^+ into plasma, thereby artificially elevating $[K^+]$ in the collected blood sample. Only needles, tubes, and tube adaptors approved for K^+ measurements should be used to prevent hemolysis. A large vein should be used (e.g., the cubital vein) without fist clenching and without prolonged application of a tourniquet. **Pseudohyperkalemia** refers to potassium >5 mmol/L in the collection tube and normal K^+ level in patient's blood. In addition to causing pseudohyperkalemia, errors of K^+ determination may conceal hypokalemia.

Hypokalemia may develop in people with chronic administration of diuretic, excessive use of laxatives, vomiting, eating disorders, or diarrheal illness. Gitelman syndrome (a genetic defect in the Na^+/Cl^- cotransporter in the apical membrane of distal renal tubule cells) also causes hypokalemia (see Chapter 34). **Hyperkalemia** may occur in patients with renal failure, or as a side effect of medications such as angiotensin-converting enzyme (ACE) inhibitors and K^+-sparing diuretics in patients with underlying kidney disease (decreased ability to renally excrete K^+), or in patients with diabetes mellitus (decreased ability to shift K^+ intracellularly).

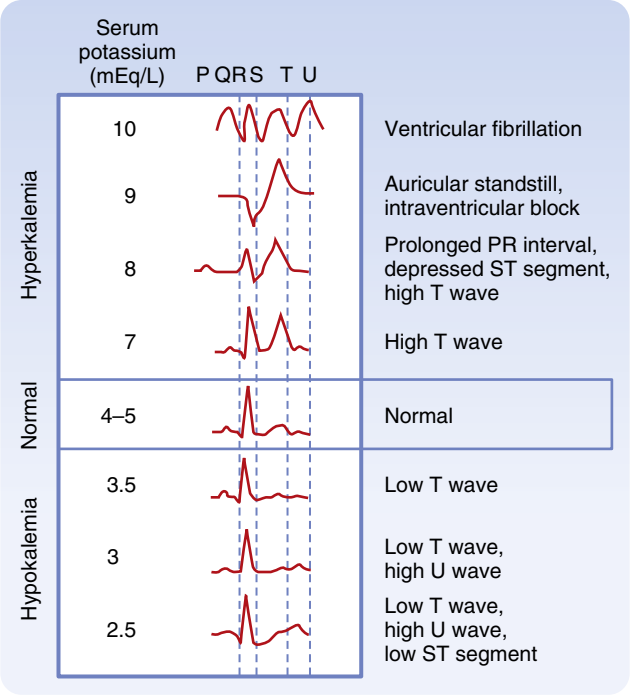
IN THE CLINIC

Cardiac arrhythmias can result from hyperkalemia and hypokalemia. The electrocardiogram (ECG; Fig. 36.2) (also see Chapter 16) monitors the electrical activity of the heart and is a fast and reliable method to determine whether changes in plasma $[K^+]$ influence the heart function. The first sign of hyperkalemia is the appearance of tall, thin T waves on the ECG. Further increases in plasma $[K^+]$ prolong the PR interval, depress the ST segment, and lengthen the QRS interval of the ECG. As plasma $[K^+]$ approaches 10 mEq/L, the P wave disappears, the QRS interval broadens, the ECG appears as a sine wave, and the ventricles fibrillate (i.e., manifest rapid, uncoordinated contractions of muscle fibers). Hypokalemia prolongs the QT interval, inverts the T wave, and lowers the ST segment of the ECG.

K^+ absorbed from the gastrointestinal (GI) tract enters the ECF within minutes (Fig. 36.3). If the K^+ ingested during a normal meal (≈33 mEq) were to remain in the ECF compartment (14 L) plasma $[K^+]$ would increase by 2.4 mEq/L (33 mEq added to 14 L of ECF):



• **Fig. 36.1** Effects of variations in plasma $[K^+]$ on resting membrane potential of skeletal muscle. Hyperkalemia causes membrane potential to become less negative, which decreases excitability by inactivating the fast Na^+ channels responsible for the depolarizing phase of the action potential. Hypokalemia hyperpolarizes the membrane potential and thereby reduces excitability because a larger stimulus is required to depolarize the membrane potential to the threshold potential. *Resting* indicates "normal" resting membrane potential. *Normal threshold* indicates the membrane threshold potential.



• **Fig. 36.2** Electrocardiographs from individuals with varying plasma $[K^+]$. See text for details. (Modified from Barker LR, Burton JR, Zieve PD. *Principles of Ambulatory Medicine.* 5th ed. Baltimore: Williams & Wilkins; 1999.)

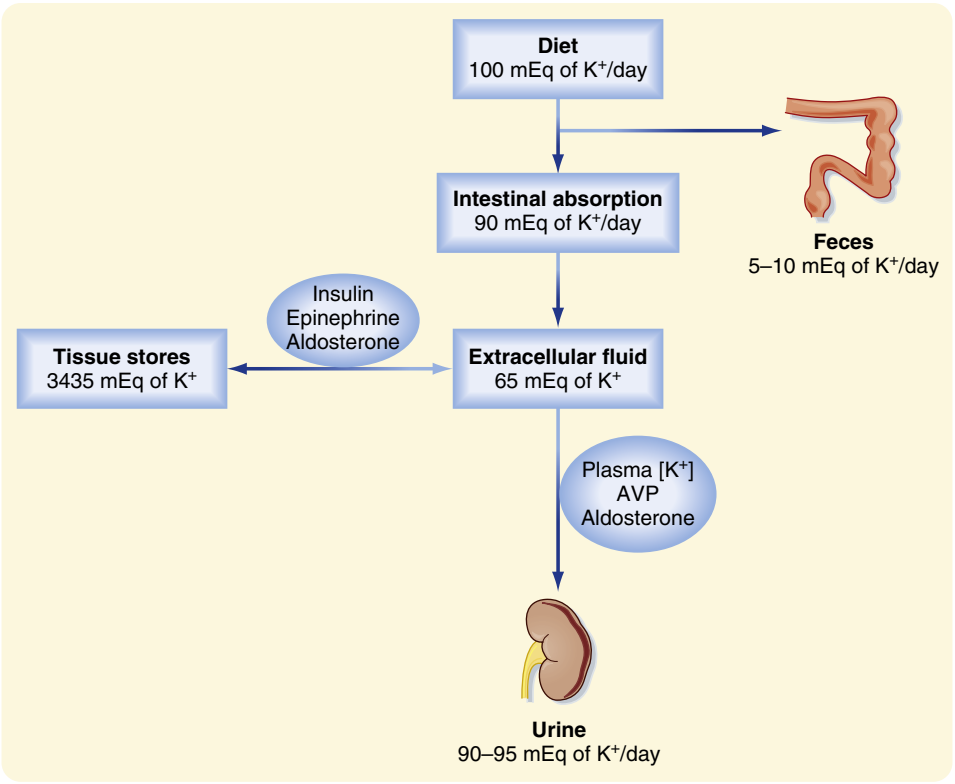
Equation 36.1

$$33\ \text{mEq}/14\text{L} = 2.4\ \text{mEq/L}$$

Rapid (seconds to minutes) intracellular uptake of K^+ is essential to prevent life-threatening hyperkalemia. Excretion of K^+ by the kidneys is relatively slow (hours). Maintaining total body $[K^+]$ constant requires that almost all the K^+ absorbed from the GI tract is eventually excreted by the kidneys. The colon is responsible for the remaining small fraction of K+ excretion, and in patients with end-stage kidney disease the colon may increase fecal K^+ excretion.

Regulation of Plasma $[K^+]$

Several hormones, including epinephrine, insulin, and aldosterone, increase uptake of K^+ into skeletal muscle, liver, bone, and red blood cells (Box 36.1; see Fig. 36.3) by stimulating Na^+,K^+-ATPase and the $Na^+/K^+/2Cl^-$ and Na^+/Cl^- cotransporters in these cells. Acute stimulation of K^+ uptake (i.e., within minutes) is mediated by increased activity of existing Na^+,K^+-ATPase and the $Na^+/K^+/2Cl^-$ and Na^+/Cl^- cotransporters, whereas a chronic increase in K^+ uptake (i.e., within hours to days) is mediated by increased abundance of Na^+,K^+-ATPase. The rise in plasma $[K^+]$ that follows K^+ absorption by the GI tract stimulates secretion of insulin from the pancreas, release of aldosterone from the adrenal cortex, and secretion of epinephrine from the adrenal medulla (see Fig. 36.3). In contrast, a decrease in plasma



• **Fig. 36.3** Overview of K^+ homeostasis. An increase in plasma insulin, epinephrine, or aldosterone stimulates movement of K^+ into cells and decreases plasma $[K^+]$, whereas a fall in plasma concentration of these hormones has the opposite effect and increases plasma $[K^+]$. The amount of K^+ in the body is determined by the kidneys. An individual is in K^+ balance when dietary intake and urinary output (plus output by the GI tract) are equal. Excretion of K^+ by the kidneys is regulated by plasma $[K^+]$, aldosterone, and arginine vasopressin *(AVP)*.

• BOX 36.1 Major Factors, Hormones, and Drugs Influencing Distribution of K^+ Between Intracellular and Extracellular Fluid Compartments

Physiological: Keep Plasma $[K^+]$ Constant

Epinephrine
Insulin
Aldosterone

Pathophysiological: Displace Plasma $[K^+]$ From Normal

Acid-base disorders
Plasma osmolality
Cell lysis
Vigorous exercise

Drugs That Induce Hyperkalemia

Dietary K^+ supplements
ACE inhibitors
K^+-sparing diuretics
Heparin

$[K^+]$ inhibits release of these hormones. Whereas insulin and epinephrine act within a few minutes, aldosterone requires about an hour to stimulate uptake of K^+ into cells.

Epinephrine

Catecholamines affect the distribution of K^+ across cell membranes by activating α- and β_2-adrenergic receptors. Stimulation of α-adrenoceptors releases K^+ from cells, especially in the liver, whereas stimulation of β_2-adrenoceptors promotes K^+ uptake by cells.

For example, activation of β_2-adrenoceptors after exercise is important in preventing hyperkalemia. The rise in plasma $[K^+]$ after a K^+-rich meal is greater if the patient has been pretreated with a β-adrenoceptor antagonist (e.g., propranolol). Furthermore, release of epinephrine during stress (e.g., myocardial ischemia) can rapidly lower plasma $[K^+]$.

Insulin

Insulin is the most important hormone that shifts K^+ into cells after ingestion of dietary K^+. Insulin and glucose infusion can be used to correct life-threatening hyperkalemia. In patients with diabetes mellitus (i.e., insulin deficiency), the rise in plasma $[K^+]$ after a K^+-rich meal is greater than in healthy people. In patients with chronic kidney disease, although insulin-stimulated glucose uptake into cells is impaired, insulin stimulation of K^+ uptake into cells is preserved.

Aldosterone

Aldosterone, like catecholamines and insulin, also promotes uptake of K^+ into cells. A rise in aldosterone levels (e.g., primary aldosteronism) causes hypokalemia, whereas a fall in aldosterone levels (e.g., Addison's disease) causes hyperkalemia. As discussed later and as illustrated in Fig. 36.3, aldosterone also stimulates urinary K^+ excretion. Thus aldosterone alters plasma [K^+] by acting on uptake of K^+ into cells and altering urinary K^+ excretion.

Alterations in Plasma [K^+]

Hyperkalemia usually develops when the amount of K^+, either enteral (dietary or bleeding into the GI tract) or parenteral (intravenous administration or hemolysis), exceeds the ability of intracellular uptake and the kidneys to excrete K^+ (see Box 36.1). Hypokalemia usually develops when intracellular K^+ uptake and renal K^+ loss exceeds K^+ intake (dietary or intravenous) (see Box 36.1). In some situations (see later), changes in the distribution of K^+ between the ECF and ICF alone can result in acute and clinically relevant disturbances of plasma [K^+].

Acid-Base Balance

Metabolic acidosis increases plasma [K^+], whereas metabolic alkalosis decreases it. Respiratory alkalosis causes hypokalemia. In contrast, respiratory acidosis has little or no effect on plasma [K^+]. Metabolic acidosis produced by addition of inorganic acids (e.g., HCl, H_2SO_4) increases plasma [K^+] much more than an equivalent acidosis produced by accumulation of organic acids (e.g., lactic acid, acetic acid, ketoacids). The reduced pH (i.e., increased [H^+]) promotes movement of H^+ into cells and the reciprocal movement of K^+ out of cells to maintain electroneutrality. This effect of acidosis occurs in part because acidosis inhibits the transporters that accumulate K^+ inside cells, including Na^+,K^+-ATPase and the $Na^+/K^+/2Cl^-$ cotransporter. In addition, movement of H^+ into cells occurs as the cells buffer changes in [H^+] of the ECF (see Chapter 37). As H^+ moves across cell membranes, K^+ moves in the opposite direction, and thus cations are neither gained nor lost across cell membranes. Metabolic alkalosis has the opposite effect; plasma [K^+] decreases as K^+ moves into cells and H^+ exits.

Although organic acids produce a metabolic acidosis, they do not cause significant hyperkalemia. Two explanations have been suggested for the reduced ability of organic acids to cause hyperkalemia. First, the organic anion may enter the cell with H^+ and thereby eliminate the need for K^+-H^+ exchange across the membrane. Second, organic anions may stimulate insulin secretion, which moves K^+ into cells. This movement may counteract the direct effect of the acidosis, which moves K^+ out of cells.

Plasma Osmolality

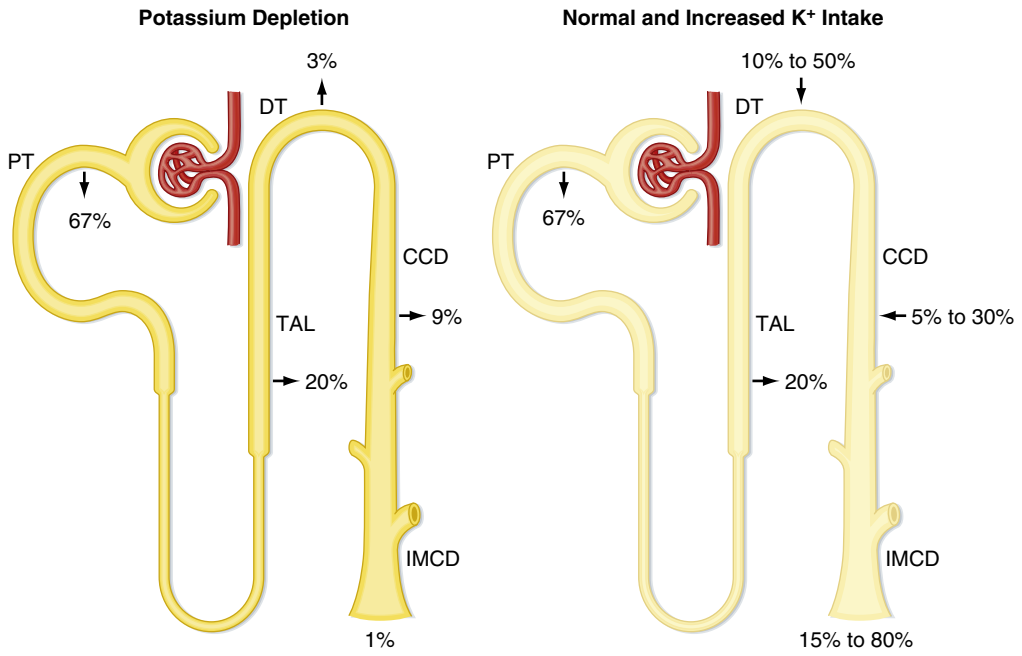
The osmolality of plasma also influences the distribution of K^+ across cell membranes. An increase in the osmolality of ECF enhances the release of K^+ by cells and thus increases extracellular [K^+]. Plasma [K^+] may increase by 0.4 to 0.8 mEq/L with a 10 mOsm/kg H_2O elevation in plasma osmolality. In patients with diabetes mellitus who do not take insulin, plasma [K^+] is often elevated, in part because of the lack of insulin and in part because of the increase in plasma [glucose] (i.e., from a normal value of ≈100 mg/dL to as high as ≈1200 mg/dL in some cases), which increases plasma osmolality. Hypoosmolality has the opposite action. The alterations in plasma [K^+] associated with changes in osmolality are related to changes in cell volume. For example, as plasma osmolality increases, water leaves cells because of the osmotic gradient across the plasma membrane (see Chapter 1). Water leaves cells until the intracellular osmolality equals that of ECF. This loss of water shrinks cells and causes [K^+] in cells to rise. The rise in intracellular [K^+] provides a driving force for the exit of K^+ from cells. This sequence increases plasma [K^+]. A fall in plasma osmolality has the opposite effect.

Cell Lysis

Cell lysis causes hyperkalemia as a result of release of intracellular K^+ into the ECF. Severe trauma (e.g., burns), **tumor lysis** (i.e., destruction of tumor cells by chemotherapy or natural processes), and **rhabdomyolysis** (i.e., destruction of skeletal muscle cells) destroy cells and release K^+ and other cellular contents into the ECF.

Exercise

During high-intensity exercise or physical exertion, repetitive action potentials in skeletal muscles lead to K^+ loss from the muscle cells followed by redistribution between plasma and the interstitial fluid (ECF compartment). Because skeletal muscles contain the major pool of K^+ in the body, plasma K^+ level may increase up to 8 mEq/L and the level may be sustained during exercise. Physical conditioning or training reduces exercise-induced hyperkalemia by increasing in the number of Na,K-ATPase pumps in the skeletal muscle cells. Upon cessation of exercise, recovering muscle cells regain lost K^+ by the Na,K-ATPase–mediated K^+ uptake followed by normalization of plasma K^+ level within minutes, which may be preceded by a temporary undershoot of K^+ level and transient hypokalemia. Changes in the K^+ level during exercise are accompanied by changes in the volume of muscle cells. The contracting muscle cells swell as they lose K^+. At cessation of exercise, water moves quickly out of the muscle cells into the interstitial space from where it is slowly redistributed into intravascular space. However, movement of K^+ does not seem be important for control of the muscle cell volume.



• **Fig. 36.4** K^+ transport along the nephron. Excretion of K^+ depends on the rate and direction of K^+ transport by the late segment of the distal tubule and collecting duct. *Percentages* refer to the amount of filtered K^+ reabsorbed or secreted by each nephron segment. *Arrows* indicate direction of transport. *Left,* Dietary K^+ depletion. An amount of K^+ equal to 1% of the filtered load of K^+ is excreted. *Right,* Normal and increased dietary K^+ intake. An amount of K^+ equal to 15% to 80% of the filtered load is excreted. *CCD*, cortical collecting duct; *DT*, distal tubule; *IMCD*, inner medullary collecting duct; *PT*, proximal tubule; *TAL*, thick ascending limb.

K^+ Excretion by the Kidneys

The kidneys play a major role in maintaining K^+ balance. As illustrated in Fig. 36.3 the kidneys excrete 90% to 95% of the K^+ ingested from the diet. Excretion equals intake even when intake increases by as much as 10-fold. This balance in urinary excretion and dietary intake underscores the importance of the kidneys in maintaining K^+ homeostasis. Although small amounts of K^+ are lost each day in feces and sweat (≈5%–10% of the K^+ ingested in the diet), except during severe diarrhea, this amount is essentially constant, is not regulated, and therefore is relatively less important than the K^+ excreted by the kidneys. K^+ secretion from blood into tubular fluid by cells of the distal tubule (DT) and collecting duct system is the key factor in determining urinary K^+ excretion (Fig. 36.4).

Because K^+ is not bound to plasma proteins, it is freely filtered at the glomerulus and is nearly completely reabsorbed in the proximal tubule (through the paracellular pathway in proportion to Na^+ and water) and ascending limb of Henle (where transcellular K^+ transport is mediated by the apical membrane $Na^+/K^+/2Cl^-$ cotransporter). The reabsorptive component of K^+ is independent of K^+ intake. Urinary K^+ excretion results primarily from secretion along the aldosterone-sensitive distal nephron (ASDN), which comprises the last portion of the distal tubule (DT), connecting tubule, and cortical collecting duct (CCD). A rise in dietary K^+ intake increases K^+ secretion (see Fig. 36.4, *right panel*). In contrast, a low-K^+ diet activates K^+ reabsorption along the ASDN (see Fig. 36.4, *left panel*).

IN THE CLINIC

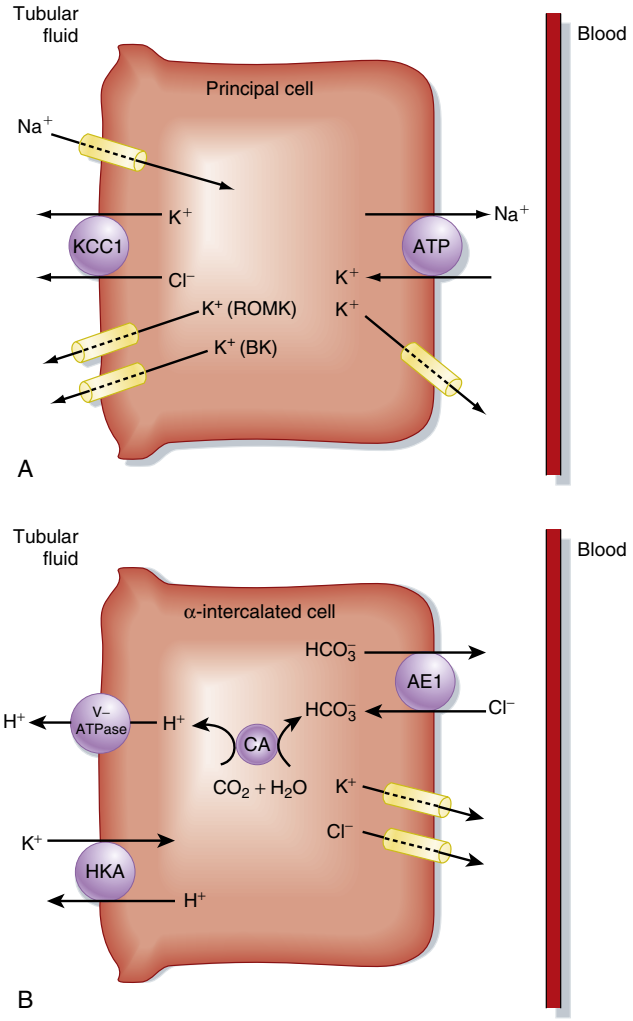
Exercise-induced changes in plasma [K^+] do not usually produce symptoms and are reversed after several minutes of rest. However, vigorous exercise can lead to life-threatening hyperkalemia in individuals (1) who have endocrine disorders that affect release of insulin, epinephrine (a β-adrenergic agonist), or aldosterone; (2) whose ability to excrete K^+ is impaired (e.g., renal failure); or (3) who take certain medications, such as β_1-adrenergic blockers. For example, during vigorous exercise, plasma [K^+] may increase by at least 2 to 4 mEq/L in individuals who take β_1-adrenergic receptor antagonists for hypertension. The heart may be also exposed to a major drop in K^+ level at cessation of exercise (see earlier). This drop seems to be associated with impaired cardiac repolarization, which could potentially induce arrhythmia and sudden cardiac death in individuals with pre-existing hypokalemia, ischemic heart disease, heart failure, ventricular arrhythmia, or inherited or acquired long QT-syndrome.

IN THE CLINIC

In individuals with **end-stage kidney disease,** the kidneys are unable to excrete ingested K^+ and plasma $[K^+]$ rises. The resulting hyperkalemia reduces the resting membrane potential (i.e., the voltage becomes less negative). The reduced membrane potential decreases the excitability of neurons, cardiac cells, and muscle cells by inactivating fast Na^+ channels, which are critical for the depolarization phase of the action potential (see Fig. 36.1). Severe rapid increases in plasma $[K^+]$ can lead to cardiac arrest and death. In contrast, in patients taking diuretics, urinary K^+ excretion often exceeds dietary K^+ intake. Accordingly, K^+ balance is negative and hypokalemia develops. This decline in extracellular $[K^+]$ hyperpolarizes the resting cell membrane (i.e., the voltage becomes more negative) and reduces the excitability of neurons, cardiac cells, and muscle cells. Severe hypokalemia can lead to cardiac arrhythmias, paralysis, and death. Hypokalemia can also impair the ability of the kidneys to concentrate urine and can stimulate renal production of NH_4^+, which affects acid-base balance (see Chapter 37). Therefore, maintenance of high intracellular $[K^+]$, low extracellular $[K^+]$, and a high $[K^+]$ gradient across cell membranes is essential for cellular functions.

Cellular Mechanism of K^+ Transport by Principal and Intercalated Cells in the DT and CCD

Fig. 36.5A illustrates the cellular mechanisms of K^+ secretion by principal cells. Secretion from blood into the tubular lumen is a two-step process: (1) uptake of K^+ from blood across the basolateral membrane by Na^+,K^+-ATPase and (2) transport of K^+ from the cell into tubular fluid via renal outer medullary K^+ (ROMK) channel and Big K^+ (BK) channel. A K^+/Cl^- cotransporter (KCC1) in the apical plasma membrane also secretes K^+. The Na^+, K^+-ATPase creates a high intracellular $[K^+]$ that provides the chemical



• **Fig. 36.5** Cellular mechanism of K^+ secretion by principal cells **(A)** and α-intercalated cells **(B)** in the late segment of the distal tubule (DT) and cortical collecting duct (CCD). α-Intercalated cells contain very low levels of Na^+,K^+-ATPase in the basolateral membrane (not shown). K^+ depletion increases K^+ reabsorption by α-intercalated cells by stimulating the H^+,K^+-ATPase *(HKA)*. *AE1*, Anion exchanger 1; *CA*, carbonic anhydrase.

driving force for exit of K^+ across the apical membrane through K^+ channels. Although K^+ channels are also present in the basolateral membrane, K^+ preferentially leaves the cell across the apical membrane and enters the tubular fluid. K^+ transport follows this route for two reasons. First, the electrochemical gradient of K^+ across the apical membrane favors its downhill movement into tubular fluid. Second, the permeability of the apical membrane to K^+ is greater than that of the basolateral membrane. Therefore K^+ preferentially diffuses across the apical membrane into tubular fluid. K^+ secretion across the apical membrane via the K^+/Cl^- cotransporter is driven by the favorable concentration gradient of K^+ between the cell and tubular fluid. The three major factors that control the rate of K^+ secretion by principal cells in DT and CCD include: (1) the activity of Na^+,K^+-ATPase, (2) the driving forces (electrochemical gradient for K^+ channels and the chemical concentration gradient for the K^+/Cl^- cotransporter) for movement of K^+ across the apical membrane, and (3) the permeability of apical membrane K^+ channels to K^+. In the DT and CCD α-intercalated cells reabsorb K^+ by a H^+,K^+-ATPase (HKA) transport mechanism located in the apical membrane (see Fig. 36.5B). This transporter mediates K^+ uptake across the apical plasma membrane in exchange for H^+. The exit of K^+ from intercalated cells into the blood is mediated by a K^+ channel. Reabsorption of K^+ is activated by a low-K^+ diet.

K^+ Excretion by the DT and CCD

K^+ excretion by the ASDN is determined by plasma $[K^+]$, Na^+ delivery and tubular fluid flow (i.e., K^+ sensing), aldosterone, arginine vasopressin (AVP), glucocorticoid levels, and acid-base status.

Plasma $[K^+]$

Plasma $[K^+]$ is an important determinant of K^+ secretion by the DT and CCD. Hyperkalemia stimulates secretion of K^+ within minutes by several mechanisms. First, hyperkalemia stimulates Na^+, K^+-ATPase and thereby increases K^+ uptake across the basolateral membrane. This uptake raises intracellular $[K^+]$ and increases the electrochemical driving force for exit of K^+ across the apical membrane. Second, hyperkalemia also increases the permeability of the apical membrane to K^+. Third, hyperkalemia stimulates secretion of aldosterone by the adrenal cortex, which as discussed later, acts synergistically with plasma $[K^+]$ to stimulate its secretion. Fourth, hyperkalemia also increases the flow rate of tubular fluid, which as discussed later, stimulates secretion of K^+ by the DT and CCD.

Hypokalemia decreases K^+ secretion via actions opposite to those described for hyperkalemia. Hence hypokalemia inhibits Na^+, K^+-ATPase, decreases the electrochemical driving force for efflux of K^+ across the apical membrane, reduces permeability of the apical membrane to K^+, and decreases plasma aldosterone levels.

AT THE CELLULAR LEVEL

ROMK is the primary channel in the apical membrane of principal cells that mediates constitutive (as opposed flow-stimulated) K^+ secretion. ROMK has a low conductance and high probability of being open under physiologic conditions. In addition, the Ca^{++}-activated BK channel is also expressed in the apical membrane. The BK channel has large single channel conductance and is quiescent in the basal state and mediates K^+ secretion under conditions of increased flow discussed earlier. Interestingly, knockout of the *KCNJ1* gene encoding ROMK channel causes increased excretion of NaCl and K^+ by the kidneys, thereby leading to reduced ECFV and hypokalemia. Although this effect is somewhat perplexing, it should be noted that ROMK is also expressed in the apical membrane of the thick ascending limb (TAL) of Henle's loop, where it plays a very important role in recycling of K^+ across the apical membrane, an effect that is critical for operation of the $Na^+/K^+/2Cl^-$ cotransporter. In the absence of ROMK, reabsorption of NaCl by the TAL is reduced, which leads to loss of NaCl in urine. Reduction of NaCl reabsorption by the TAL also reduces the positive transepithelial luminal voltage, which is the driving force for reabsorption of K^+ by this nephron segment. Thus the reduction in paracellular K^+ reabsorption by the TAL increases urinary K^+ excretion even when the cortical collecting duct is unable to secrete the normal amount of K^+ because of a lack of ROMK channels. The CCD, however, does secrete K^+ even in ROMK knockout mice via the flow and Ca^{++}-dependent BK channel expressed in the apical membrane of principal cells.

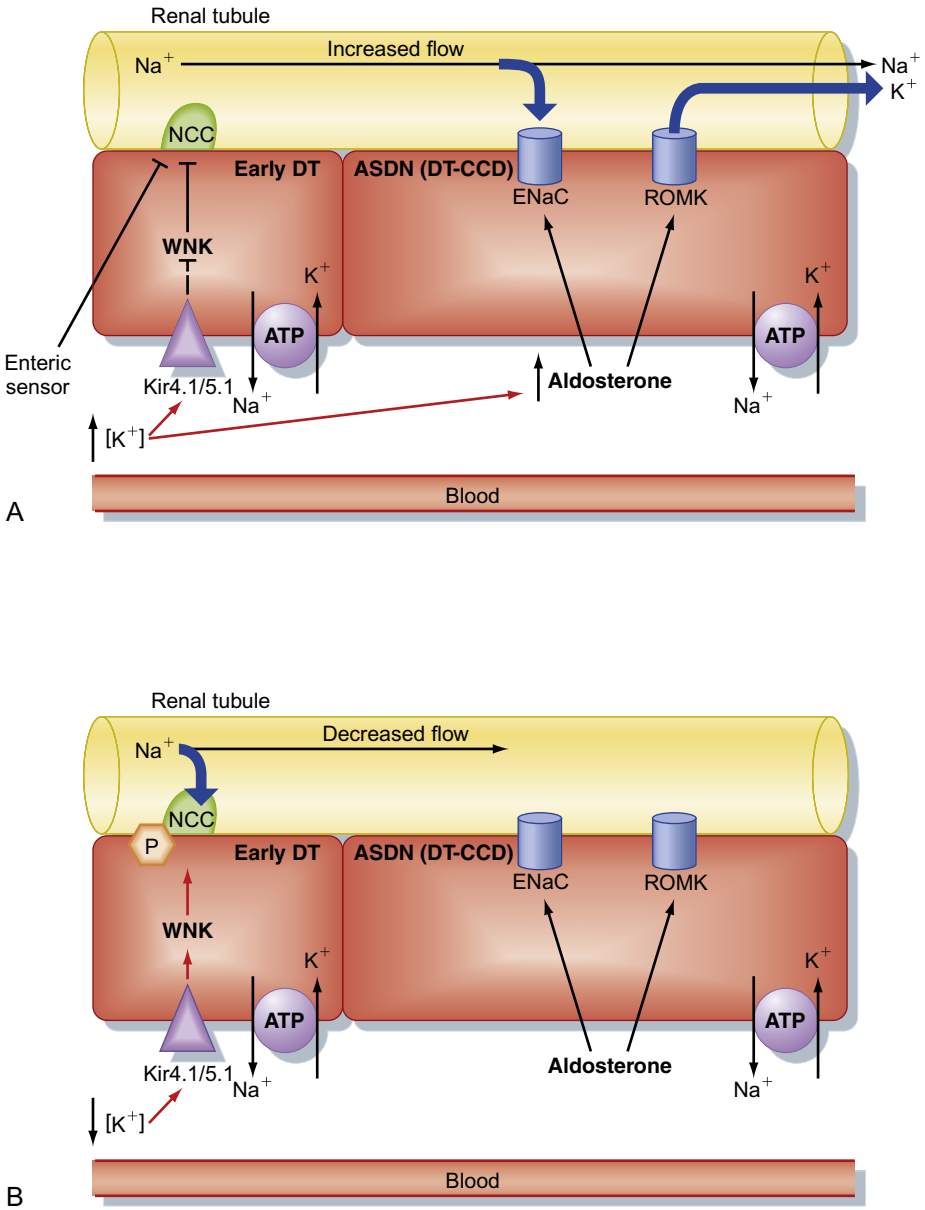
IN THE CLINIC

Chronic hypokalemia ($[K^+] < 3.5$ mEq/L) may occur in patients who receive diuretics, abuse laxatives, have profound vomiting or diarrhea, undergo nasogastric suction, or have hyperaldosteronism. Hypokalemia occurs because renal K^+ excretion exceeds dietary intake of K^+. Vomiting, nasogastric suction, diuretics, and diarrhea can all decrease ECF volume, which in turn stimulates secretion of aldosterone (see Chapter 35). Because aldosterone stimulates excretion of K^+ by the kidneys, its action contributes to development of hypokalemia. **Hypokalemic nephropathy** is a chronic condition in patients with total body K^+ depletion and is characterized by volume depletion and hyperaldosteronism. It is frequently a progressive form of chronic kidney disease that may lead to end-stage kidney disease.

Chronic hyperkalemia ($[K^+] > 5.0$ mEq/L) occurs most frequently in individuals with reduced urine flow, low plasma aldosterone levels, and renal disease in which the glomerular filtration rate (GFR) falls below 20% of normal. In these individuals, hyperkalemia occurs because renal K^+ excretion is lower than dietary K^+ intake. Less common causes of hyperkalemia occur in people with deficiencies in insulin or aldosterone secretion or in people with metabolic acidosis caused by inorganic acids.

Na^+ Delivery and Tubular Fluid Flow (K^+ Sensing by Renal Epithelial Cells)

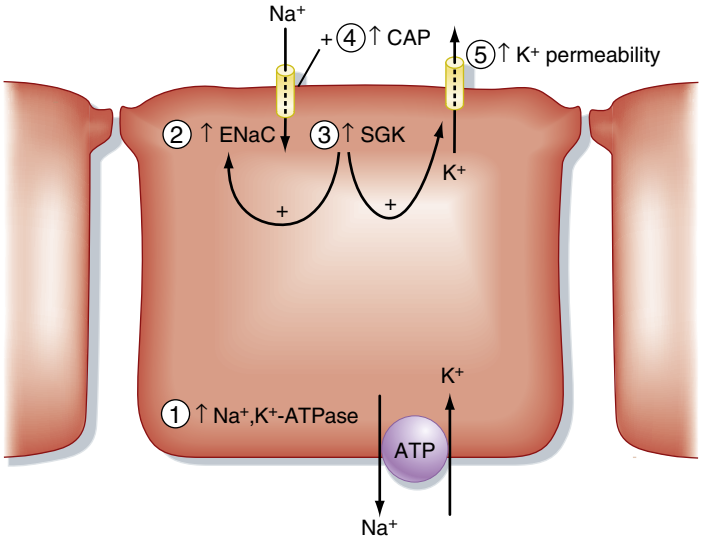
K^+ secretion is induced by increased Na^+ delivery and flow of tubular fluid to the ASDN. This effect begins in the early



• **Fig. 36.6** Mechanisms of epithelial K^+ sensing. **A,** Increased plasma [K^+] is detected by Kir4.1/5.1 channels in the early portion of the DT that inactivate *NCC* (Na^+/Cl^- cotransporter) leading to increased Na^+ delivery to the aldosterone-sensitive distal nephron *(ASDN)* increasing tubular fluid flow and renal excretion of Na^+ and K^+. **B,** Decreased plasma [K^+] activates the WNK pathway that phosphorylates NCC (Na^+/Cl^- symporter) activating it to stimulate Na^+ absorption and decrease Na^+ delivery to the ASDN decreasing tubular fluid flow and renal excretion of Na^+ and K^+. *ASDN*, aldosterone-sensitive distal nephron; *CCD*, cortical collecting duct; *DT*, distal tubule.

portion of the DT, where Na^+ transport is driven by the thiazide-sensitive Na^+/Cl^- cotransporter. Increased plasma [K^+] is detected by the K^+ sensors Kir 4.1/5.1 channels located in the basolateral membrane of the early segment of the DT (Fig. 36.6A). Sensing of increased plasma [K+] by Kir 4.1/5.1 initiates a signaling cascade that dephosphorylates and inhibits the Na^+/Cl^- cotransporter. Inhibition of the Na^+/Cl^- cotransporter results in greater Na^+ delivery and tubular fluid flow to the ASDN and leads to increased renal K^+ excretion. Decreased intake and decreased plasma [K^+] activates the Na^+/Cl^- cotransporter in the early DT and limit K^+ secretion by reducing Na^+ delivery and flow to the ASDN (Fig. 36.6B).

A rise in the flow of tubular fluid (e.g., with diuretic treatment, ECF expansion) stimulates secretion of K^+ within minutes, whereas ECF contraction caused by hemorrhage, severe vomiting, or diarrhea reduces secretion of K^+ by the ASDN. Increments in tubular fluid flow are more effective in stimulating secretion of K^+ as dietary K^+ intake is increased. Increased flow bends the primary cilium in principal cells, which activates the polycystin (PKD)1/PKD2 Ca^{++}-conducting channel complex. This allows more Ca^{++}



• **Fig. 36.7** Effects of aldosterone on secretion of K^+ by principal cells in the late segment of the distal tubule and collecting duct. *Numbers* refer to the five effects of aldosterone discussed in the text.

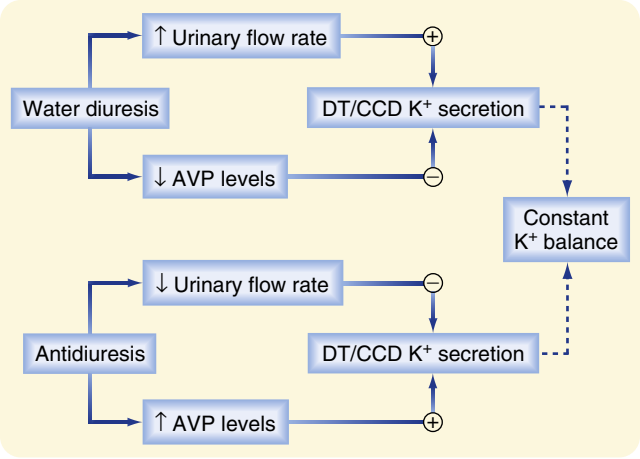
to enter principal cells and increases intracellular [Ca^{++}]. The increase in [Ca^{++}] activates BK K^+ channels in the apical plasma membrane, which enhances K^+ secretion from the cell into the tubule fluid. As flow increases, such as after administration of diuretics or as the result of an increase in ECF, so does the [Na^+] of tubule fluid. This increase in [Na^+] facilitates entry of Na^+ across the apical membrane of ASDN cells, thereby decreasing the cells' interior negative membrane potential. This depolarization of the cell membrane potential increases the electrochemical driving force that promotes secretion of K^+ across the apical cell membrane into tubule fluid. In addition, increased uptake of Na^+ into cells activates the Na^+,K^+-ATPase in the basolateral membrane, thereby increasing uptake of K^+ across the basolateral membrane and consequently elevating cell [K^+]. It is important to note that an increase in flow rate during a water diuresis does *not* have a significant effect on excretion of K^+, most likely because during a water diuresis the [Na^+] of tubule fluid does not increase as flow rises.

IN THE CLINIC

Since the agricultural revolution, the human diet evolved from a high K^+–low Na^+ to a low K^+–high Na^+ diet. Recommendations for the adequate K^+ intake for adults generally range between 90 and 100 mEq/day (3500–4000 mg/day). In a worldwide analysis, K^+ intake (estimated from urinary K^+ excretion in adults) was 40%–50% lower than the recommended intake. A low-K^+ diet is associated with increased risk of adverse cardiovascular effects including hypertension and hypokalemic nephropathy. A low-K^+ diet increases the activity of the Na^+/Cl^- cotransporter in the DT. This makes sense physiologically, because increased sodium reabsorption by the Na^+/Cl^- cotransporter reduces Na^+ delivery to downstream K^+-secreting nephron segments and therefore helps to conserve K^+. The effect of a low-K^+ diet, which reduces Na^+ excretion by the kidneys, has been linked to the pathogenesis of salt-sensitive hypertension. Conservation of K^+ and Na^+ by the kidneys when there is K^+ deficiency may have evolved because simultaneous deficiency of dietary K^+ and Na^+ was probably faced by early humans. At the present time when the dietary Na^+ intake is high and K^+ intake is low, the response of the kidneys to retain K^+ and Na^+ may lead to salt-sensitive hypertension.

Aldosterone

Chronically elevated (≥24 hours) plasma aldosterone levels enhance K^+ secretion across principal cells in the ASDN (Fig. 36.7): (1) by increasing the amount of Na^+,K^+-ATPase in the basolateral membrane; (2) by increasing expression of the epithelial sodium channel (ENaC) in the apical cell membrane; (3) by elevating SGK1 (***s***erum ***g***lucocorticoid-stimulated ***k***inase) levels, which also increases expression of Na^+ (ENaC) channels in the apical membrane and activates K^+ channels; (4) by stimulating CAP1 (***c***hannel-***a***ctivating ***p***rotease, also called **prostatin**), which directly activates ENaC; and (5) by stimulating the permeability of the apical membrane to K^+. Aldosterone increases the permeability of the apical membrane to K^+ by increasing the number of K^+ channels in the membrane. However, the cellular mechanisms involved in this response are not completely known. Increased expression of Na^+,K^+-ATPase facilitates uptake of K^+ across the basolateral membrane into cells and thereby elevates intracellular [K^+]. The increased number and activity of Na^+ channels enhance entry of Na^+ into the cell from tubular fluid, an effect that depolarizes the apical membrane voltage. Depolarization of the apical membrane and increased intracellular [K^+] enhance the electrochemical driving force for secretion of K^+ from the cell into the tubule fluid. Taken together, these actions increase uptake of K^+ into the cell across the



• **Fig. 36.8** Opposing effects of AVP and urine flow rate on secretion of K^+ by the ASDN. K^+ secretion is stimulated by an increase in urinary flow rate and reduced by a fall in AVP levels. In contrast, K^+ secretion is reduced by a decrease in urinary flow rate and increased by a rise in AVP levels. Because the effects of flow and AVP oppose each other, net K^+ secretion is not affected by water diuresis or antidiuretics. *AVP*, Arginine vasopressin; *CCD*, cortical collecting duct; *DT*, distal tubule.

basolateral membrane and enhance exit of K^+ from the cell across the apical membrane. Secretion of aldosterone is increased by hyperkalemia and by angiotensin II (after activation of the renin-angiotensin system). Secretion of aldosterone is decreased by hypokalemia and natriuretic peptides released from the heart.

Although an acute (within hours) increase in aldosterone levels enhances the activity of Na^+,K^+-ATPase, K^+ excretion does not increase immediately. The delay results from the effect of aldosterone on Na^+ reabsorption and tubular flow. Aldosterone stimulated Na^+ and water reabsorption decreases tubular flow that, in turn, decreases K^+ secretion (as discussed in more detail later). However, chronic stimulation of Na^+ reabsorption increases the ECF volume and thereby returns tubular flow to normal. These actions allow a direct stimulatory effect of aldosterone on the ASDN to enhance K^+ excretion.

AVP

Although AVP does not affect urinary K^+ excretion, this hormone promotes secretion of K^+ by the ASDN (Fig. 36.8). AVP increases the electrochemical driving force for exit of K^+ across the apical membrane of principal cells by stimulating uptake of Na^+ across the apical membrane of these cells. The increased Na^+ uptake reduces the electrical potential difference across the apical membrane (i.e., the interior of the cell becomes less negative). Despite this effect, AVP does not change K^+ secretion by these nephron segments. The reason for this relates to the effect of AVP on tubular fluid flow. AVP decreases flow of tubular fluid by stimulating water reabsorption. The decrease in tubular flow in turn reduces secretion of K^+ (explained later). The inhibitory effect of decreased flow of tubular fluid offsets the stimulatory effect of AVP on the electrochemical driving force for exit of K^+ across the apical membrane (see Fig. 36.8). If AVP did not increase the electrochemical gradient favoring K^+ secretion, urinary K^+ excretion would fall as AVP levels increased and urinary flow rates decreased. Hence K^+ balance would change in response to alterations in water balance. Thus the effects of AVP on the electrochemical driving force for exit of K^+ across the apical membrane and on tubule flow enable urinary K^+ excretion to be maintained constant despite wide fluctuations in water excretion.

Glucocorticoids

Glucocorticoids increase urinary K^+ excretion. This effect is mediated in part by increasing GFR, which enhances the urinary flow rate, a potent stimulus of K^+ excretion, and by stimulation of SGK1 activity (see earlier).

As discussed, the rate of urinary K^+ excretion is frequently determined by simultaneous changes in hormone levels, acid-base balance, or the flow rate of tubule fluid (Table 36.1). The powerful effect of flow often enhances or opposes the response of the ASDN to hormones and changes in acid-base balance. This interaction can be beneficial in the case of hyperkalemia, in which the increase in flow enhances excretion of K^+ and thereby restores K^+ homeostasis. However, this interaction can also be detrimental, as in the case of metabolic alkalosis, in which changes in flow and acid-base status alter K^+ homeostasis.

The Acid-Base Status

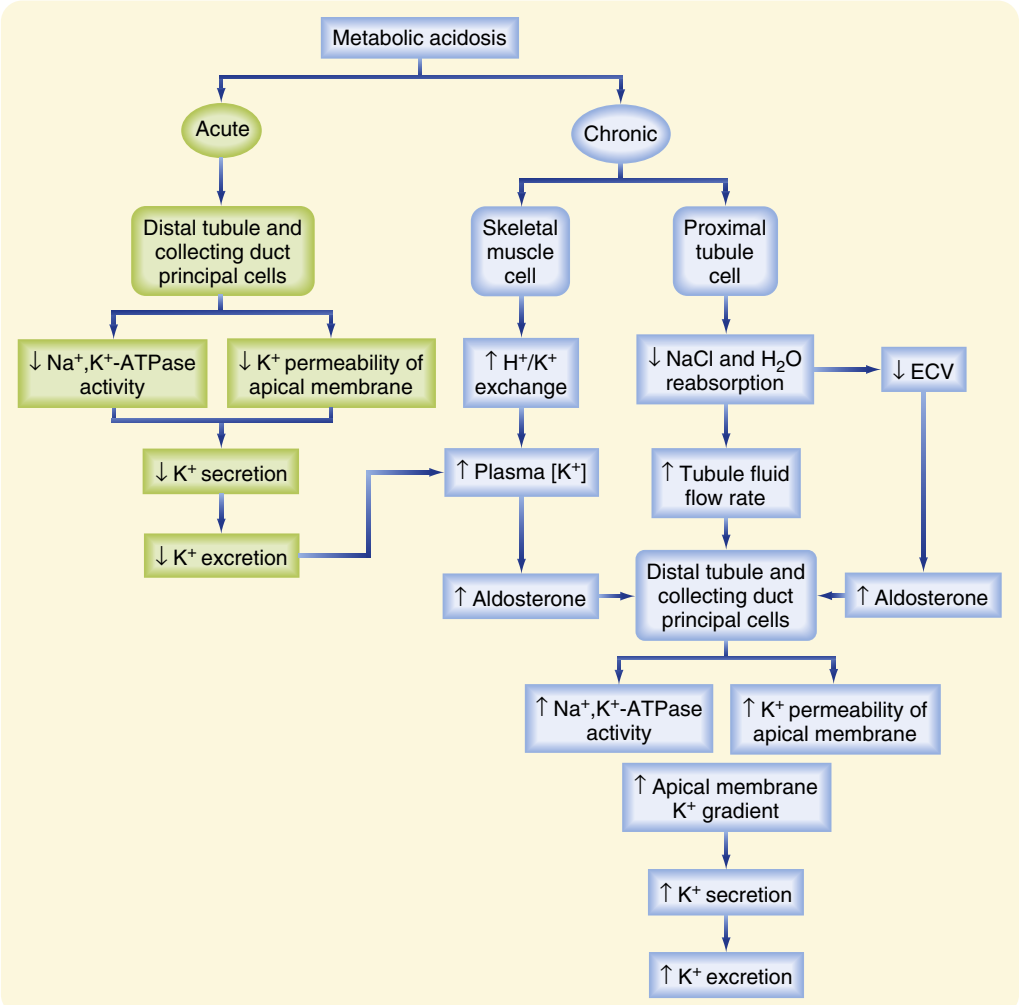
Both acute (within minutes to hours) and chronic (within days) acid-base disturbances have complex effects on K^+ handling by the ASDN and renal K^+ excretion. The effects of metabolic acidosis on renal K^+ excretion are time dependent. As illustrated in Fig. 36.9, an acute acidemia (i.e., plasma pH below normal) reduces K^+ secretion via two mechanisms: (1) inhibition of Na^+,K^+-ATPase that reduces

TABLE 36.1 Effects of Hormones and Other Factors on Renal K^+ Homeostasis and Effects on Plasma $[K^+]$

Condition	K^+ Secretion by ASDN	Tubular Fluid Flow	Renal K^+ Excretion	Change in Plasma $[K^+]$
Hyperkalemia	Increase	Increase	Increase	Decrease
Aldosterone				
Acute	Increase	Decrease	No change	Decrease
Chronic	Increase	No change	Increase	Decrease
Glucocorticoids	Increase	Increase	Increase	Decrease
AVP	Increase	Decrease	No change	Decrease
Acidosis				
Acute	Decrease	No change	Decrease	Increase
Chronic	Decrease	Large increase	Increase	Decrease
Alkalosis	Increase	Increase	Large increase	Decrease

ASDN, Aldosterone-sensitive distal nephron.

Modified from Field MJ et al. In: Narins R, ed. *Textbook of Nephrology: Clinical Disorders of Fluid and Electrolyte Metabolism*. 5th ed. New York: McGraw-Hill; 1994.



• **Fig. 36.9** Acute versus chronic effect of metabolic acidosis on excretion of K^+. See text for details. *ECV,* Effective circulating volume.

the intracellular [K^+] and the electrochemical driving force for K^+ exit across the apical membrane; and (2) by decreasing permeability of the apical membrane to K^+. Acute alkalemia (i.e., plasma pH above normal) has the opposite effects and increases K^+ secretion.

Chronic acidemia promotes renal K^+ excretion leading to negative K^+ balance (see Fig. 36.9). This occurs because chronic metabolic acidosis decreases reabsorption of water and solutes (e.g., NaCl) by inhibiting Na^+,K^+-ATPase in the proximal tubule. Hence the flow of tubular fluid is augmented along the ASDN. Inhibition of water and NaCl reabsorption by the proximal tubule also decreases ECF volume and thereby stimulates secretion of aldosterone. In addition, chronic acidosis caused by inorganic acids increases plasma [K^+], which stimulates secretion of aldosterone. The rise in tubular fluid flow, plasma [K^+], and aldosterone levels offsets the effects of acidosis on cell [K^+] and apical membrane permeability, and K^+ secretion rises. Thus metabolic acidosis may either inhibit or stimulate excretion of K^+, depending on the duration of the disturbance. As noted, acute metabolic alkalosis stimulates excretion of K^+. Chronic metabolic alkalosis, especially in association with ECF contraction, significantly increases renal K^+ excretion because of the associated increase in aldosterone levels.

The directional effects of acidemia and alkalemia on K^+ excretion are similar in respiratory acid-base disturbances as in metabolic disturbances, but the effects of respiratory disorders on K^+ excretion tend to be smaller than metabolic acid-base disturbances. Acute respiratory alkalosis, induced by hyperventilation, is associated with α-adrenergic stimulation that increases plasma [K^+] by inhibiting intracellular K^+ uptake. Acute respiratory alkalosis is a frequent acid-base disturbance in clinical settings including chest pain, anxiety, drugs, hypoxemia, and infection. Chronic respiratory alkalosis usually increases renal K^+ excretion and lowers plasma [K^+].

AT THE CELLULAR LEVEL

The cellular mechanisms whereby the dietary K^+ content and acid-base status regulate secretion of K^+ by the early segment of the ASDN have recently been elucidated. Elevated K^+ intake increases secretion of K^+ by several mechanisms. Hyperkalemia increases the activity of the ROMK channel in the apical plasma membrane of principal cells. Moreover, hyperkalemia inhibits reabsorption of NaCl and water by the proximal tubule, thereby increasing the ASDN flow rate, a potent stimulus to secretion of K^+ (Fig. 36.6). Hyperkalemia also increases aldosterone levels, which increases K^+ secretion by three mechanisms. First, aldosterone increases the number of K^+ channels in the apical plasma membrane. Second, aldosterone stimulates uptake of K^+ across the basolateral membrane by increasing the number of Na^+,K^+-ATPase pumps, thereby enhancing the electrochemical gradient driving secretion of K^+ across the apical membrane. Third, aldosterone increases movement of Na^+ across the apical membrane, which depolarizes the apical plasma membrane voltage and thus increases the electrochemical gradient, promoting secretion of K^+. A low-K^+ diet dramatically reduces secretion of K^+ by the ASDN by increasing the activity of a tyrosine kinase, which causes ROMK channels to be endocytosed from the apical plasma membrane, thereby reducing K^+ secretion. Metabolic acidosis with acidemia decreases secretion of K^+ by inhibiting the activity of ROMK channels, whereas metabolic alkalosis with alkalemia stimulates secretion of K^+ by enhancing ROMK channel activity.

Overview of Calcium and Inorganic Phosphate Homeostasis

Ca^{++} and inorganic phosphate (P_i)[a] are multivalent ions that subserve many complex and vital functions. Ca^{++} is a cofactor in enzymatic reactions and a second messenger in many signaling pathways critical for the homeostasis. P_i is essential for metabolic processes, including formation of adenosine triphosphate (ATP), and it is an important component of nucleotides, nucleosides, and phospholipids. Phosphorylation of proteins is an important mechanism of cellular signaling, and P_i is an essential buffer in cells, plasma, and urine. Ca^{++} and P_i are critical elements of the extracellular matrix, cartilage, teeth, and bone.

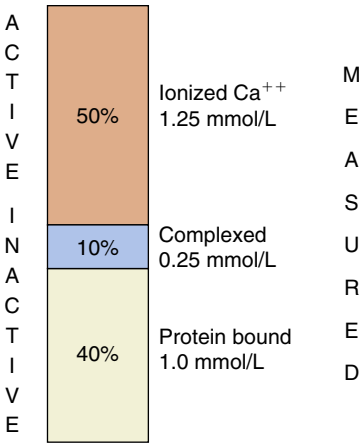
The kidneys regulate total body Ca^{++} and P_i by excreting the amount of Ca^{++} and P_i that is absorbed by the GI tract (normal bone remodeling results in no net addition of Ca^{++} and P_i to, or Ca^{++} and P_i release from, bone). If plasma concentrations of Ca^{++} and P_i decline substantially, intestinal absorption, bone resorption (i.e., loss of Ca^{++} and P_i from bone), and renal tubular reabsorption increase and return plasma concentrations of Ca^{++} and P_i to normal levels. During growth and pregnancy, intestinal absorption exceeds urinary excretion, and these ions accumulate in newly formed fetal tissue and bone. In contrast, bone disease (e.g., osteoporosis) or a decline in lean body mass increases urinary Ca^{++} and P_i loss without a change in intestinal absorption. These conditions produce a net loss of Ca^{++} and P_i from the body. Finally, during chronic renal failure, P_i accumulates in the body because the intestinal absorption of P_i exceeds the urinary excretion leading to accumulation of P_i in the body and bone remodeling (see the In The Clinic box discussion of end-stage kidney disease).

This brief introduction reveals that kidneys, in conjunction with the GI tract and bone, play a major role in maintaining plasma Ca^{++} and P_i levels as well as Ca^{++} and P_i homeostasis (see Chapter 40). Accordingly, this section of the chapter discusses Ca^{++} and P_i handling by the kidneys, with an emphasis on the hormones and factors that regulate urinary excretion.

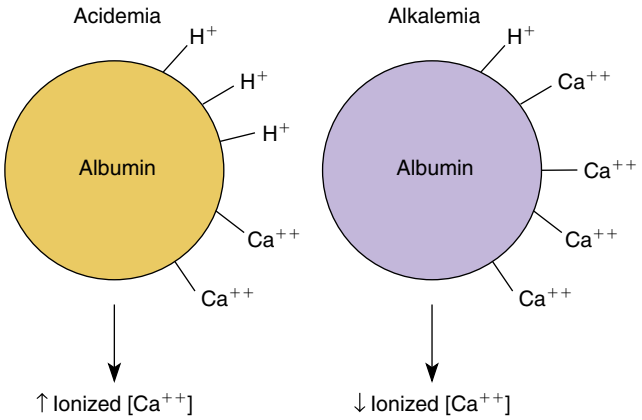
Calcium

Cellular processes in which Ca^{++} plays an important role include bone formation, cell division and growth, hemostasis, hormone-response coupling, and electrical stimulus-response coupling (e.g., muscle contraction,

[a]At physiological pH, inorganic phosphate exists as HPO_4^- and $H_2PO_4^-$ (pK = 6.8). For simplicity, we collectively refer to these ion species as P_i.



• **Fig. 36.10** Distribution of Ca^{++} in plasma. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)



• **Fig. 36.11** Effect of pH on plasma $[Ca^{++}]$. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)

neurotransmitter release). Nearly 99% of Ca^{++} is stored in bone and teeth, approximately 1% is found in ICF, and 0.1% in ECF. The total $[Ca^{++}]$ in plasma is 10 mg/dL (2.5 mM or 5 mEq/L), and its concentration is normally maintained within very narrow limits. Approximately 50% of the Ca^{++} in plasma is ionized (i.e., free), 40% is bound to plasma proteins (mainly albumin), and 10% is complexed to several anions, including PO_4^{3-}, HCO_3^-, citrate, and SO_4^{2-} (Fig. 36.10). The pH of plasma influences this distribution (Fig. 36.11). The total measured plasma $[Ca^{++}]$ does not reflect the physiologically relevant ionized $[Ca^{++}]$. Acidemia increases the ionized $[Ca^{++}]$ at the expense of Ca^{++} bound to proteins, whereas alkalemia decreases the ionized $[Ca^{++}]$ by increasing the Ca^{++} bound to proteins. Individuals with alkalemia are susceptible to **tetany** (tonic muscular spasms), whereas individuals with acidemia are less susceptible to tetany, even when total plasma Ca^{++} levels are reduced. The increase in $[H^+]$ in patients with metabolic acidosis causes more H^+ to bind to plasma proteins, PO_4^{3-}, HCO_3^-, citrate, and SO_4^{2-}, thereby displacing Ca^{++}. This displacement increases the plasma ionized $[Ca^{++}]$. In alkalemia the $[H^+]$ of plasma decreases. Some H^+ ions dissociate from plasma proteins, PO_4^{3-}, HCO_3^-, citrate, and SO_4^{2-} in exchange for Ca^{++}, thereby decreasing the ionized $[Ca^{++}]$. The plasma albumin concentration also affects $[Ca^{++}]$. **Hypoalbuminemia** decreases the total $[Ca^{++}]$ and may not accurately reflect the ionized $[Ca^{++}]$, whereas **hyperalbuminemia** has the opposite effect on total $[Ca^{++}]$. It is widely accepted in clinical practice to assume that the total $[Ca^{++}]$ falls by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL (10 g/L) fall in the serum albumin concentration.

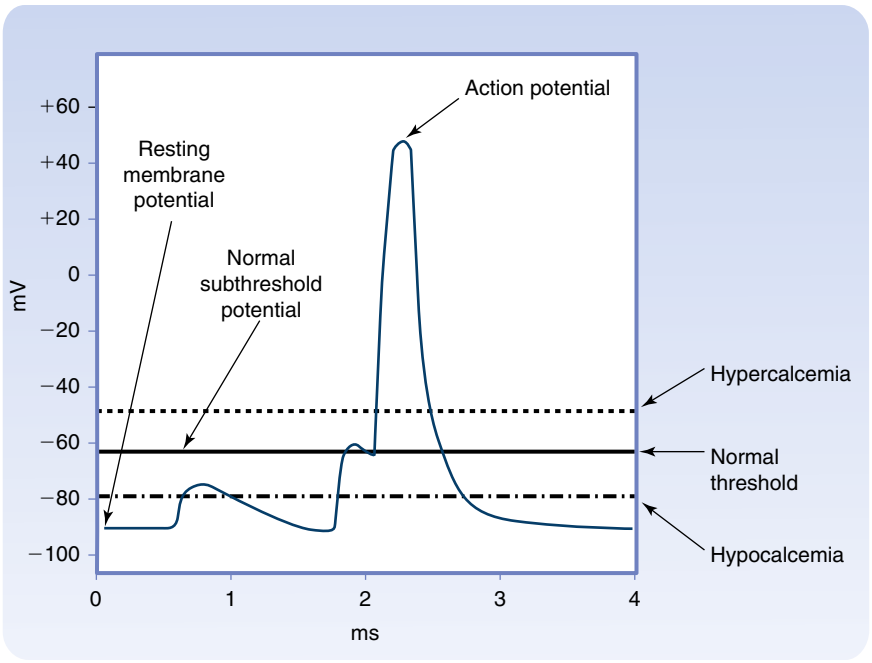
A low ionized $[Ca^{++}]$ increases the excitability of nerve and muscle cells and can lead to hypocalcemic tetany. Tetany associated with hypocalcemia occurs because hypocalcemia causes the threshold potential to shift to more negative values (i.e., closer to the resting membrane voltage) (Fig. 36.12). An elevated ionized $[Ca^{++}]$ may decrease neuromuscular excitability or produce cardiac arrhythmias, lethargy, disorientation, and even death. This effect of hypercalcemia occurs because an elevated ionized $[Ca^{++}]$ causes the threshold potential to shift to less negative values (i.e., farther from the resting membrane voltage). The $[Ca^{++}]$ is regulated within a very narrow range, primarily by **parathyroid hormone** (**PTH**) and the active metabolite of vitamin D **calcitriol (1,25-dihydroxyvitamin D_3)**.

Intracellular Ca^{++} is sequestered in the endoplasmic reticulum and mitochondria, or it is bound to proteins. Thus the intracellular ionized $[Ca^{++}]$ is very low (≈100 nM). The large concentration gradient for $[Ca^{++}]$ across cell membranes is maintained by a Ca^{++}-ATPase pump (PMCa1b) in all cells and by a $3Na^+/Ca^{++}$ exchanger (NCX1) in some cells.

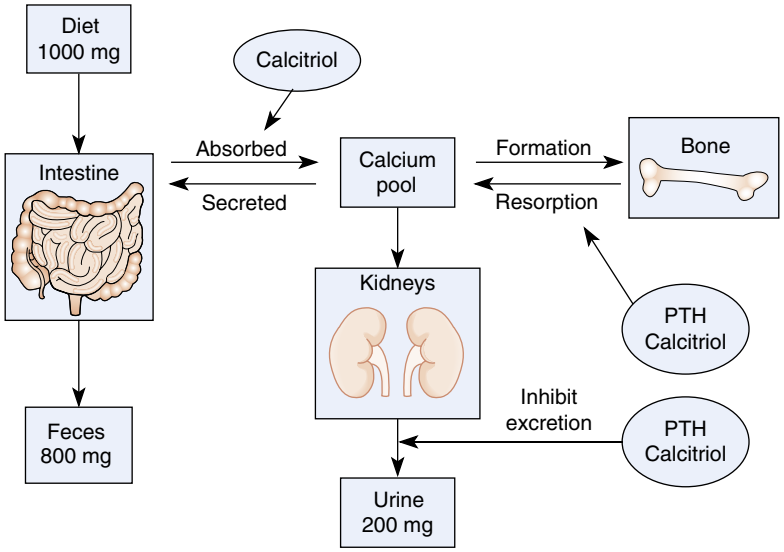
Overview of Calcium Homeostasis

Ca^{++} homeostasis depends on: (1) the Ca^{++} absorption from the GI tract, (2) the distribution of Ca^{++} between the bone and ECF, and (3) the regulation of Ca^{++} excretion by the kidneys. The total body Ca^{++} content is determined by the amounts of Ca^{++} absorbed from the GI tract and excreted by the kidneys (Fig. 36.13). The GI tract absorbs Ca^{++} through an active carrier-mediated transport mechanism that is stimulated by calcitriol produced in the proximal tubule of the kidneys. Net Ca^{++} absorption from the GI tract is approximately 200 mg/day, but it can increase to 600 mg/day when calcitriol levels rise. Daily Ca^{++} excretion by the kidneys equals the amount absorbed by the GI tract (200 mg/day), and it changes in parallel with intestinal absorption. Thus Ca^{++} balance is maintained because the amount of Ca^{++} ingested in an average diet (1000 mg/day) equals the amount lost in feces (800 mg/day) plus the amount excreted in urine (200 mg/day).

The control of Ca^{++} distribution between the bone and ECF is mediated by PTH and calcitriol (see Fig. 36.13). PTH is secreted by the parathyroid glands in response to decreased plasma $[Ca^{++}]$ (i.e., hypocalcemia). PTH increases plasma $[Ca^{++}]$ by: (1) stimulating bone resorption, (2) increasing Ca^{++} reabsorption by the DT of the kidneys, and (3) stimulating the production of calcitriol, which in turn increases Ca^{++} absorption by the GI tract. Production of calcitriol in the kidneys is stimulated by hypocalcemia and



• **Fig. 36.12** Effect of Ca^{++} on nerve and muscle excitability. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)



• **Fig. 36.13** Overview of Ca^{++} homeostasis. *PTH,* parathyroid hormone. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)

hypophosphatemia. Calcitriol increases plasma [Ca^{++}], primarily by stimulating Ca^{++} absorption from the GI tract. It also enhances renal Ca^{++} reabsorption by increasing expression of the Ca^{++} binding and transporting proteins in the kidneys (details discussed later). Plasma Ca^{++} is an agonist of the **calcium-sensing receptor** (**CaSR**), expressed on the surface of cells involved in Ca^{++} homeostasis: PTH-secreting parathyroid cells, calcitonin-secreting thyroid cells, calcitriol-producing proximal tubular cells, and TAL cells (discusser later). CaSR, activated by increased ionized [Ca^{++}], inhibits PTH release by the parathyroid gland and calcitriol production by the proximal tubule. The net effects of CaSR activation are decreased renal Ca^{++} reabsorption, decreased plasma [Ca^{++}] and blunted PTH-mediated phosphaturic effect (less renal P_i excretion). CaSR plays a major role in the steady-state plasma [Ca^{++}] by responding immediately to small changes plasma [Ca^{++}]. Calcitonin is secreted by thyroid C cells (parafollicular cells), and its secretion is stimulated by hypercalcemia. Calcitonin decreases plasma [Ca^{++}], mainly by stimulating bone formation (i.e., deposition of Ca^{++} in bone). Although it plays an important role in Ca^{++} homeostasis in lower vertebrates, calcitonin plays only a minor role in Ca^{++} homeostasis in humans, so it will not be discussed further.

IN THE CLINIC

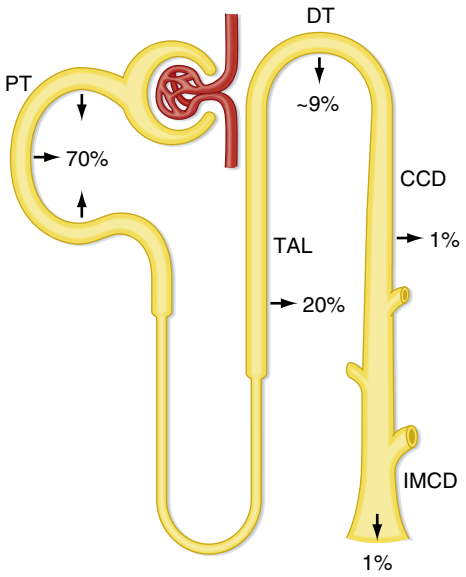
Conditions that lower PTH levels (i.e., hypoparathyroidism after parathyroidectomy for an adenoma) reduce plasma [Ca^{++}], which can cause **hypocalcemic tetany** (intermittent muscular contractions). In severe cases, hypocalcemic tetany can cause death by asphyxiation. Hypercalcemia can cause lethal cardiac arrhythmias and decreased neuromuscular excitability. Clinically hypercalcemia is most commonly caused by primary hyperparathyroidism and malignancy. Primary hyperparathyroidism results from overproduction of PTH by a benign tumor of the parathyroid glands. In contrast, malignant tumors such as carcinomas secrete a PTH-like hormone maned **parathyroid hormone–related peptide (PTHrP)**. Increased levels of PTH and PTHrP lead to hypercalcemia and hypercalciuria (increased urinary calcium excretion).

Calcium Transport Along the Nephron

The Ca^{++} available for glomerular filtration consists of the ionized fraction and the Ca^{++} complexed with anions. Thus about 60% of the Ca^{++} in plasma is available for glomerular filtration. Normally 99% of filtered Ca^{++} is reabsorbed by the nephron (Fig. 36.14). The proximal tubule reabsorbs about 50% to 60% of the filtered Ca^{++}. Another 15% is reabsorbed in the loop of Henle (mainly the cortical portion of the TAL), about 10% to 15% is reabsorbed by the DT, and less than 1% is reabsorbed by the collecting duct. About 1% (200 mg/day) is excreted in urine. This fraction is equal to the net amount absorbed daily by the GI tract.

Ca^{++} reabsorption by the proximal tubule occurs primarily via the paracellular pathway. This passive paracellular reabsorption of Ca^{++} is driven by the lumen-positive transepithelial voltage across the second half of the proximal tubule and by a favorable concentration gradient of Ca^{++}, both of which are established by transcellular Na^+ and water reabsorption in the first half of the proximal tubule (see Chapter 34).

Ca^{++} reabsorption by the loop of Henle also occurs primarily via the paracellular pathway. Like the proximal tubule, Ca^{++} and Na^+ reabsorption in the TAL parallel each other. These processes are parallel because Ca^{++} is reabsorbed passively via the paracellular route secondary to Na^+ reabsorption that generates a lumen-positive voltage. Loop diuretics inhibit Na^+ reabsorption by the TAL of the loop of Henle, and in so doing reduce the magnitude of the lumen-positive voltage (see Chapter 34). This action in turn inhibits reabsorption of Ca^{++} via the paracellular pathway. Thus loop diuretics can be used to increase renal Ca^{++} excretion in patients with hypercalcemia.

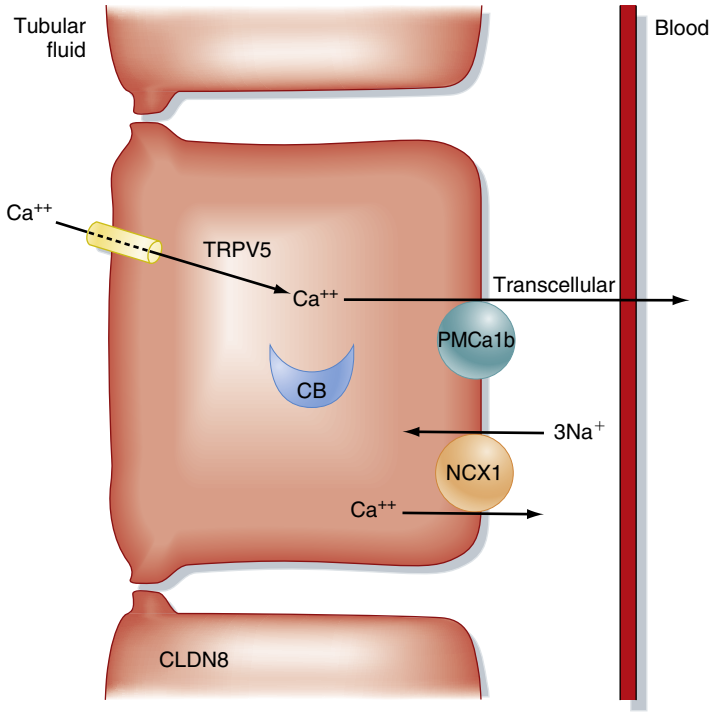


• **Fig. 36.14** Overview of Ca^{++} transport along the nephron. *Percentages* refer to amount of filtered Ca^{++} reabsorbed by each segment. *CCD,* cortical collecting duct; *DT,* distal tubule; *IMCD,* inner medullary collecting duct; *PT,* proximal tubule; *TAL,* thick ascending limb.

AT THE CELLULAR LEVEL

Mutations in the tight junction protein **claudin-16 (CLDN16)** reduce the permeability of the paracellular pathway to Ca^{++} and Mg^{++} and thereby reduce the diffusive reabsorptive movement of Ca^{++} and Mg^{++} across tight junctions in the TAL of Henle's loop. **Familial hypomagnesemic hypercalciuria** is caused by mutations in claudin-16, which is a component of the tight junctions in TAL cells. This disorder is characterized by enhanced excretion of Ca^{++} and Mg^{++} due to a fall in passive reabsorption of these ions across the paracellular pathway in the TAL. Affected individuals have high levels of Ca^{++} in their urine, which may lead to kidney stone formation (nephrolithiasis).

In the DT where the voltage in the tubule lumen is electrically negative with respect to blood, reabsorption of Ca^{++} is entirely active because Ca^{++} is reabsorbed against its electrochemical gradient (Fig. 36.15). Thus Ca^{++} reabsorption by the DT is exclusively transcellular. Ca^{++} enters the cell across the apical membrane through Ca^{++}-permeable ion channels (TRPV5). Inside the cell, Ca^{++} binds to calbindin-D28K. The calbindin-Ca^{++} complex carries Ca^{++} across the cell and delivers Ca^{++} to the basolateral membrane, where it is extruded from the cell primarily by the $3Na^+/1Ca^{++}$ antiporter (NCX1); however, plasma membrane Ca^{++}-ATPase isoform 1b (PMCA1b) may also contribute. Urinary Na^+ and Ca^{++} excretion usually change in parallel. However, excretion of these ions does not always change in parallel, because reabsorption of Ca^{++} and Na^+ by the DT is independent and differentially regulated. For example, **thiazide diuretics** inhibit Na^+ reabsorption by the DT and stimulate Ca^{++} reabsorption by this segment. Accordingly, the net effects of thiazide diuretics are to increase urinary Na^+ excretion and reduce urinary Ca^{++} excretion. Because thiazide diuretics reduce urinary Ca^{++} excretion, they are often used to reduce urinary Ca^{++} excretion in individuals who produce Ca^{++}-containing kidney stones.



• **Fig. 36.15** Cellular mechanism of Ca^{++} reabsorption by the distal tubule. Ca^{++} is reabsorbed exclusively by a cellular pathway. Ca^{++} enters the cell across the apical membrane via a Ca^{++}-permeable ion channel *(TRPV5)*. Inside cells, Ca^{++} binds to calbindin (calbindin-D_{28K}), and the Ca^{++}-calbindin complex diffuses across the cell to deliver Ca^{++} to the basolateral membrane. Ca^{++} is transported across the basolateral membrane primarily by a 3 (or 4) Na^{+}/Ca^{++} antiporter *(NCX1)* and also by a Ca^{++}-H^{+}-ATPase *(PMCa1b)*. Claudin 8 *(CLDN8)* is a tight junction protein that is impermeable to Ca^{++} and thereby prevents the back diffusion of Ca^{++} across the tight junction into the tubule lumen, which is electrically negative compared to the blood side of the cell. *CB*, Calbindin-D_{28K}.

Regulation of Urinary Calcium Excretion

Several hormones and factors influence urinary Ca^{++} excretion. PTH exerts the most powerful control (Table 36.2). PTH stimulates Ca^{++} reabsorption by the kidneys (i.e., inhibits renal Ca^{++} excretion). Although PTH inhibits reabsorption of Na+ and water, and therefore Ca^{++} reabsorption by the proximal tubule, it stimulates Ca^{++} reabsorption by the TAL of the loop of Henle and the DT. Thus the net effect of PTH is to enhance renal Ca^{++} reabsorption.

Changes in plasma [Ca^{++}] also regulate urinary Ca^{++} excretion, with hypercalcemia increasing excretion and hypocalcemia decreasing excretion. Hypercalcemia increases urinary Ca^{++} excretion by: (1) reducing proximal tubule Ca^{++} reabsorption (reduced paracellular reabsorption due to increased interstitial fluid [Ca^{++}]); (2) inhibiting Ca^{++} reabsorption by the TAL of the loop of Henle via activation of the CaSR located in the basolateral membrane of these cells (Na^{+} reabsorption is decreased, thereby reducing the magnitude of the lumen-positive); and (3) suppressing Ca^{++} reabsorption by the DT by reducing PTH levels. As a result, urinary Ca^{++} excretion increases. Hypocalcemia has the opposite effect on urinary Ca^{++} excretion, primarily by increasing Ca^{++} reabsorption by the proximal tubule and TAL. Calcitriol enhances Ca^{++} reabsorption by the DT, but it is less effective than PTH.

Several factors affect renal Ca^{++} excretion. Increased plasma [P_i] (e.g., caused by increased dietary P_i load or reduced kidney function) inhibits renal Ca^{++} excretion by reducing plasma ionized [Ca^{++}] with subsequent stimulation of PTH secretion. A decline in plasma [P_i] (e.g., caused by dietary P_i depletion) has the opposite effect (NOTE: with normal kidney function, changes in dietary P_i intake over a sevenfold range have no effect on plasma [P_i]). The CaSR expressed in the TAL directly increases renal Ca^{++} excretion in response to elevated plasma ionized [Ca^{++}] (discussed earlier). By contrast, a fall in plasma [Ca^{++}] leads to an increase in Ca^{++} absorption by the TAL and a corresponding decrease in urinary Ca^{++} excretion. The direct effect of plasma [Ca^{++}] on CaSR in the TAL acts in parallel with PTH, which regulates Ca^{++} absorption by the DT and controls urinary Ca^{++} excretion to maintain its homeostasis. Changes in ECF volume alter Ca^{++} excretion mainly by affecting Na^{+} and water reabsorption in the proximal tubule. ECF contraction increases Na^{+} and water reabsorption by the proximal tubule and thereby enhances Ca^{++} reabsorption. Accordingly, urinary Ca^{++} excretion declines. ECF expansion has the opposite effect. Acidemia increases Ca^{++} excretion, whereas alkalemia decreases excretion. Regulation of Ca^{++} reabsorption by pH occurs primarily in the

TABLE 36.2 Summary of Hormones, Factors, and Diuretics Affecting Ca^{++} Reabsorption

	Nephron Location		
Factor/Hormone	**Proximal Tubule**	**TAL**	**Distal Tubule**
PTH (PTHrP)[a]	Decrease	Increase	Increase
Calcitriol			Increase
Volume expansion	Decrease	No change	Decrease
Hypercalcemia	Decrease	Decrease (via CaSR)	Decrease (via PTH)
Hypocalcemia	Increase	Increase	
Hyperphosphatemia			Increase (via PTH)
Hypophosphatemia	Decrease		Decrease (via PTH)
Acidemia			Decrease
Alkalemia			Increase
Loop diuretics		Decrease	
Thiazide diuretics			Increase

[a]PTH inhibits Ca^{++} reabsorption by the proximal tubule but stimulates reabsorption by the TAL and distal tubule. Overall the net effect is to increase Ca^{++} reabsorption and thereby reduce urinary Ca^{++} excretion. *CaSR*, calcium-sensing receptor; *PTH*, parathyroid hormone; *PTHrP*, parathyroid hormone–related peptide; *TAL*, thick ascending limb. Modified from Mount DB, Yu A. Transport of inorganic solutes: sodium, chloride, potassium, magnesium, calcium and phosphate. In: Brenner BM, ed. *Brenner and Rector's The Kidney.* 8th ed. Philadelphia: Saunders; 2008.

DT. Alkalosis stimulates the apical membrane Ca^{++} channel (TRPV5), thereby increasing Ca^{++} reabsorption. By contrast, acidosis inhibits the same channel, thereby reducing Ca^{++} reabsorption. As noted earlier, loop diuretics inhibit Ca^{++} reabsorption by the TAL, and thiazide diuretics stimulate Ca^{++} reabsorption by the DT.

IN THE CLINIC

Mutations in the gene coding for CaSR cause disorders in the Ca^{++} homeostasis. **Familial hypocalciuric hypercalcemia (FHH)** is a haploinsufficient state caused by an inactivating mutation in the *CaSR* gene. The hypercalcemia is caused by altered Ca^{++}-regulated PTH secretion (i.e., the set point for Ca^{++}-regulated PTH secretion is shifted) such that PTH levels are elevated at any level of plasma [Ca^{++}] and are not suppressed by hypercalcemia. Enhanced Ca^{++} reabsorption in the TAL and DT owing to elevated PTH levels and defective CaSR regulation of Ca^{++} transport in the kidneys lead to hypocalciuria. **Autosomal dominant hypoparathyroidism** is caused by an activating mutation in the *CaSR* gene. Activation of CaSR changes the set point for Ca^{++}-regulated PTH secretion such that PTH levels are decreased at any level of plasma [Ca^{++}]. Decreased PTH levels and defective CaSR-regulated Ca^{++} transport in the kidneys lead to hypercalciuria. CaSR activates the thiazide-sensitive Na^+/Cl^- cotransporter in the early segment of the DT via the WNK (with no K = lysine) kinase signaling pathway (see Chapter 34). Activation of the Na^+/Cl^- cotransporter reduces Ca^{++} reabsorption leading to hypercalciuria. Inactivation of the cotransporter increases Ca^{++} reabsorption and hypercalciuria resolves. Thus activation of CaSR increases activity of the Na^+/Cl^- cotransporter leading to increased NaCl reabsorption, exacerbation of renal Ca^{++} excretion, and hypercalcuria.

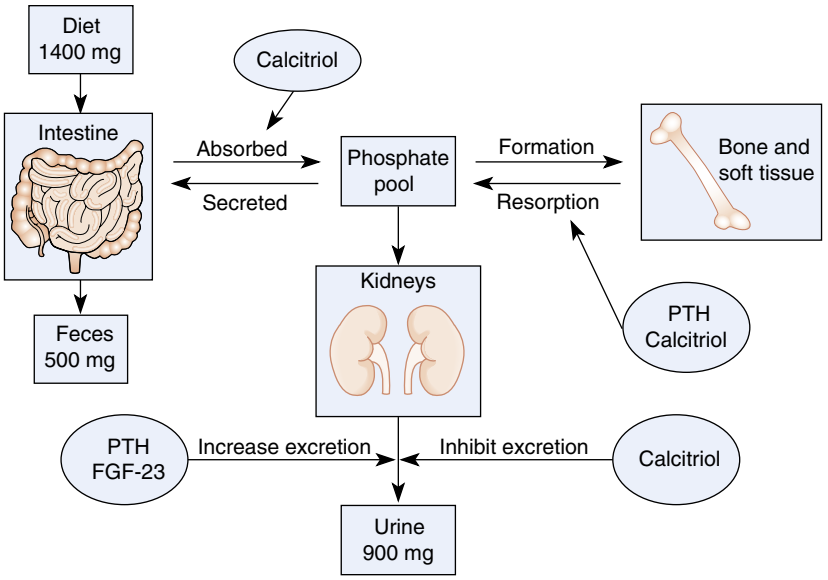
Phosphate

P_i is an important component of many essential cellular components, including DNA, RNA, ATP, nucleotides, nucleosides, phospholipids and intermediates of metabolic pathways. Like Ca^{++} it is a major constituent of bone. Its concentration in plasma is an important determinant of bone formation and resorption. In addition, urinary P_i is an important buffer (i.e., it is one of many titratable acids) involved in the maintenance of acid-base balance (see Chapter 37). Approximately 85% of P_i is located in bone and teeth, 14% is located in the ICF, and 1% in the ECF. Normal plasma [P_i] is 3 to 4 mg/dL (1–1.5 mM). Plasma P_i is ionized (45%), complexed (30%), or bound to protein (25%). P_i deficiency causes muscle weakness, rhabdomyolysis, and reduced bone mineralization resulting in **rickets** (in children) and **osteomalacia** (in adults).

Overview of Phosphate Homeostasis

P_i homeostasis depends on: (1) the P_i absorption from the GI tract, (2) the distribution of P_i between bone and ECF, and (3) the regulation of P_i excretion by the kidneys (see Fig. 36.16).

The total body P_i level is determined by the amounts of P_i absorbed from the GI tract and excreted by the kidneys. P_i absorption from the GI tract occurs via active and passive mechanisms; P_i absorption increases as dietary P_i rises, and it is stimulated by calcitriol. Despite variations in P_i intake between 800 and 1500 mg/day, in adults at the steady state the kidneys maintain total body P_i balance constant by excreting an amount of P_i in



• **Fig. 36.16** Overview of P_i homeostasis. *PTH*, parathyroid hormone. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)

the urine equal to the amount absorbed by the GI tract (normal bone remodeling results in no net P_i addition or release from bone). By contrast, during growth, P_i is accumulated in the body. Renal P_i excretion is the primary mechanism by which the body regulates P_i balance and homeostasis.

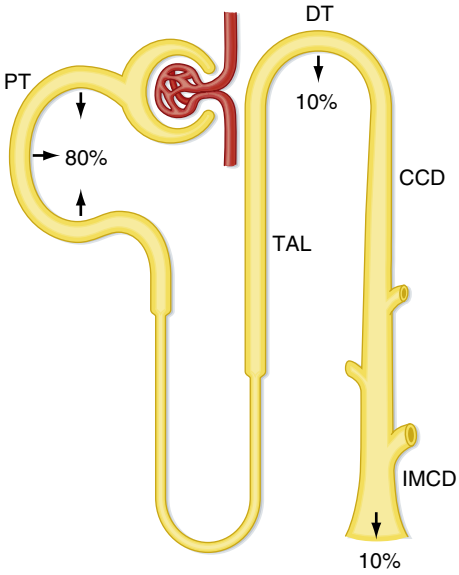
Plasma [P_i] is controlled by PTH, calcitriol, and FGF-23. PTH releases P_i from bone (see Fig. 36.16). Renal P_i excretion is increased by PTH and inhibited by calcitriol.

Maintenance of plasma [P_i] is essential for optimal Ca^{++}-P_i complex formation required for bone mineralization without deposition of Ca^{++}-P_i in vascular and other soft tissues. A rise in plasma [P_i] directly stimulates PTH synthesis and release and decreases the ionized [Ca^{++}], which stimulates PTH release by its interaction with CaSR. PTH enhances urinary P_i excretion by inhibiting P_i reabsorption in the proximal tubule. Hyperphosphatemia also decreases calcitriol production by the proximal tubule, which leads to a reduction in P_i absorption from the GI tract. Both the increase in PTH and the decrease in calcitriol reduce plasma [P_i].

Phosphate Transport Along the Nephron

Fig. 36.17 summarizes P_i transport by the various portions of the nephron. The proximal tubule reabsorbs 80% of the P_i filtered by the glomerulus; the loop of Henle, DT, and CCD reabsorb negligible amounts of P_i. Therefore approximately 20% of the P_i filtered across the glomerular capillaries is excreted in urine.

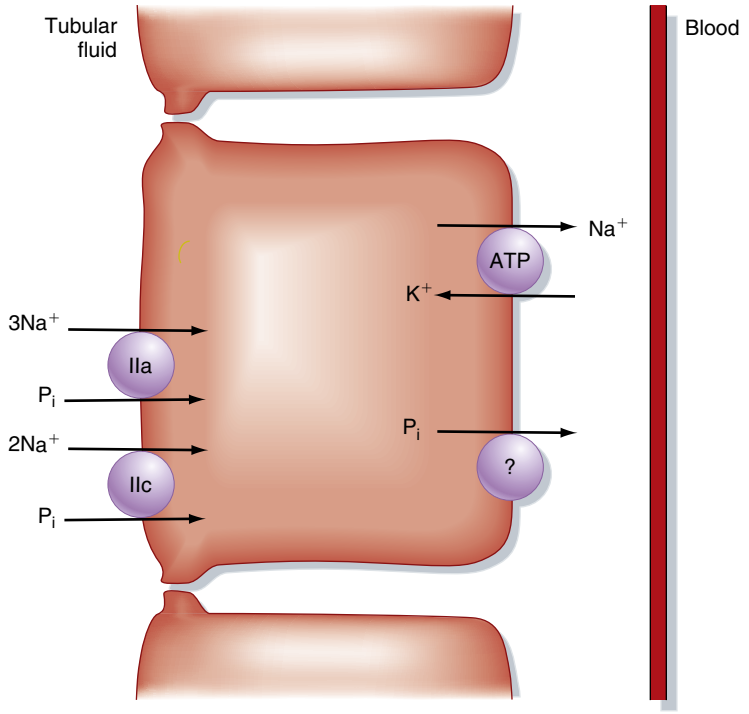
P_i reabsorption by the proximal tubule occurs by a transcellular route (Fig. 36.18). P_i uptake across the apical membrane of the proximal tubule occurs via two Na^+/P_i cotransporters (IIa and IIc). Na^+/P_i IIa transports $3Na^+$ with



• **Fig. 36.17** P_i transport along the nephron. P_i is reabsorbed primarily by the proximal tubule. *Percentages* refer to the amount of the filtered P_i reabsorbed by each nephron segment. Approximately 20% of the filtered P_i is excreted. *CCD*, Cortical collecting duct; *DT*, distal tubule; *IMCD*, inner medullary collecting duct; *PT*, proximal tubule; *TAL*, thick ascending limb.

one divalent P_i (HPO_4^{2-}), and carries positive charge into the cell. Na^+/P_i IIc transports $2Na^+$ with one monovalent P_i ($H_2PO_4^-$) and is electrically neutral. P_i exits across the basolateral membrane by a P_i-inorganic anion antiporter that has not been characterized.

Fibroblast growth factor 23 (**FGF-23**) increases renal P_i excretion and thereby contributes to regulation of plasma [P_i] (see Fig. 36.16). FGF-23 is secreted by osteocytes and osteoblasts and inhibits P_i reabsorption and calcitriol production



• **Fig. 36.18** Cellular mechanisms of P_i reabsorption by the proximal tubule. The apical transport pathway contains two Na^+/P_i symporters, one that transports three Na^+ for each P_i*(IIa)* and one that transports two Na^+ for each P_i*(IIc)*. P_i leaves the cell across the basolateral membrane by an unknown mechanism. *ATP*, adenosine triphosphate.

IN THE CLINIC

In patients with **end-stage kidney disease,** the kidneys cannot excrete P_i. Because of continued P_i absorption by the GI tract, P_i accumulates in the body and plasma $[P_i]$ rises. The excess P_i complexes with Ca^{++} and reduces the ionized plasma $[Ca^{++}]$. P_i accumulation also decreases production of calcitriol. This response reduces Ca^{++} absorption by the GI tract, an effect that further reduces plasma $[Ca^{++}]$. This reduction in plasma $[Ca^{++}]$ increases PTH secretion and Ca^{++} release from bone. These actions result in **renal osteodystrophy** (i.e., increased bone resorption with replacement by fibrous tissue, which renders bone more susceptible to fracture).

Chronic hyperparathyroidism (i.e., elevated PTH levels due the elevated plasma P_i) during end-stage kidney disease can lead to metastatic calcifications in which Ca^{++} and P_i precipitate in arteries, soft tissues, and viscera. Deposition of Ca^{++} and P_i in the heart may cause myocardial failure. Prevention and treatment of hyperparathyroidism and P_i retention include a low-P_i diet and administration of a "phosphate binder" (i.e., an agent that forms insoluble P_i salts and thereby renders P_i unavailable for absorption from the GI tract) in the diet. Supplemental calcitriol is also prescribed to suppress PTH release.

by the proximal tubule. Secretion of FGF-23 is stimulated by sustained hyperphosphatemia, PTH, and calcitriol. Activating mutations in the *FGF23* gene cause hypophosphatemia, low plasma calcitriol, and rickets/osteomalacia, whereas inactivating mutations cause hyperphosphatemia, high calcitriol levels, and calcifications in the soft tissue.

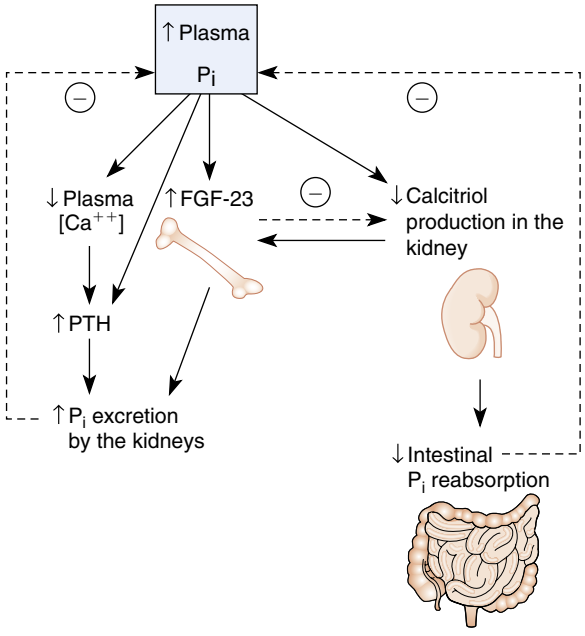
Regulation of Urinary Phosphate Excretion

Several hormones and factors regulate urinary P_i excretion (Table 36.3 and Fig. 36.19). Increased plasma $[P_i]$ reduces $[Ca^{++}]$ and therefore increases PTH levels, which increases renal P_i excretion. PTH inhibits P_i reabsorption by the proximal tubule and thereby increases P_i excretion. PTH reduces P_i reabsorption by stimulating endocytic removal of Na^+/P_i cotransporters from the brush border membrane in proximal tubular cells. Increased plasma $[P_i]$ also increases FGF-23, which inhibits P_i reabsorption and calcitriol production by the proximal tubule. Elevated plasma $[P_i]$ directly suppresses calcitriol production, which decreases intestinal P_i reabsorption. Dietary P_i intake also regulates P_i excretion by mechanisms unrelated to changes in PTH levels. P_i loading increases excretion, whereas P_i depletion decreases it. Changes in dietary P_i intake modulate P_i transport by altering the transport rate and the number of Na^+/P_i IIa and IIc cotransporters in the apical membrane of the proximal tubule.

TABLE 36.3 Summary of Hormones and Factors Affecting P_i Reabsorption by Proximal Tubule

Factor/Hormone	Proximal Tubule Reabsorption
PTH	Decrease
FGF-23	Decrease
Hyperphosphatemia	Decrease
Hypophosphatemia	Increase
Metabolic acidosis: chronic	Decrease
Metabolic alkalosis: chronic	Increase
ECF expansion	Decrease
Growth hormone	Increase
Glucocorticoids	Decrease

FGF-23, fibroblast growth factor 23; *PTH*, parathyroid hormone.



• **Fig. 36.19** Response to elevated plasma [P_i]. *FGF-23*, fibroblast growth factor 23; *PTH*, parathyroid hormone. *Dashed lines* indicate negative feedback. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)

ECF volume affects P_i excretion. ECF expansion enhances P_i excretion by: (1) increasing GFR and thus the filtered amount of P_i; (2) decreasing the Na^+/P_i-coupled reabsorption, which reduces ECF volume; and (3) reducing plasma [Ca^{++}], thereby increasing PTH, which inhibits P_i reabsorption in the proximal tubule. Acid-base balance also influences P_i excretion. Chronic acidemia increases P_i excretion, and chronic alkalemia decreases it. These effects of acid-base status, like the effect of PTH, are mediated by altered expression of the Na^+/P_i cotransporters in the apical membrane. Metabolic acidosis increases the secretion of glucocorticoids, which inhibit P_i reabsorption by the proximal tubule and increase renal P_i excretion. This inhibition, together with the direct effect of acidosis on P_i reabsorption by the proximal tubule, enables the DT and collecting duct to secrete more H^+ as titratable acid and to generate more HCO_3^- because P_i is an important urinary buffer. Growth hormone decreases P_i excretion.

IN THE CLINIC

Klotho is highly expressed in the early DT of the kidney. Klotho knockout mice have a phenotype that resembles chronic kidney disease (CKD), including soft tissue calcification, hyperphosphatemia, and elevated plasma FGF-23. Klotho exists as a membrane-bound and a soluble protein. The membrane-bound form is a coreceptor for FGF-23, thus Klotho promotes P_i excretion by the kidneys and reduces serum levels of calcitriol. Soluble circulating Klotho affects ion transport, Wnt signaling, and FGF-23-dependent PTH synthesis, and inhibits the renin-angiotensin axis. Klotho may be a biomarker for CKD, and its deficiency may contribute to development of CKD. Moreover, experimental data also suggest that Klotho therapy may slow the progression of CKD.

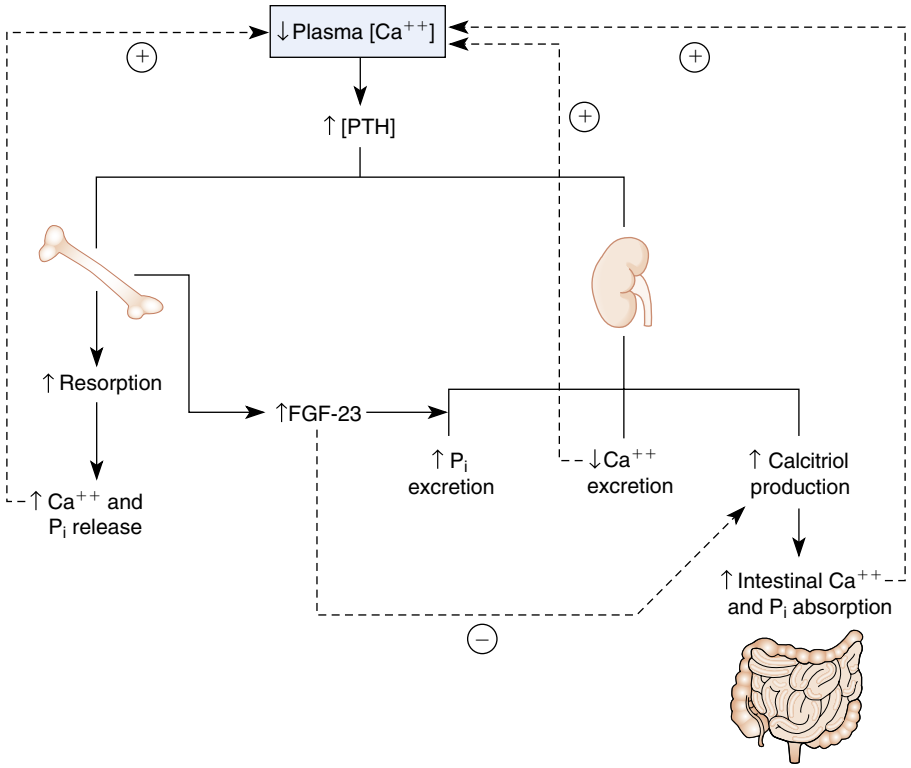
Integrative Review of Parathyroid Hormone and Calcitriol on Ca^{++} and P_i Homeostasis

As summarized in Fig. 36.20, PTH regulates Ca^{++} and P_i homeostasis. Hypocalcemia is the major stimulus of PTH secretion. PTH causes bone resorption, increases urinary P_i excretion, decreases urinary Ca^{++} excretion, and stimulates production of calcitriol, which stimulates intestinal Ca^{++} and P_i absorption. Because changes in P_i handling in bone, the GI tract, and kidneys tend to balance out, PTH increases plasma [Ca^{++}] while having little effect on plasma [P_i]. Overall, a rise in PTH levels in response to hypocalcemia returns plasma [Ca^{++}] to normal. Hypercalcemia has the opposite effect.

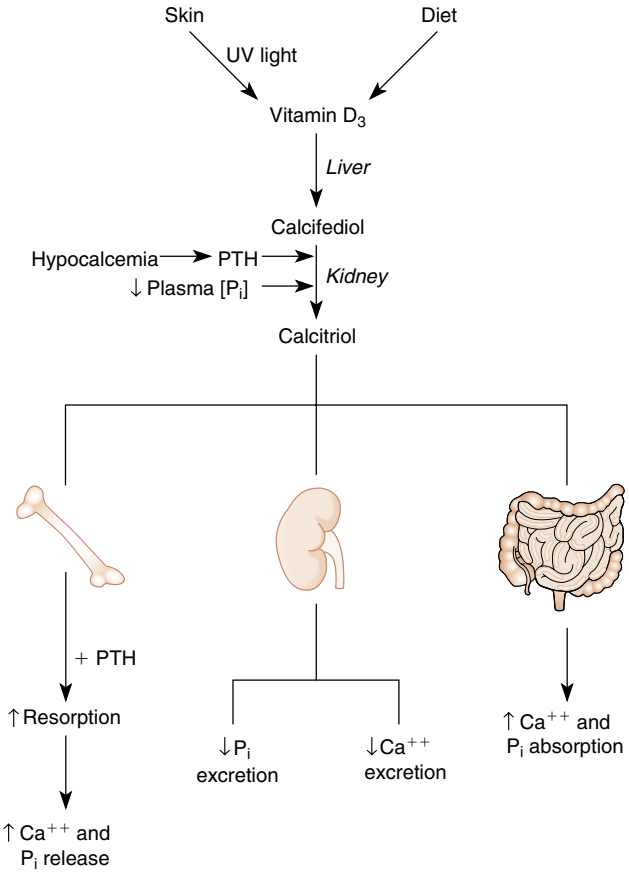
Calcitriol plays an important role in Ca^{++} and P_i homeostasis (Fig. 36.21). The net effect of calcitriol is to increase plasma [Ca^{++}] and [P_i]. Thus the major stimuli of calcitriol production are hypocalcemia and hypophosphatemia. The primary action of calcitriol is to stimulate Ca^{++} and P_i absorption from the GI tract. To a lesser degree, calcitriol acts with PTH to decrease renal Ca^{++} excretion. Calcitriol may enhance the bone resorptive effect of PTH to release Ca^{++} and P_i from bone during a Ca^{++} deficient diet.

IN THE CLINIC

In the absence of glucocorticoids (e.g., in **Addison's disease**), excretion of P_i is depressed, as is the ability of the kidneys to excrete titratable acid and to generate new HCO_3^-. Growth hormone increases reabsorption of P_i by the proximal tubule. As a result, children are in positive P_i balance and have a higher plasma [P_i] than adults, and the elevated [P_i] is important for bone formation and growth.



• **Fig. 36.20** Response to decreased plasma [Ca^{++}]. *Dashed lines* indicate negative feedback. *FGF-23*, fibroblast growth factor 23; *PTH*, parathyroid hormone. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)



• **Fig. 36.21** Vitamin D metabolism and effects on Ca^{++} and P_i homeostasis. Hypocalcemia (via PTH) and hypophosphatemia are the major stimuli of the metabolism of calcifediol to calcitriol in the kidneys. The net effect of calcitriol is to increase plasma [Ca^{++}] and [P_i]. *PTH*, parathyroid hormone. (From Koeppen BM, Stanton BA. *Renal Physiology.* 5th ed. Philadelphia: Elsevier; 2013.)

Key Concepts

1. K^+ homeostasis is maintained by the kidneys, which adjust K^+ excretion to match dietary K^+ intake, and by insulin, epinephrine, aldosterone, AVP, and glucocorticoids, which regulate the distribution of K^+ between the ICF and ECF and the renal K^+ excretion. Other conditions, such as cell lysis, exercise, changes in acid-base balance and plasma osmolality, affect K^+ homeostasis and plasma $[K^+]$.
2. Excretion of K^+ by the kidneys is determined by the rate and direction of K^+ transport by the DT and CCD. Secretion of K^+ by these tubular segments is regulated by plasma $[K^+]$, aldosterone, and AVP. Changes in tubular fluid flow and acid-base balance alter K^+ excretion by the kidneys. In K^+-depleted states, K^+ secretion is inhibited and its reabsorption increased by the DT and CCD.
3. The kidneys, in conjunction with the GI tract and bone, regulate plasma $[Ca^{++}]$ and $[P_i]$.
4. Plasma $[Ca^{++}]$ is regulated by PTH and calcitriol. Calcitonin is not a major regulatory hormone in humans. Ca^{++} excretion by the kidneys is regulated by PTH, plasma $[Ca^{++}]$, and calcitriol and is altered by changes in acid-base status, ECF volume, and plasma P_i.
5. Ca^{++} reabsorption is stimulated by PTH and calcitriol acting in the TAL and DT, and by elevated plasma $[Ca^{++}]$.
6. Plasma $[P_i]$ is regulated by PTH, FGF-23, and calcitriol. P_i excretion is regulated by PTH, FGF-23, dietary P_i, and growth hormone and is altered by acid-base dysregulation, ECF expansion, and glucocorticoids.