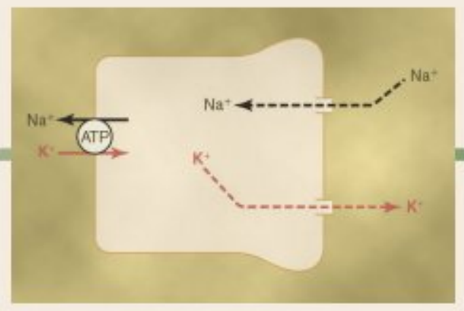

CHAPTER 30

Renal Regulation of Potassium, Calcium, Phosphate, and Magnesium; Integration of Renal Mechanisms for Control of Blood Volume and Extracellular Fluid Volume

REGULATION OF EXTRACELLULAR FLUID POTASSIUM CONCENTRATION AND POTASSIUM EXCRETION

The extracellular fluid potassium concentration normally is regulated at about 4.2 mEq/L, seldom rising or falling more than ±0.3 mEq/L. This precise control is necessary because many cell functions are sensitive to changes in extracellular fluid potassium concentration. For example, an increase in plasma potassium concentration of only 3 to 4 mEq/L can cause cardiac arrhythmias, and higher concentrations can lead to cardiac arrest or fibrillation.

A special difficulty in regulating extracellular potassium concentration is the fact that more than 98% of the total body potassium is contained in the cells, and only 2% is contained in the extracellular fluid (**Figure 30-1**). For a 70-kg adult, who has about 28 liters of intracellular fluid (40% of body weight) and 14 liters of extracellular fluid (20% of body weight), about 3920 mEq of potassium are inside the cells, and only about 59 mEq are in the extracellular fluid. Also, the potassium contained in a single meal may be as high as 50 mEq, and the daily intake usually ranges between 50 and 200 mEq/day; therefore, failure to rapidly rid the extracellular fluid of the ingested potassium could cause life-threatening *hyperkalemia* (increased plasma potassium concentration). Likewise, a small loss of potassium from the extracellular fluid could cause severe *hypokalemia* (low plasma potassium concentration) in the absence of rapid and appropriate compensatory responses.

Maintenance of a balance between intake and output of potassium depends primarily on excretion by the kidneys because the amount excreted in the feces is only about 5% to 10% of the potassium intake. Thus, the maintenance of a normal potassium balance requires the kidneys to adjust their potassium excretion rapidly and precisely in response to wide variations in intake, as is also true for most other electrolytes.

Control of potassium distribution between the extracellular and intracellular compartments also plays an important role in potassium homeostasis. Because more than 98% of the total body potassium is contained in the cells, they can serve as an overflow site for excess extracellular fluid potassium during hyperkalemia or as a source of potassium during hypokalemia. Thus, redistribution of potassium between the intracellular and extracellular fluid compartments provides a first line of defense against changes in extracellular fluid potassium concentration.

REGULATION OF INTERNAL POTASSIUM DISTRIBUTION

After ingestion of a potassium-rich meal, extracellular fluid potassium concentration would rise to a dangerous level if the ingested potassium did not move into the cells rapidly. For example, absorption of 40 mEq of potassium (the amount contained in a meal rich in vegetables and fruit) into an extracellular fluid volume of 14 liters would raise plasma potassium concentration by about 2.9 mEq/L if all the potassium remained in the extracellular compartment. Fortunately, most of the ingested potassium rapidly moves into the cells until the kidneys can eliminate the excess. Between meals, plasma potassium concentration also remains nearly constant as potassium

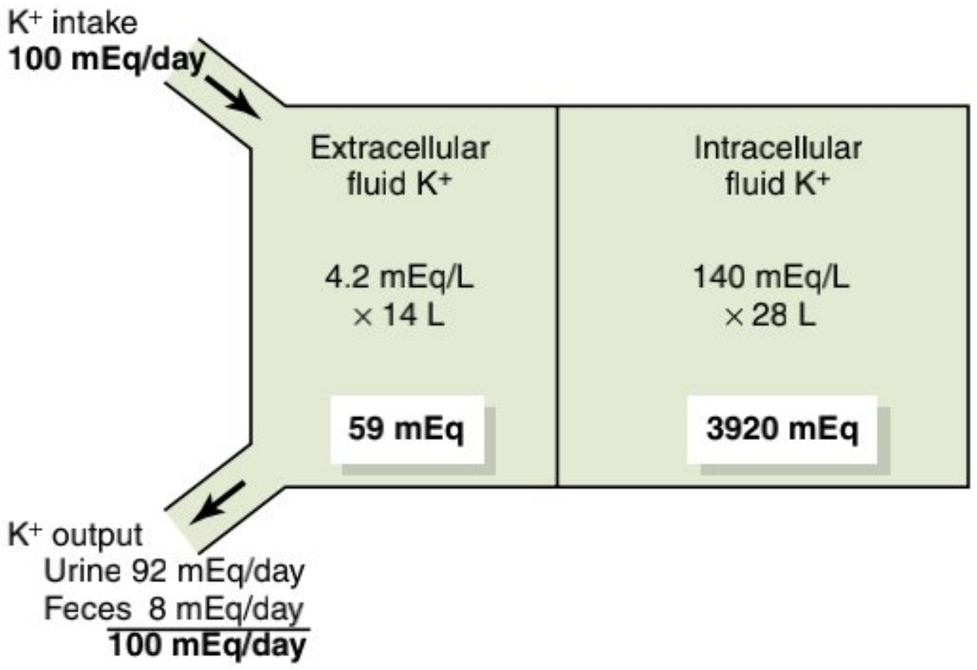

Figure 30-1. Normal potassium intake, distribution of potassium in the body fluids, and potassium output from the body.

Table 30-1 Factors That Can Alter Potassium Distribution Between Intracellular and Extracellular Fluids

Factors That Shift K^+ Into Cells (Decrease Extracellular $[K^+]$)	Factors That Shift K^+ Out of Cells (Increase Extracellular $[K^+]$)
Insulin	Insulin deficiency (diabetes mellitus)
Aldosterone	Aldosterone deficiency (Addison disease)
β-Adrenergic stimulation	β-Adrenergic blockade
Alkalosis	Acidosis Cell lysis Strenuous exercise Increased extracellular fluid osmolarity

is released by the cells to balance the extracellular fluid potassium excreted by the kidneys. Table 30-1 summarizes some of the factors that can influence the distribution of potassium between the intracellular and extracellular compartments.

Insulin Stimulates Potassium Uptake Into Cells. Insulin stimulates sodium-potassium adenosine triphosphatase (ATPase) activity in many tissues, including skeletal muscle, which in turn transports potassium into the cells. Insulin is important for increasing cell potassium uptake after a meal. In people who have insulin-deficient diabetes mellitus, the rise in plasma potassium concentration after eating a meal is much greater than normal. Injections of insulin, however, can help correct the hyperkalemia.

Aldosterone Increases Potassium Uptake Into Cells. Increased potassium intake also stimulates secretion of aldosterone, which increases cell potassium uptake. Excess aldosterone secretion (*Conn syndrome*) is almost invariably associated with hypokalemia, due in part to movement of extracellular potassium into the cells. Conversely, patients with deficient aldosterone production (*Addison disease*) often have clinically significant hyperkalemia due to accumulation of potassium in the extracellular space, as well as renal retention of potassium.

β-Adrenergic Stimulation Increases Cellular Uptake of Potassium. Increased secretion of catecholamines, especially epinephrine, can cause movement of potassium from the extracellular to the intracellular fluid, mainly by activation of β_2-adrenergic receptors. Conversely, treatment of hypertension with β-adrenergic receptor blockers, such as propranolol, causes potassium to move out of the cells and creates a tendency toward hyperkalemia.

Acid–Base Abnormalities Can Cause Changes in Potassium Distribution. Metabolic acidosis increases extracellular potassium concentration, in part by causing loss of potassium from the cells, whereas metabolic alkalosis decreases extracellular fluid potassium concentration. Although the mechanisms responsible for the effect of hydrogen ion concentration on internal distribution of potassium are not completely understood, one effect of increased hydrogen ion concentration is to reduce activity of the Na^+-K^+ ATPase pump. This reduction, in turn, decreases cellular uptake of potassium and raises extracellular potassium concentration. Alkalosis has the opposite effect, shifting potassium from the extracellular fluid into the cells and tending to cause hypokalemia.

Cell Lysis Causes Increased Extracellular Potassium Concentration. As cells are destroyed, the large amounts of potassium contained in the cells are released into the extracellular fluid. This release of potassium can cause significant hyperkalemia if large amounts of tissue are destroyed, as occurs with severe muscle injury or with red blood cell lysis.

Strenuous Exercise Can Cause Hyperkalemia by Releasing Potassium From Skeletal Muscle. During prolonged exercise, potassium is released from skeletal muscle into the extracellular fluid. Usually the hyperkalemia is mild, but it may be clinically significant after heavy exercise, especially in patients treated with β-adrenergic blockers or in individuals with insulin deficiency. In rare cases, hyperkalemia after exercise may be severe enough to cause cardiac toxicity.

Increased Extracellular Fluid Osmolarity Causes Redistribution of Potassium From Cells to Extracellular Fluid. Increased extracellular fluid osmolarity causes osmotic flow of water out of the cells. The cellular dehydration increases intracellular potassium concentration, thereby promoting diffusion of potassium out of the cells and increasing extracellular fluid potassium concentration. Decreased extracellular fluid osmolarity has the opposite effect.

OVERVIEW OF RENAL POTASSIUM EXCRETION

Renal potassium excretion is determined by the sum of three processes: (1) the rate of potassium filtration (glomerular filtration rate [GFR] multiplied by the plasma potassium concentration); (2) the rate of potassium reabsorption by the tubules; and (3) the rate of potassium secretion by the tubules. The normal rate of potassium filtration by the glomerular capillaries is about 756 mEq/day (GFR, 180 L/day, multiplied by plasma potassium concentration, 4.2 mEq/L). This rate of filtration is relatively

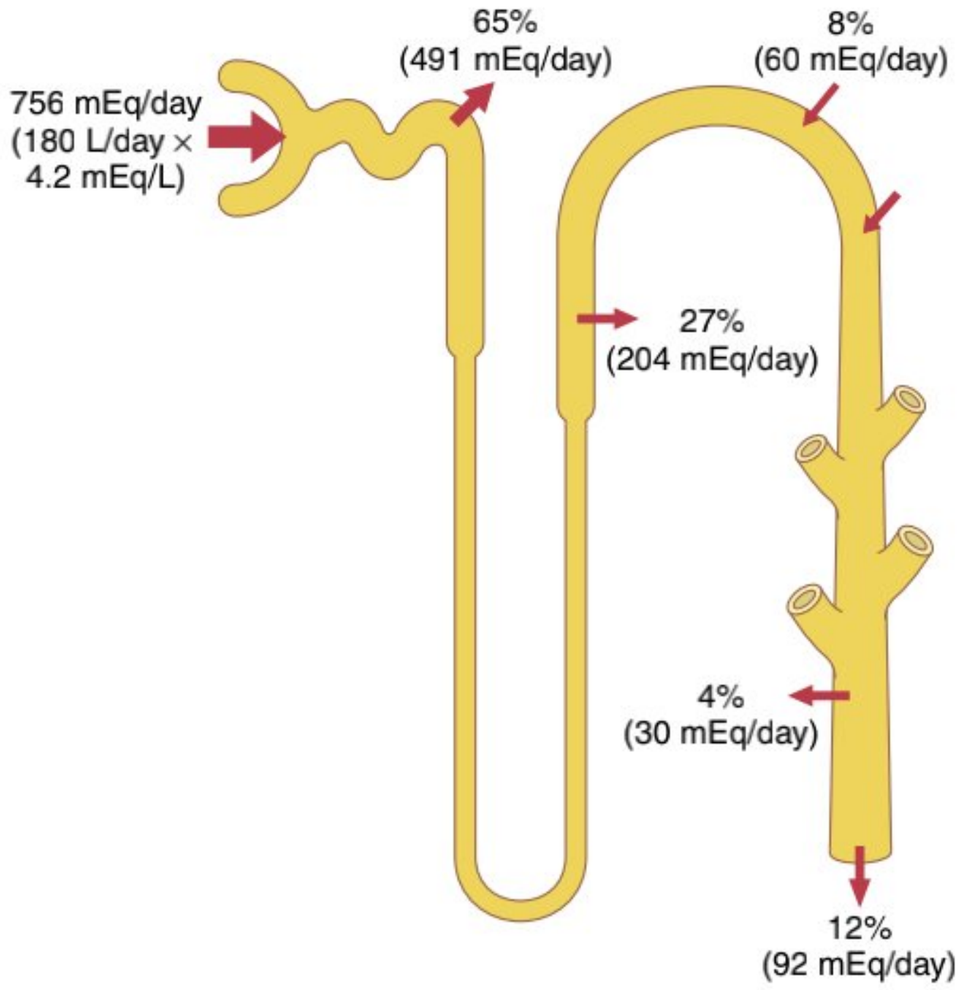

Figure 30-2. Renal tubular sites of potassium reabsorption and secretion. Potassium is reabsorbed in the proximal tubule and ascending loop of Henle, so only about 8% of the filtered load is delivered to the distal tubule. Secretion of potassium by the principal cells of the late distal tubules and collecting ducts adds to the amount delivered, but there is some additional reabsorption by the intercalated cells; therefore, the daily excretion is about 12% of the potassium filtered at the glomerular capillaries. The percentages indicate how much of the filtered load is reabsorbed or secreted into the different tubular segments.

constant in healthy persons because of the autoregulatory mechanisms for GFR discussed previously and the precision with which plasma potassium concentration is regulated. Severe decreases in GFR in certain renal diseases, however, can cause serious potassium accumulation and hyperkalemia.

Figure 30-2 summarizes the tubular handling of potassium under normal conditions. About 65% of the filtered potassium is reabsorbed in the proximal tubule. Another 25% to 30% of the filtered potassium is reabsorbed in the loop of Henle, especially in the thick ascending part, where potassium is actively co-transported along with sodium and chloride. In the proximal tubule and loop of Henle, a relatively constant fraction of the filtered potassium load is reabsorbed. Changes in potassium reabsorption in these segments can influence potassium excretion, but most of the daily variation of potassium excretion is not due to changes in reabsorption in the proximal tubule or loop of Henle. The collecting tubules and collecting ducts reabsorb potassium at variable rates, depending on the potassium intake.

Variable Potassium Secretion in Distal and Collecting Tubules Mediates Most Daily Changes in Potassium Excretion. The most important sites for regulating potassium excretion are the principal cells of the late distal tubules and cortical collecting tubules. In these tubular segments, potassium can at times be reabsorbed or at other times can be secreted, depending on the needs of the body. With a normal potassium intake of 100 mEq/day, the kidneys must excrete about 92 mEq/day (the remaining 8 mEq are lost in the feces). About 60 mEq/day of potassium are secreted into the distal and collecting tubules, accounting for most of the excreted potassium.

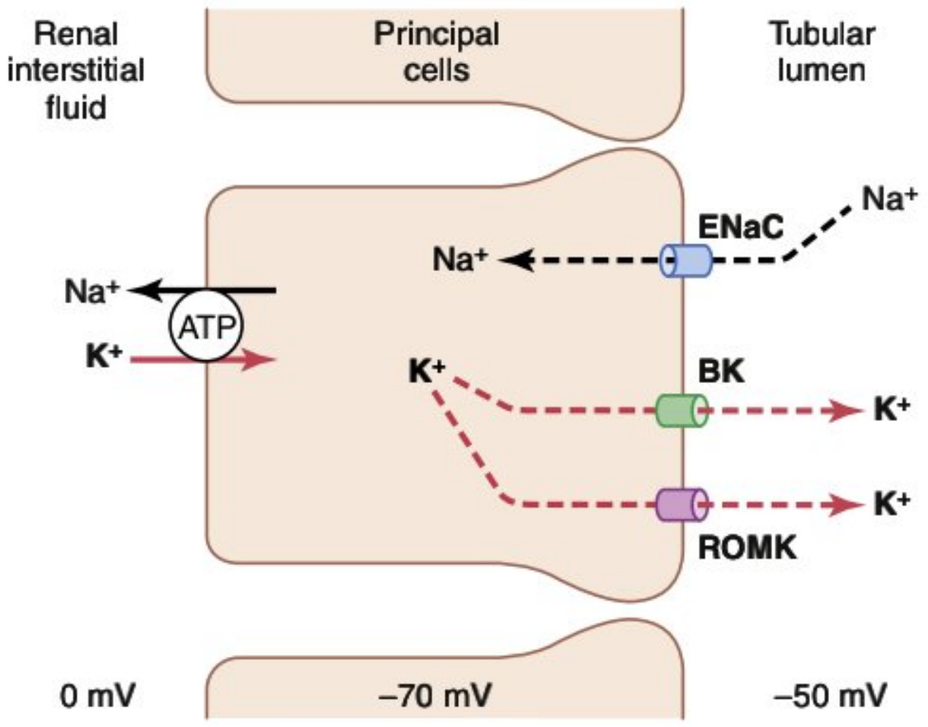

Figure 30-3. Mechanisms of potassium secretion and sodium reabsorption by the principal cells of the late distal and collecting tubules. BK, "big" potassium channel; ENaC, epithelial sodium channel; ROMK, renal outer medullary potassium channel.

With a high potassium intake, the required extra excretion of potassium is achieved almost entirely by increasing the secretion of potassium into the distal and collecting tubules. In fact, in those who consume extremely high-potassium diets, the rate of potassium excretion can exceed the amount of potassium in the glomerular filtrate, indicating a powerful mechanism for secreting potassium.

When potassium intake is low, secretion of potassium in the distal and collecting tubules decreases, causing a reduction in urinary potassium excretion. There is also increased reabsorption of potassium by the intercalated cells in the distal segments of the nephron, and potassium excretion can fall to less than 1% of the potassium in the glomerular filtrate (to <10 mEq/day). With potassium intakes below this level, severe hypokalemia can develop.

Thus, most of the daily regulation of potassium excretion occurs in the late distal and cortical collecting tubules, where potassium can be reabsorbed or secreted, depending on the needs of the body. In the next section, we consider the basic mechanisms of potassium secretion and the factors that regulate this process.

PRINCIPAL CELLS OF LATE DISTAL AND CORTICAL COLLECTING TUBULES SECRETE POTASSIUM

The cells in the late distal and cortical collecting tubules that secrete potassium are called *principal cells* and make up most of the epithelial cells in these regions. Figure 30-3 shows the basic cellular mechanisms of potassium secretion by the principal cells.

Secretion of potassium from the blood into the tubular lumen is a two-step process, beginning with uptake from the interstitium into the cell by the Na^+-K^+ ATPase pump in the basolateral cell membrane. This pump moves sodium out of the cell into the interstitium and, at the same time, moves potassium to the interior of the cell.

The second step of the process is passive diffusion of potassium from the interior of the cell into the tubular fluid. The Na^+-K^+ ATPase pump creates a high intracellular potassium concentration, which provides the driving force for passive diffusion of potassium from the cell into the tubular lumen. The luminal membrane of the principal cells is highly permeable to potassium because there are two types of special channels that allow potassium ions to diffuse across the membrane rapidly: (1) the *renal outer medullary potassium* (ROMK) *channels*, and (2) high-conductance, *"big" potassium* (BK) *channels*. Both types of potassium channels are required for efficient renal potassium excretion, and their abundance in the luminal membrane is increased during high potassium intake.

Control of Potassium Secretion by Principal Cells. The primary factors that control potassium secretion by the principal cells of the late distal and cortical collecting tubules are the following: (1) the activity of the Na^+-K^+ ATPase pump; (2) the electrochemical gradient for potassium secretion from the blood to the tubular lumen; and (3) the permeability of the luminal membrane for potassium. These three determinants of potassium secretion are, in turn, regulated by several factors, discussed later.

Intercalated Cells Can Reabsorb or Secrete Potassium. In circumstances associated with severe potassium depletion, there is a cessation of potassium secretion and a net reabsorption of potassium in the late distal and collecting tubules. This reabsorption occurs through the *type A intercalated cells*. Although this reabsorptive process is not completely understood, one mechanism believed to contribute is a *hydrogen-potassium ATPase* transport mechanism located in the luminal membrane (see Chapter 28, **Figure 28-13**). This transporter reabsorbs potassium in exchange for hydrogen ions secreted into the tubular lumen, and the potassium then diffuses through basolateral membrane potassium channels into the interstitial fluid. This abundance of intercalated cell hydrogen-potassium ATPase transporters is enhanced with potassium depletion and hypokalemia, causing increased hydrogen ion secretion and alkalosis. Under normal conditions, however, potassium reabsorption by intercalated cells plays only a small role in controlling potassium excretion.

When there is excess potassium in the body fluids, *type B intercalated cells* in the late distal tubules and collecting tubules actively secrete potassium into the tubular lumen and have functions that are opposite to those of type A cells (see Chapter 28, **Figure 28-13**). Potassium is pumped into the type B intercalated cell by a hydrogen-potassium ATPase transporter on the basolateral membrane, and it then diffuses into the tubular lumen through potassium channels.

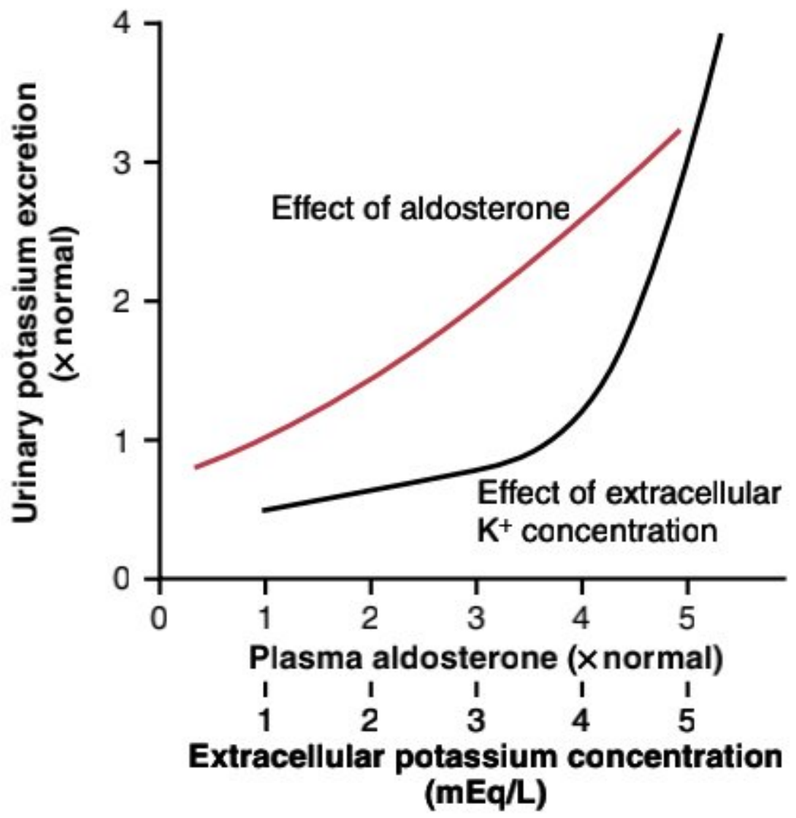

Figure 30-4. Effect of plasma aldosterone concentration (*red line*) and extracellular potassium ion concentration (*black line*) on the rate of urinary potassium excretion. These factors stimulate potassium secretion by the principal cells of the cortical collecting tubules. *(Data from Young DB, Paulsen AW: Interrelated effects of aldosterone and plasma potassium on potassium excretion. Am J Physiol 244:F28, 1983.)*

SUMMARY OF MAJOR FACTORS THAT REGULATE POTASSIUM SECRETION

Because the normal regulation of potassium excretion occurs mainly as a result of changes in potassium secretion by the principal cells of the late distal and collecting tubules, in this chapter we discuss the primary factors that influence secretion by these cells. The most important factors that *stimulate* potassium secretion by the principal cells include the following: (1) increased extracellular fluid potassium concentration; (2) increased aldosterone; and (3) increased tubular flow rate.

One factor that *decreases* potassium secretion is an increased hydrogen ion concentration (acidosis).

Increased Extracellular Fluid Potassium Concentration Stimulates Potassium Secretion. The rate of potassium secretion in the late distal and cortical collecting tubules is directly stimulated by increased extracellular fluid potassium concentration, leading to increases in potassium excretion, as shown in **Figure 30-4**. This effect is especially pronounced when extracellular fluid potassium concentration rises above about 4.1 mEq/L, slightly less than the normal concentration. Increased plasma potassium concentration, therefore, serves as one of the most important mechanisms for increasing potassium secretion and regulating extracellular fluid potassium ion concentration.

Increased dietary potassium intake and increased extracellular fluid potassium concentration stimulate potassium secretion by at least four mechanisms:

1. Increased extracellular fluid potassium concentration stimulates the Na^+-K^+ ATPase pump, thereby increasing potassium uptake across the basolateral membrane. This increased potassium uptake in turn increases intracellular potassium ion concentration, causing potassium to diffuse across the luminal membrane into the tubule.
2. Increased extracellular potassium concentration increases the potassium gradient from the renal interstitial fluid to the interior of the epithelial cell, which reduces backleakage of potassium ions from inside the cells through the basolateral membrane.
3. Increased potassium intake stimulates synthesis of potassium channels and their translocation from the cytosol to the luminal membrane, which, in turn, increases the ease of potassium diffusion through the membrane.
4. Increased potassium concentration stimulates aldosterone secretion by the adrenal cortex, which further stimulates potassium secretion, as discussed next.

Aldosterone Stimulates Potassium Secretion. Aldosterone stimulates active reabsorption of sodium ions by the principal cells of the late distal tubules and collecting ducts (see Chapter 28). This effect is mediated through a Na^+-K^+ ATPase pump that transports sodium outward through the basolateral membrane of the cell and into the renal interstitial fluid at the same time that it pumps potassium into the cell. Thus, aldosterone also has a powerful effect on controlling the rate at which the principal cells secrete potassium and reabsorb sodium.

A second effect of aldosterone is to increase the number of potassium channels in the luminal membrane and therefore its permeability for potassium, further adding to the effectiveness of aldosterone in stimulating potassium secretion. Therefore, aldosterone has a powerful effect to increase potassium excretion, as shown in **Figure 30-4.**

Increased Extracellular Potassium Ion Concentration Stimulates Aldosterone Secretion. In negative feedback control systems, the factor that is controlled usually has a feedback effect on the controller. In the case of the aldosterone-potassium control system, the rate of aldosterone secretion by the adrenal gland is controlled strongly by extracellular fluid potassium ion concentration. **Figure 30-5** shows that an increase in plasma potassium concentration of about 3 mEq/L can increase the plasma aldosterone concentration from nearly 0 to as high as 60 ng/100 ml, a concentration almost 10 times normal.

The effect of potassium ion concentration to stimulate aldosterone secretion is part of a powerful feedback system for regulating potassium excretion, as shown

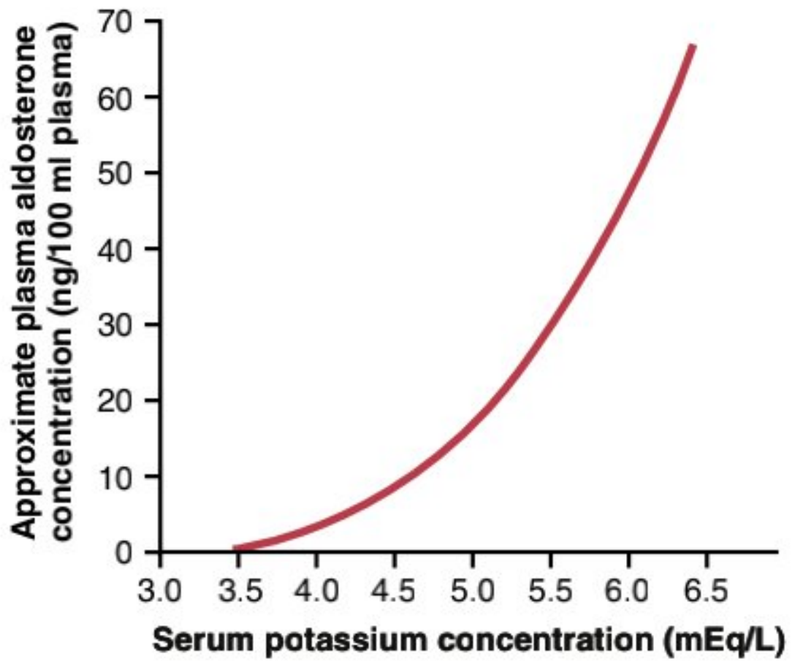

Figure 30-5. Effect of extracellular fluid potassium ion concentration on plasma aldosterone concentration. Note that small changes in potassium concentration cause large changes in aldosterone concentration.

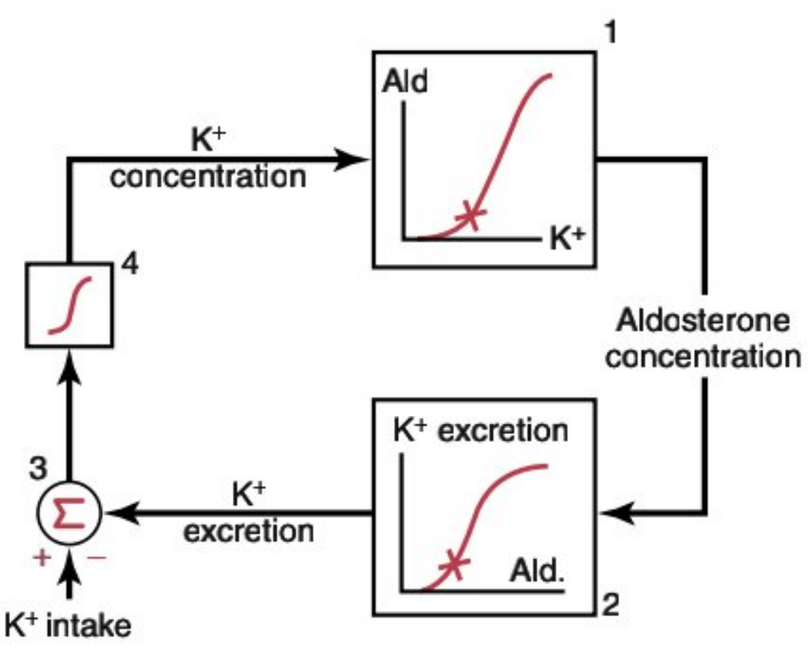

Figure 30-6. Basic feedback mechanism for control of extracellular fluid potassium concentration by aldosterone (*Ald*).

in **Figure 30-6**. In this feedback system, an increase in plasma potassium concentration stimulates aldosterone secretion and, therefore, increases plasma aldosterone concentration (block 1). The increase in plasma aldosterone then causes a marked increase in potassium excretion by the kidneys (block 2). The increased potassium excretion then reduces the extracellular fluid potassium concentration back toward normal (circle 3 and block 4). Thus, this feedback mechanism acts synergistically, with the direct effect of increased extracellular potassium concentration to elevate potassium excretion when potassium intake is raised (**Figure 30-7**).

Blockade of Aldosterone Feedback System Greatly Impairs Potassium Regulation. In the absence of aldosterone secretion, as occurs in patients with Addison disease, renal secretion of potassium is impaired, thus causing the extracellular fluid potassium concentration to rise to dangerously high levels. Conversely, with excess aldosterone secretion (primary aldosteronism), potassium secretion becomes greatly increased, causing potassium loss by the kidneys, thus leading to hypokalemia.

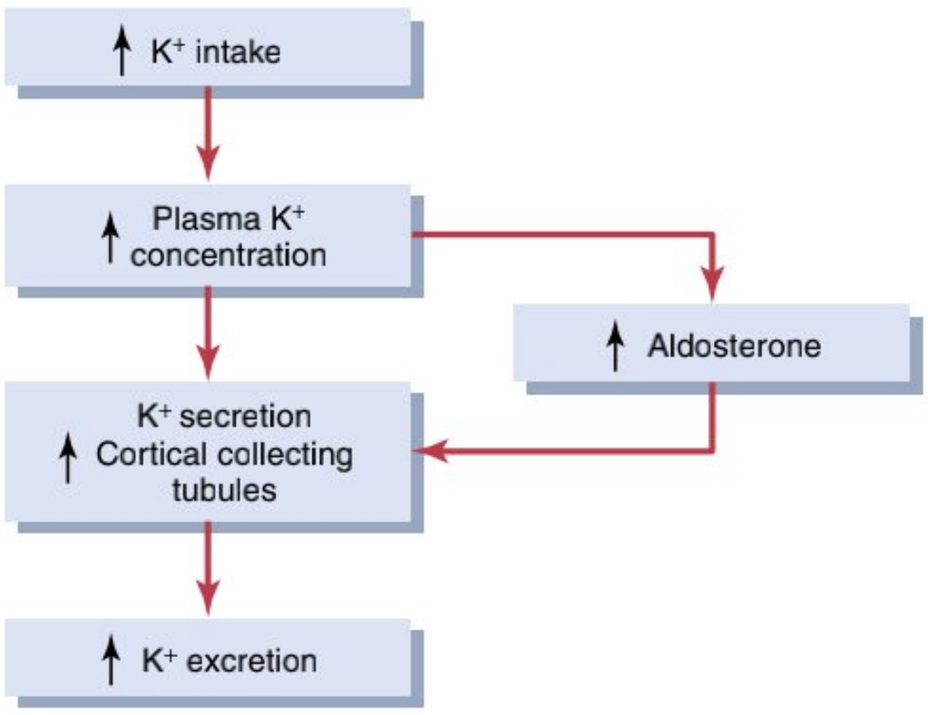

Figure 30-7. Primary mechanisms whereby high potassium intake raises potassium excretion. Note that increased plasma potassium concentration directly raises potassium secretion by the cortical collecting tubules and indirectly increases potassium secretion by raising plasma aldosterone concentration.

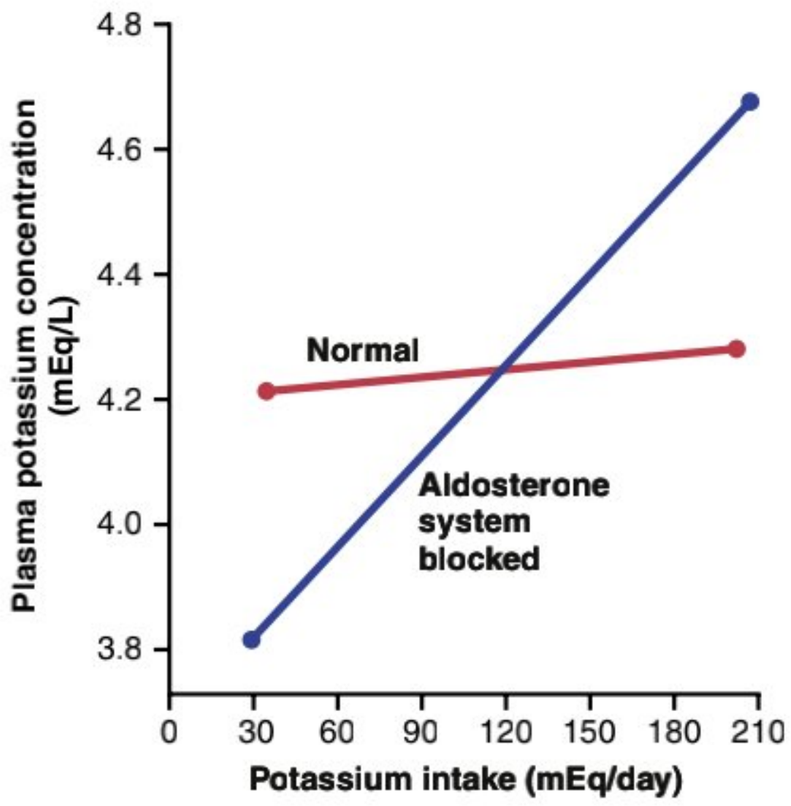

Figure 30-8. Effect of large changes in potassium intake on plasma potassium concentration under normal conditions (*red line*) and after the aldosterone feedback was blocked (*blue line*). Note that after blockade of the aldosterone system, regulation of potassium concentration was greatly impaired. *(Courtesy Dr. David B. Young.)*

In addition to its stimulatory effect on renal secretion of potassium, aldosterone also increases cellular uptake of potassium. This contributes to the powerful aldosterone-potassium feedback system, as discussed previously.

The special quantitative importance of the aldosterone feedback system in controlling potassium concentration is shown in **Figure 30-8**. In this experiment, potassium intake was increased almost sevenfold in dogs under two conditions: (1) under normal conditions; and (2) after the aldosterone feedback system had been blocked by removing the adrenal glands and placing the animals on a fixed rate of aldosterone infusion, so that plasma aldosterone concentration was maintained at a normal level but could neither increase nor decrease as potassium intake was altered.

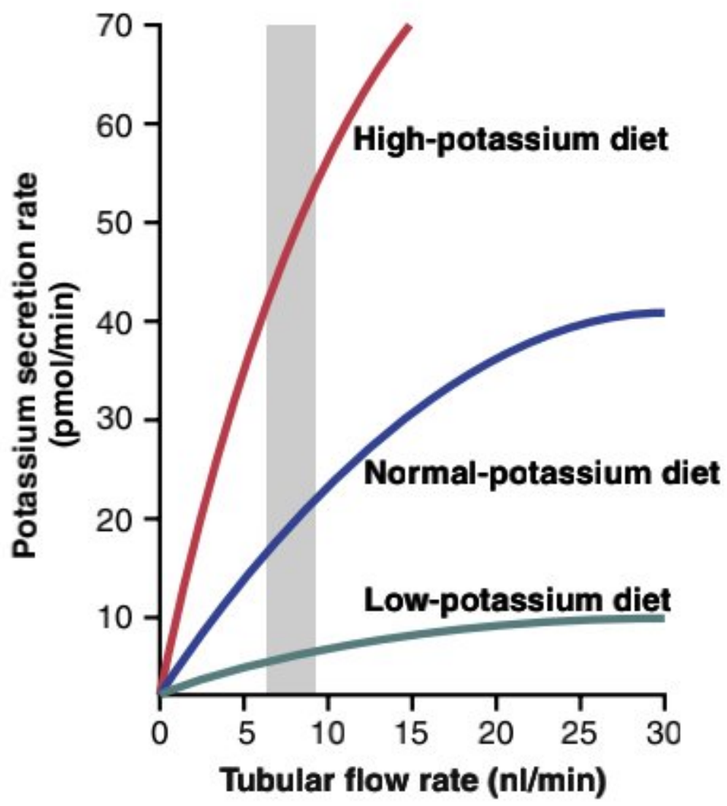

Figure 30-9. Relationship between flow rate in the cortical collecting tubules and potassium secretion and the effect of changes in potassium intake. Note that a high dietary potassium intake greatly enhances the effect of increased tubular flow rate to increase potassium secretion. The *shaded bar* shows the approximate normal tubular flow rate under most physiological conditions. *(Data from Malnic G, Berliner RW, Giebisch G: Flow dependence of K+ secretion in cortical distal tubes of the rat. Am J Physiol 256:F932, 1989.)*

Note that in the normal animals, a sevenfold increase in potassium intake caused only a slight increase in plasma potassium concentration, from 4.2 to 4.3 mEq/L. Thus, when the aldosterone feedback system is functioning normally, potassium concentration is precisely controlled, despite large changes in potassium intake.

When the aldosterone feedback system was blocked, the same increases in potassium intake caused a much larger increase in plasma potassium concentration, from 3.8 to almost 4.7 mEq/L. Thus, control of potassium concentration is greatly impaired when the aldosterone feedback system is blocked. A similar impairment of potassium regulation is observed in people with poorly functioning aldosterone feedback systems, such as occurs in patients with primary aldosteronism (too much aldosterone) or Addison disease (too little aldosterone).

Increased Distal Tubular Flow Rate Stimulates Potassium Secretion. A rise in distal tubular flow rate, as occurs with volume expansion, high sodium intake, or treatment with some diuretics, stimulates potassium secretion (**Figure 30-9**). Conversely, a decrease in distal tubular flow rate, as caused by sodium depletion, reduces potassium secretion.

The effect of the tubular flow rate on potassium secretion in the distal and collecting tubules is strongly influenced by potassium intake. When potassium intake is high, increased tubular flow rate has a much greater effect to stimulate potassium secretion than when potassium intake is low (see **Figure 30-9**).

There are two main effects of a high-volume flow rate that increase potassium secretion:

1. When potassium is secreted into the tubular fluid, the luminal concentration of potassium increases,

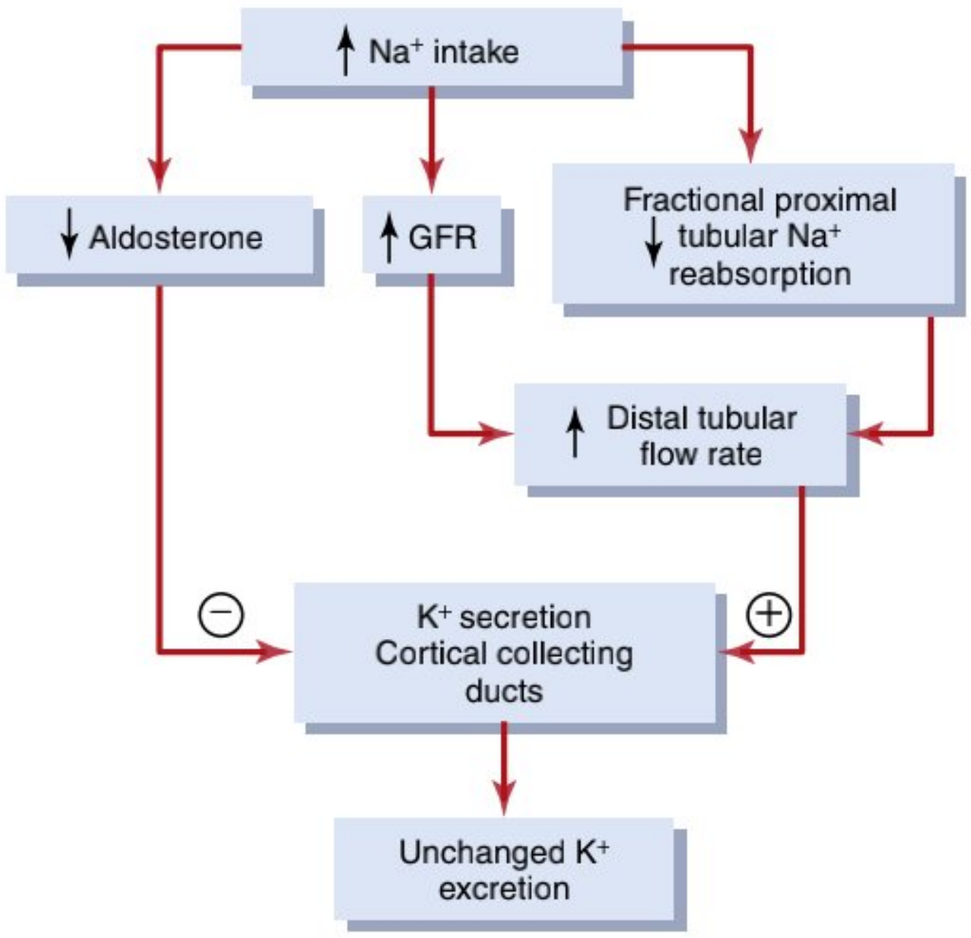

Figure 30-10. Effect of high sodium intake on renal excretion of potassium. Note that a high-sodium diet decreases plasma aldosterone, which tends to decrease potassium secretion by the cortical collecting tubules. However, the high-sodium diet simultaneously increases fluid delivery to the cortical collecting duct, which tends to increase potassium secretion. The opposing effects of a high-sodium diet counterbalance each other, so there is little change in potassium excretion. GFR, Glomerular filtration rate.

thereby reducing the driving force for potassium diffusion across the luminal membrane. With increased tubular flow rate, the secreted potassium is continuously flushed down the tubule, minimizing the rise in tubular potassium concentration and increasing net potassium secretion.

2. A high tubular flow rate also increases the number of high-conductance BK channels in the luminal membrane. Although the BK channels are normally quiescent, they become active in response to increases in flow rate, thereby greatly increasing potassium conductance across the luminal membrane.

The effect of increased tubular flow rate is especially important in helping preserve normal potassium excretion during changes in sodium intake. For example, with a high sodium intake, there is decreased aldosterone secretion, which by itself would tend to decrease the rate of potassium secretion and, therefore, reduce urinary excretion of potassium. However, the high distal tubular flow rate that occurs with a high sodium intake tends to increase potassium secretion (**Figure 30-10**). Therefore, the two effects of a high sodium intake—decreased aldosterone secretion and high tubular flow rate—counterbalance each other, so there is little change in potassium excretion. Likewise, with a low sodium intake, there is little change in potassium excretion because of the counterbalancing effects of increased aldosterone secretion and decreased tubular flow rate on potassium secretion.

Acute Acidosis Decreases Potassium Secretion. Acute increases in extracellular fluid hydrogen ion concentration (acidosis) reduce potassium secretion, whereas decreased hydrogen ion concentration (alkalosis) increases potassium secretion. The primary mechanism whereby increased hydrogen ion concentration inhibits potassium secretion is by reducing activity of the Na^+-K^+ ATPase pump. This reduction in turn decreases intracellular potassium concentration and subsequent passive diffusion of potassium across the luminal membrane into the tubule. Acidosis may also reduce the number of potassium channels in the luminal membrane.

With more prolonged acidosis, lasting over a period of several days, there is an increase in urinary potassium excretion. The mechanism for this effect is due in part to an effect of chronic acidosis to inhibit proximal tubular sodium chloride and water reabsorption, which increases distal volume delivery, thereby stimulating potassium secretion. This effect overrides the inhibitory effect of hydrogen ions on the Na^+-K^+ ATPase pump. *Thus, chronic acidosis leads to a loss of potassium, whereas acute acidosis leads to decreased potassium excretion.*

Beneficial Effects of Diet High in Potassium and Low in Sodium Content

For most of human history, the typical diet has been one that is low in sodium and high in potassium content, compared with the typical modern diet. In isolated populations that have not experienced industrialization, such as the Yanomamo tribe living in the Amazon region of Northern Brazil, sodium intake may be as low as 10 to 20 mmol/day, and potassium intake may be as high as 200 mmol/day. This intake is due to their consumption of a diet containing large amounts of fruits and vegetables and no processed foods. Populations consuming this type of diet typically do not experience age-related increases in blood pressure and cardiovascular diseases.

With industrialization and increased consumption of processed foods, which often have high sodium and low potassium content, there have been dramatic increases in sodium intake and decreases in potassium intake. In most industrialized countries, potassium consumption averages only 30 to 70 mmol/day, and sodium intake averages 140 to 180 mmol/day.

Experimental and clinical studies have shown that the combination of a high-sodium and low-potassium diet increases the risk for hypertension and associated cardiovascular and kidney diseases. A diet rich in potassium, however, seems to protect against the adverse effects of a high-sodium diet, reducing blood pressure and the risk for stroke, coronary artery disease, and kidney disease. The beneficial effects of increasing potassium intake are especially apparent when combined with a low-sodium diet.

Dietary guidelines published by various organizations have recommended reducing the dietary intake of sodium chloride to about 65 to 100 mmol/day (corresponding to 1.5–2.3 g/day of sodium or 3.8–5.8 g/day sodium chloride) while increasing potassium intake to 120 mmol/day (4.7 g/day) for healthy adults.

REGULATION OF RENAL CALCIUM EXCRETION AND EXTRACELLULAR CALCIUM ION CONCENTRATION

The mechanisms for regulating calcium ion concentration are discussed in detail in Chapter 80, along with the endocrinology of the calcium-regulating hormones, parathyroid hormone (PTH), and calcitonin. Therefore, calcium ion regulation is discussed only briefly in this chapter.

The extracellular fluid calcium ion concentration normally remains tightly controlled within a few percentage points of its normal level, 2.4 mEq/L. When the calcium ion concentration falls to low levels (*hypocalcemia*), the excitability of nerve and muscle cells increases markedly and can, in extreme cases, result in *hypocalcemic tetany*. This condition is characterized by spastic skeletal muscle contractions. *Hypercalcemia* (increased calcium concentration) depresses neuromuscular excitability and can lead to cardiac arrhythmias.

About 50% of the *total* calcium in the plasma (5 mEq/L) exists in the ionized form, which is the form that has biological activity at cell membranes. The remainder is bound to plasma proteins (≈40%) or complexed in the nonionized form with anions such as phosphate and citrate (≈10%).

Changes in plasma hydrogen ion concentration influence calcium binding to plasma proteins. With acidosis, less calcium is bound to the plasma proteins. Conversely, with alkalosis, a greater amount of calcium is bound to the plasma proteins. Therefore, *patients with alkalosis are more susceptible to hypocalcemic tetany*.

As with other substances in the body, calcium intake must be balanced with the net loss of calcium over the long term. Unlike ions such as sodium and chloride, however, much of the calcium excretion occurs in the feces. The usual rate of dietary calcium intake is about 1000 mg/day, with about 900 mg/day of calcium excreted in the feces. Under certain conditions, fecal calcium excretion can exceed calcium ingestion because calcium can also be secreted into the intestinal lumen. Therefore, the gastrointestinal tract and regulatory mechanisms that influence intestinal calcium absorption and secretion play a major role in calcium homeostasis, as discussed in Chapter 80.

Almost all the calcium in the body (99%) is stored in the bone, with only about 0.1% in the extracellular fluid and 1.0% in the intracellular fluid and cell organelles. The bone, therefore, acts as a large reservoir for calcium and as a source of calcium when extracellular fluid calcium concentration tends to decrease.

One of the most important regulators of bone uptake and release of calcium is PTH. When extracellular fluid calcium concentration falls below normal, activity of *calcium-sensing receptors* (CSRs) on the cell membrane of the parathyroid glands is reduced, promoting increased secretion of PTH. This hormone then acts directly on the bones to increase resorption of bone salts (release of salts from the bones) and release large amounts of calcium into the extracellular fluid, thereby returning calcium levels back toward normal. When the calcium ion concentration is elevated, CSR activity of the parathyroid cells is stimulated, causing a reduction in PTH secretion, so almost no bone resorption occurs; instead, excess calcium is deposited in the bones. Thus, the daily regulation of calcium ion concentration is mediated in large part by the effects of PTH on bone resorption.

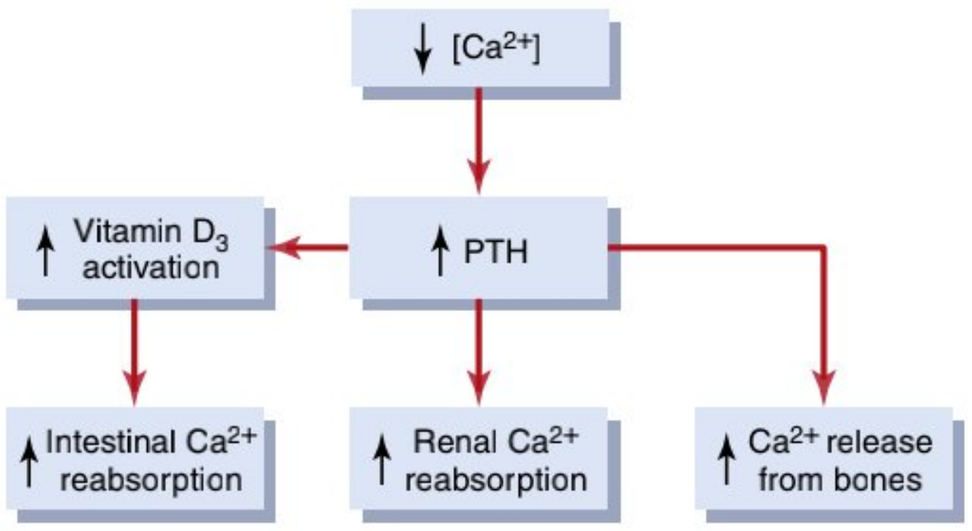

Figure 30-11. Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone (*PTH*) and vitamin D.

The bones, however, do not have an inexhaustible supply of calcium. Therefore, over the long term, intake of calcium must be balanced with calcium excretion by the gastrointestinal tract and kidneys. The most important regulator of calcium reabsorption at both these sites is PTH, which regulates the plasma calcium concentration through three main effects: *(1) by stimulating bone resorption; (2) by stimulating activation of vitamin D, which then increases intestinal reabsorption of calcium; and (3) by increasing renal tubular calcium reabsorption* (**Figure 30-11**). The control of gastrointestinal calcium reabsorption and calcium exchange in the bones is discussed elsewhere; the remainder of this section focuses on the mechanisms that control renal calcium excretion.

CONTROL OF CALCIUM EXCRETION BY THE KIDNEYS

Calcium is filtered and reabsorbed in the kidneys but is not secreted. Therefore, the rate of renal calcium excretion is calculated as follows:

$$\text{Renal calcium excretion} = \text{Calcium filtered} - \text{Calcium reabsorbed}$$

Only about 60% of the plasma calcium is ionized, with 40% being bound to the plasma proteins and 10% complexed with anions such as phosphate. Therefore, only about 60% of the plasma calcium is filtered at the glomerulus. Normally, about 99% of the filtered calcium is reabsorbed by the tubules, with only about 1% of the filtered calcium being excreted. About 65% of the filtered calcium is reabsorbed in the proximal tubule, 25% to 30% is reabsorbed in the loop of Henle, and 4% to 9% is reabsorbed in the distal and collecting tubules. This pattern of reabsorption is similar to that for sodium.

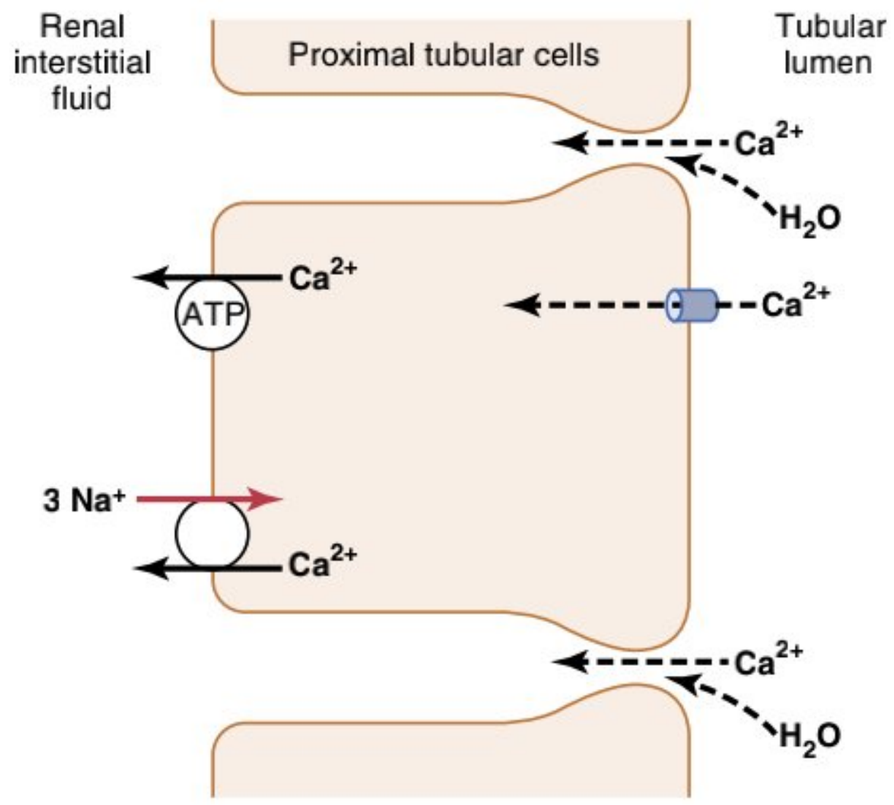

Figure 30-12. Mechanisms of calcium reabsorption by paracellular and transcellular pathways in the proximal tubular cells.

As is true with the other ions, calcium excretion is adjusted to meet the body's needs. With an increase in calcium intake, there is also increased renal calcium excretion, although much of the increase of calcium intake is eliminated in the feces. With calcium depletion, calcium excretion by the kidneys decreases as a result of enhanced tubular reabsorption.

Proximal Tubular Calcium Reabsorption. Most of the calcium reabsorption in the proximal tubule occurs through the paracellular pathway; it is dissolved in water and carried with the reabsorbed fluid as it flows between the cells. Only about 20% of proximal tubular calcium reabsorption occurs through the transcellular pathway in two steps;

1. Calcium diffuses from the tubular lumen into the cell down an electrochemical gradient due to the much higher concentration of calcium in the tubular lumen, compared with the epithelial cell cytoplasm, and because the cell interior has a negative charge relative to the tubular lumen.
2. Calcium exits the cell across the basolateral membrane by a calcium-ATPase pump and by the sodium-calcium counter-transporter (Figure 30-12).

Loop of Henle and Distal Tubule Calcium Reabsorption. In the loop of Henle, calcium reabsorption is restricted to the thick ascending limb. Approximately 50% of calcium reabsorption in the thick ascending limb occurs through the paracellular route by passive diffusion due to the slight positive charge of the tubular lumen relative to the interstitial fluid. The remaining 50% of calcium reabsorption in the thick ascending limb occurs through the transcellular pathway, a process that is stimulated by PTH.

In the distal tubule, calcium reabsorption occurs almost entirely by active transport through the cell membrane. The mechanism for this active transport is similar to that in the proximal tubule and thick ascending limb. It involves diffusion across the luminal membrane through calcium channels and exit across the basolateral membrane by a calcium-ATPase pump, as well as a sodium-calcium counter-transport mechanism. In this segment, as well as in the loops of Henle, PTH stimulates calcium reabsorption. Vitamin D (calcitriol) and calcitonin also stimulate calcium reabsorption in the thick ascending limb of Henle's loop and in the distal tubule, although these hormones are not as important quantitatively as PTH in reducing renal calcium excretion.

Regulation of Tubular Calcium Reabsorption. One of the primary controllers of renal tubular calcium reabsorption is PTH. Increased levels of PTH stimulate calcium reabsorption in the thick ascending loops of Henle and distal tubules, which reduces urinary excretion of calcium. Conversely, reduction of PTH promotes calcium excretion by decreasing reabsorption in the loops of Henle and distal tubules.

Increased extracellular fluid calcium ion concentration also directly stimulates CSRs, which inhibit calcium reabsorption in the thick ascending loops of Henle. Conversely, reductions in calcium concentration decrease CSR activity and increase calcium reabsorption in the thick ascending loop of Henle.

In the proximal tubule, calcium reabsorption usually parallels sodium and water reabsorption and is independent of PTH. Therefore, in cases of extracellular volume expansion or increased arterial pressure—both of which decrease proximal sodium and water reabsorption—there is also reduction in calcium reabsorption and, consequently, increased urinary calcium excretion. Conversely, with reduced extracellular volume or decreased blood pressure, calcium excretion decreases primarily because of increased proximal tubular reabsorption.

Another factor that influences calcium reabsorption is the plasma concentration of phosphate. Increased plasma phosphate stimulates PTH, which increases calcium reabsorption by the renal tubules, thereby reducing calcium excretion. The opposite occurs with a reduction in plasma phosphate concentration.

Calcium reabsorption is also stimulated by metabolic alkalosis and inhibited by metabolic acidosis. Thus, acidosis tends to increase calcium excretion, whereas alkalosis tends to reduce calcium excretion. Most of the effect of hydrogen ion concentration on calcium excretion results from changes in calcium reabsorption in the distal tubule.

A summary of the factors known to influence calcium excretion is shown in Table 30-2.

REGULATION OF RENAL PHOSPHATE EXCRETION

Phosphate excretion by the kidneys is controlled primarily by an overflow mechanism that can be explained as follows. The