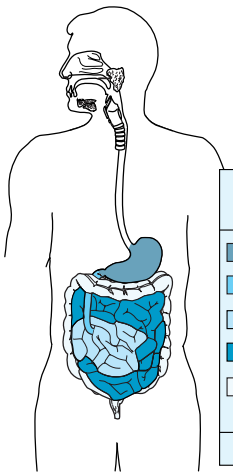
Gastrointestinal Absorption of Calcium



Gastrointestinal absorption of dietary calcium (Ca)

Site	Net Ca absorption mmol/d	Net Ca absorption mg/d	% of intake absorbed
Stomach	0	0	0
Duodenum	0.75	30	3
Jejunum	1.0	40	4
Ileum	3.25	130	13
Colon	0	0	0
Total*	5	200	20

*Normal dietary Ca intake =1000 mg (25 mmol) per day

FIGURE 5-11

Gastrointestinal absorption of dietary calcium (Ca). The normal recommended dietary intake of Ca for an adult is 800 to 1200 mg/d (20–30 mmol/d). Foods high in Ca content include milk, dairy products, meat, fish with bones, oysters, and many leafy green vegetables (*eg*, spinach and collard greens). Although serum Ca levels can be maintained in the normal range by bone resorption, dietary intake is the only source by which the body can replenish stores of Ca in bone. Ca is absorbed almost exclusively within the duodenum, jejunum, and ileum. Each of these intestinal segments has a high absorptive capacity for Ca, with their relative Ca absorption being dependent on the length of each respective intestinal segment and the transit time of the food bolus. Approximately 400 mg of the usual 1000 mg dietary Ca intake is absorbed by the intestine, and Ca loss by way of intestinal secretions is approximately 200 mg/d. Therefore, a net absorption of Ca is approximately 200 mg/d (20%). Biliary and pancreatic secretions are extremely rich in Ca. 1,25-dihydroxy-vitamin D_3 is an extremely important regulatory hormone for intestinal absorption of Ca [1,2,17,18].

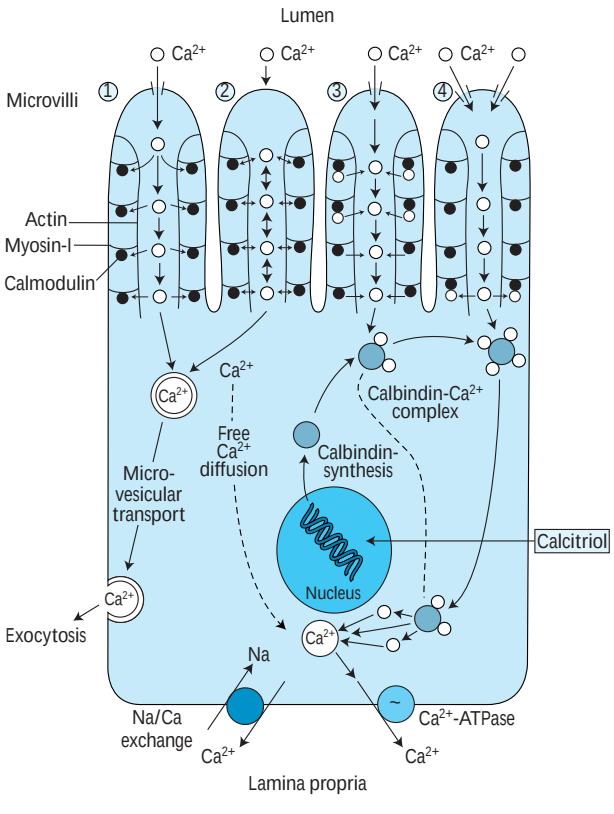


FIGURE 5-12

Proposed pathways for calcium (Ca) absorption across the intestinal epithelium. Two routes exist for the absorption of Ca across the intestinal epithelium: the paracellular pathway and the transcellular route. The paracellular pathway is passive, and it is the predominant means of Ca absorption when the luminal concentration of Ca is high. This is a nonsaturable pathway and can account for one half to two thirds of total intestinal Ca absorption. The paracellular absorptive route may be indirectly influenced by 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$) because it may be capable of altering the structure of intercellular tight junctions by way of activation of protein kinase C, making the tight junction more permeable to the movement of Ca. However, $1,25(OH)_2D_3$ primarily controls the active absorption of Ca. (1) Ca moves down its concentration gradient through a Ca channel or Ca transporter into the apical section of the microvillae. Because the intestinal concentration of Ca usually is 10^{-3} mol and the intracellular Ca concentration is 10^{-6} mol, a large concentration gradient favors the passive movement of Ca. Ca is rapidly and reversibly bound to the calmodulin-actin-myosin I complex. Ca may then move to the basolateral area of the cell by way of microvesicular transport, or ionized Ca may diffuse to this area of the cell. (2) As the calmodulin complex becomes saturated with Ca, the concentration gradient for the movement of Ca into the microvillae is not as favorable, which slows Ca absorption. (3) Under the influence of calcitriol, intestinal epithelial cells increase their synthesis of calbindin. (4) Ca binds to calbindin, thereby unloading the Ca-calmodulin complexes, which then remove Ca from the microvillae region. This decrease in Ca concentration again favors the movement of Ca into the microvillae. As the calbindin-Ca complex dissociates, the free intracellular Ca is actively extruded from the cell by either the Ca-adenosine triphosphatase (ATPase) or Na-Ca exchanger. Calcitriol may also increase the synthesis of the plasma membrane Ca-ATPase, thereby aiding in the active extrusion of Ca into the lamina propria [2,7,9,17,18].

Renal Handling of Calcium

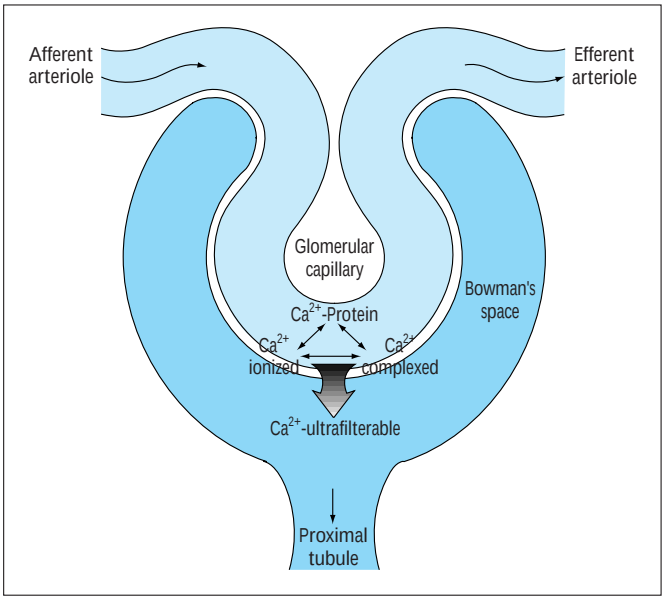


FIGURE 5-13

Glomerular filtration of calcium (Ca). Total serum Ca consists of ionized, protein bound, and complexed fractions (47.5%, 46.0%, and 6.5%, respectively). The complexed Ca is bound to molecules such as phosphate and citrate. The ultrafilterable Ca equals the total of the ionized and complexed fractions. Normal total serum Ca is approximately 8.9 to 10.1 mg/dL (about 2.2–2.5 mmol/L). Ca can be bound to albumin and globulins. For each 1.0 gm/dL decrease in serum albumin, total serum Ca decreases by 0.8 mg/dL; for each 1.0 gm/dL decrease in serum globulin fraction, total serum Ca decreases by 0.12 mg/dL. Ionized Ca is also affected by pH. For every 0.1 change in pH, ionized Ca changes by 0.12 mg/dL. Alkalosis decreases the ionized Ca [1,6,7].

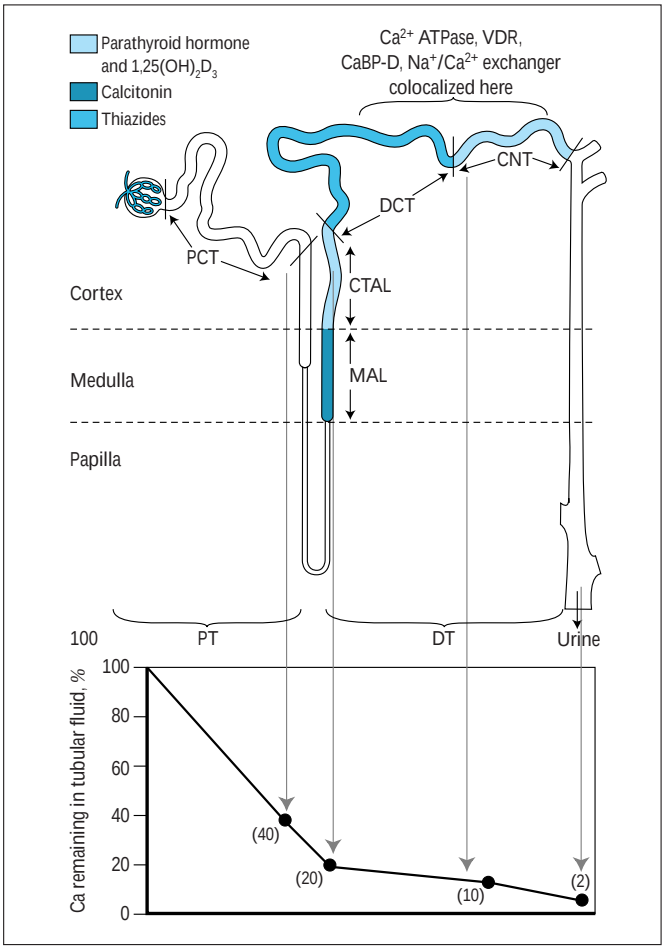


FIGURE 5-14

Renal handling of calcium (Ca). Ca is filtered at the glomerulus, with the ultrafilterable fraction (UF_{Ca}) of plasma Ca entering the proximal tubule (PT). Within the proximal convoluted tubule (PCT) and the proximal straight tubule (PST), isosmotic reabsorption of Ca occurs such that at the end of the PST the UF_{Ca} to TF_{Ca} ratio is about 1.1 and 60% to 70% of the filtered Ca has been reabsorbed. Passive paracellular pathways account for about 80% of Ca reabsorption in this segment of the nephron, with the remaining 20% dependent on active transcellular Ca movement. No reabsorption of Ca occurs within the thin segment of the loop of Henle. Ca is reabsorbed in small amounts within the medullary segment of the thick ascending limb (MAL) of the loop of Henle and calcitonin (CT) stimulates Ca reabsorption here. However, the cortical segments (cTAL) reabsorb about 20% of the initially filtered load of Ca. Under normal conditions, most of the Ca reabsorption in the cTAL is passive and paracellular, owing to the favorable electrochemical gradient. Active transcellular Ca transport can be stimulated by both parathyroid hormone (PTH) and 1,25-dihydroxy-vitamin D_3 (1,25$(OH)_2D_3$) in the cTAL. In the early distal convoluted tubule (DCT), thiazide-activated Ca transport occurs. The DCT is the primary site in the nephron at which Ca reabsorption is regulated by PTH and 1,25$(OH)_2D_3$. Active transcellular Ca transport must account for Ca reabsorption in the DCT, because the transepithelial voltage becomes negative, which would not favor passive movement of Ca out of the tubular lumen. About 10% of the filtered Ca is reabsorbed in the DCT, with another 3% to 10% of filtered Ca reabsorbed in the connecting tubule (CNT) by way of mechanisms similar to those in the DCT [1,2,6, 7,18]. ATPase—adenosine triphosphatase; CaBP-D—Ca-binding protein D; DT—distal tubule; VDR—vitamin D receptor. (*Adapted from* Kumar [1].)

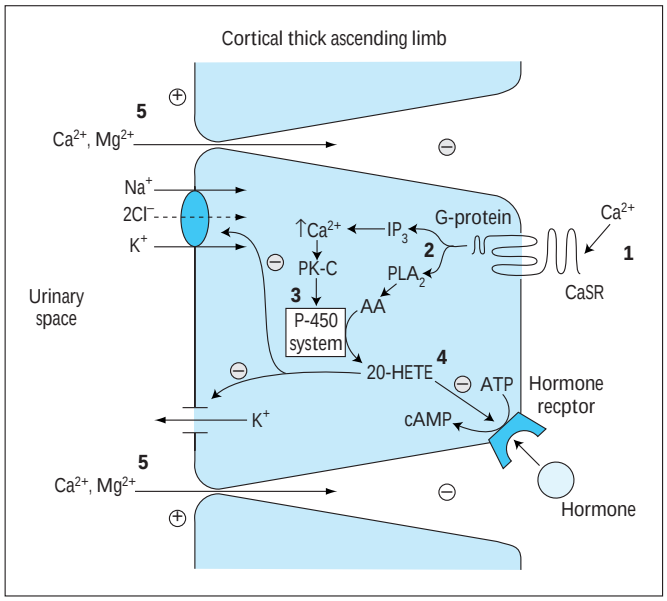


FIGURE 5-15

Effects of hypercalcemia on calcium (Ca) reabsorption in the cortical thick ascending limb (cTAL) of the loop of Henle and urinary concentration. (1) Hypercalcemia stimulates the Ca-sensing receptor (CaSR) of cells in the cTAL. (2) Activation of the G-protein increases intracellular free ionized Ca (Ca^{2+}) by way of the inositol 1,4,5-trisphosphate (IP3) pathway, which increases the activity of the P450 enzyme system. The G-protein also increases activity of phospholipase A2 (PLA_A), which increases the concentration of arachidonic acid (AA). (3) The P450 enzyme system increases production of 20-hydroxy-eicosatetraenoic acid (20-HETE) from AA. (4) 20-HETE inhibits hormone-stimulated production of cyclic adenosine monophosphate (cAMP), blocks sodium reabsorption by the sodium-potassium-chloride (Na-K-2Cl) cotransporter, and inhibits movement of K out of K-channels. (5) These changes alter the electrochemical forces that would normally favor the paracellular movement of Ca (and Mg) such that Ca (and Mg) is not passively reabsorbed. Both the lack of movement of Na into the renal interstitium and inhibition of hormonal (*eg*, vasopressin) effects impair the ability of the nephron to generate maximally concentrated urine [3,4,14]. ATP—adenosine triphosphate; PK-C—protein kinase C.

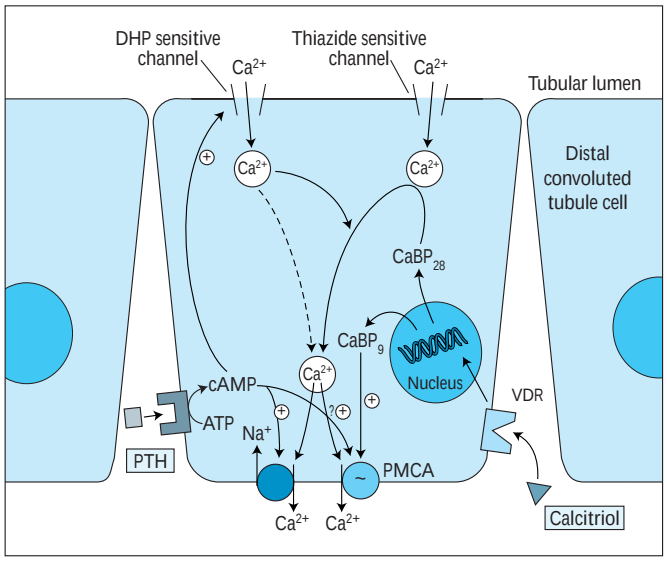


FIGURE 5-16

Postulated mechanism of the Ca transport pathway shared by PTH and $1,25(OH)_2D_3$. Cyclic adenosine monophosphate (cAMP) generated by PTH stimulation leads to increased influx of Ca into the apical dihydropyridine-sensitive Ca channel. There also is increased activity of the basolateral Na-Ca exchanger and, perhaps, of the plasma membrane–associated Ca-adenosine triphosphatase (PMCA), which can rapidly extrude the increased intracellular free Ca (Ca^{2+}). Calcitriol ($1,25(OH)_2D_3$), by way of the vitamin D receptor (VDR), stimulates transcription of calbindin D28k ($CaBP_{28}$) and calbindin D9k ($CaBP_9$). $CaBP_{28}$ increases apical uptake of Ca by both the dihydropyridine- and thiazide-sensitive Ca channels by decreasing the concentration of unbound free Ca^{2+} and facilitates Ca movement to the basolateral membrane. $CaBP_9$ stimulates PMCA activity, which increases extrusion of Ca by the cell. Similar hormonally induced mechanisms of Ca transport are believed to exist throughout the cortical thick ascending limb, the DCT, and the connecting tubule (CNT) [6]. ATP—adenosine triphosphate; Na^+—ionized sodium.