Divalent Cation Metabolism: Calcium

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Calcium is an essential element in the human body. Although over 99% of the total body calcium is located in bone, calcium is a critical cation in both the extracellular and intracellular spaces. Its concentration is held in a very narrow range in both spaces. In addition to its important role in the bone mineral matrix, calcium serves a vital role in nerve impulse transmission, muscular contraction, blood coagulation, hormone secretion, and intercellular adhesion. Calcium also is an important intracellular second messenger for processes such as exocytosis, chemotaxis, hormone secretion, enzymatic activity, and fertilization. Calcium balance is tightly regulated by the interplay between gastrointestinal absorption, renal excretion, bone resorption, and the vitamin D–parathyroid hormone (PTH) system [1–7].

CHAPTER 5

Calcium Distribution

TOTAL DISTRIBUTION OF CALCIUM IN THE BODY

Location	Concentration	Ca Content*	
		mmol	mg
Bone	99%	~31.4 × 10^3	~1255 × 10^3
Extracellular fluid	2.4 mmol	35	~1400
Intracellular fluid	0.1 μmol	<1	<40
Total		~31.5 × 10^3	~1260 × 10^3

*data for a 70 kg person

FIGURE 5-1

Total distribution of calcium (Ca) in the body. Ca (molecular weight, 40.08 D) is predominantly incorporated into bone. Total body Ca content is about 1250 g (31 mol) in a person weighing 70 kg. Bone Ca is incorporated into the hydroxyapatite crystals of bone, and about 1% of bone Ca is available as an exchangeable pool. Only 1% of the total body calcium exists outside of the skeleton.

Intracellular Calcium Metabolism

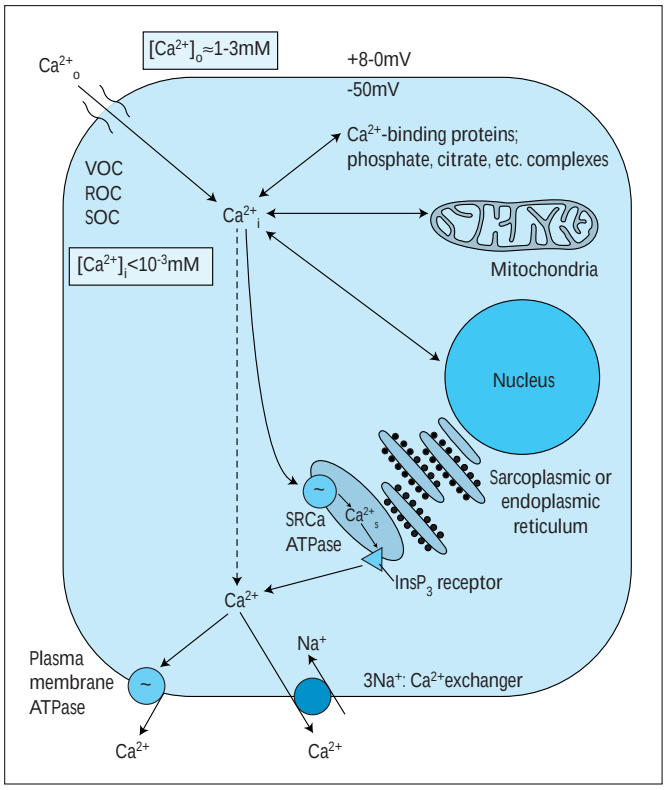


FIGURE 5-2

General scheme of the distribution and movement of intracellular calcium (Ca). In contrast to magnesium, Ca has a particularly adaptable coordination sphere that facilitates its binding to the irregular geometry of proteins, a binding that is readily reversible. Low intracellular Ca concentrations can function as either a first or second messenger. The extremely low concentrations of intracellular Ca are necessary to avoid Ca-phosphate microprecipitation and make Ca an extremely sensitive cellular messenger. Less than 1% of the total intracellular Ca exists in the free ionized form, with a concentration of approximately 0.1 μmol/L. Technical methods available to investigate intracellular free Ca concentration include Ca-selective microelectrodes, bioluminescent indicators, metallochromic dyes, Ca-sensitive fluorescent indicators, electron-probe radiographic microanalysis, and fluorine-19 nuclear magnetic resonance imaging. Intracellular Ca is predominantly sequestered within the endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR). Some sequestration of Ca occurs within mitochondria and the nucleus. Ca can be bound to proteins such as calmodulin and calbindin, and Ca can be complexed to phosphate, citrate, and other anions. Intracellular Ca is closely regulated by balancing Ca entry by way of voltage-operated channels (VOC), receptor-operated channels (ROC), and store-operated channels (SOC), with active Ca efflux by way of plasma membrane–associated Ca-adenosine triphosphatase (ATPase) and a Na-Ca exchanger. Intracellular Ca also is closely regulated by balancing Ca movement into the SR (SR Ca-ATPase) and efflux from the SR by an inositol 1,4,5-trisphosphate ($InsP_3$) receptor [1–7].

The highest concentration of intracellular Ca is found in the brush border of epithelial cells, where there is also the highest concentration of Ca-binding proteins such as actin-myosin and calbindin. Intracellular Ca messages are closely modulated by the phospholipase C-$InsP_3$ pathway and also the phospholipase A_2–arachidonic acid pathway, along with intracellular Ca, which itself modulates the $InsP_3$ receptor.

Vitamin D and Parathyroid Hormone Actions

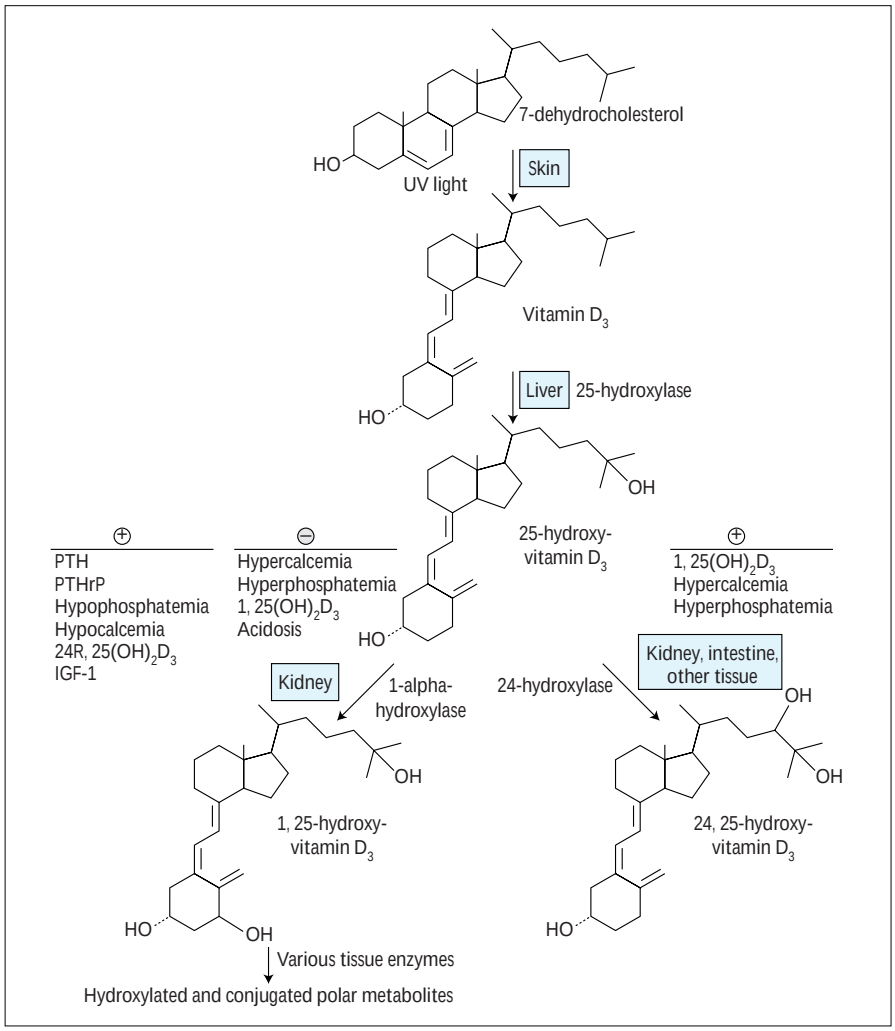


FIGURE 5-3

Metabolism of vitamin D. The compound 7-dehydrocholesterol, through the effects of heat (37°C) and (UV) light (wavelength 280–305 nm), is converted into vitamin D_3 in the skin. Vitamin D_3 is then transported on vitamin D binding proteins (VDBP) to the liver. In the liver, vitamin D_3 is converted to 25-hydroxy-vitamin D_3 by the hepatic microsomal and mitochondrial cytochrome P450–containing vitamin D_3 25-hydroxylase enzyme. The 25-hydroxy-vitamin D_3 is transported on VDBP to the proximal tubular cells of the kidney, where it is converted to 1,25-dihydroxy-vitamin D_3 by a 1-α-hydroxylase enzyme, which also is a cytochrome P450–containing enzyme. The genetic information for this enzyme is encoded on the 12q14 chromosome. Alternatively, 25-hydroxy-vitamin D_3 can be converted to 24R,25-dihydroxy-vitamin D_3, a relatively inactive vitamin D metabolite. 1,25-dihydroxy-vitamin D_3 can then be transported by VDBP to its most important target tissues in the distal tubular cells of the kidney, intestinal epithelial cells, parathyroid cells, and bone cells. VDBP is a 58 kD α-globulin that is a member of the albumin and α-fetoprotein gene family. The DNA sequence that encodes for this protein is on chromosome 4q11-13. 1,25-dihydroxy-vitamin D_3 is eventually metabolized to hydroxylated and conjugated polar metabolites in the enterohepatic circulation. Occasionally, 1,25-dihydroxy-vitamin D_3 also may be produced in extrarenal sites, such as monocyte-derived cells, and may have an antiproliferative effect in certain lymphocytes and keratinocytes [1,7–9]. (*Adapted from* Kumar [1].)

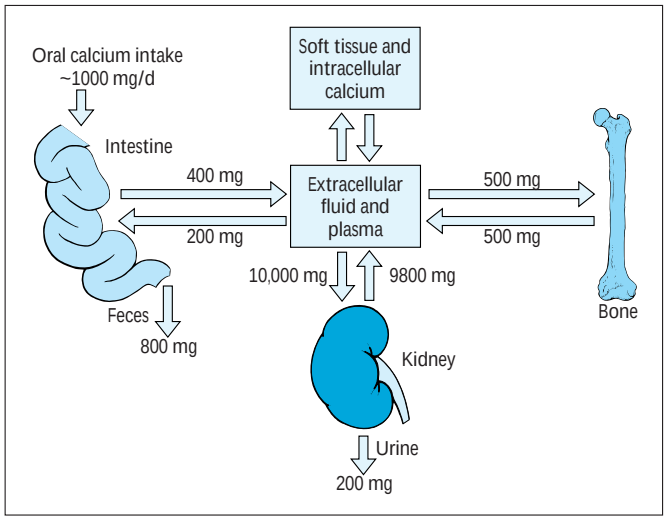


FIGURE 5-4

Calcium (Ca) flux between body compartments. Ca balance is a complex process involving bone, intestinal absorption of dietary Ca, and renal excretion of Ca. The parathyroid glands, by their production of parathyroid hormone, and the liver, through its participation in vitamin D metabolism, also are integral organs in the maintenance of Ca balance. (*From* Kumar [1]; with permission.)

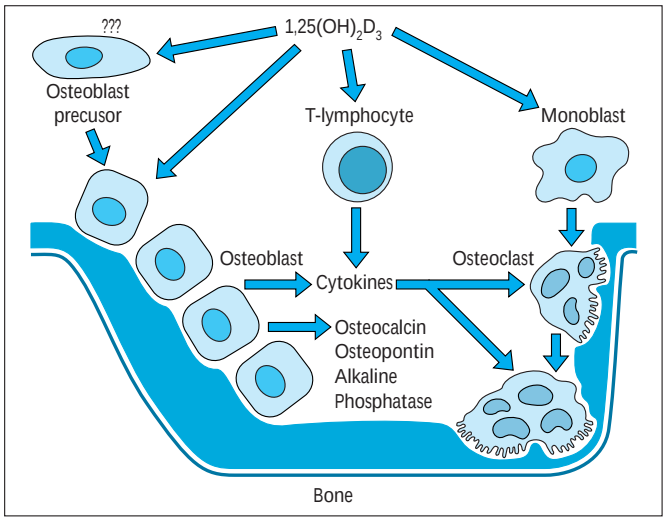


FIGURE 5-5

Effects of 1,25-dihydroxy-vitamin D_3 (calcitriol) on bone. In addition to the effects on parathyroid cells, the kidney, and intestinal epithelium, calcitriol has direct effects on bone metabolism. Calcitriol can promote osteoclast differentiation and activity from monocyte precursor cells. Calcitriol also promotes osteoblast differentiation into mature cells. (*From* Holick [8]; with permission.)

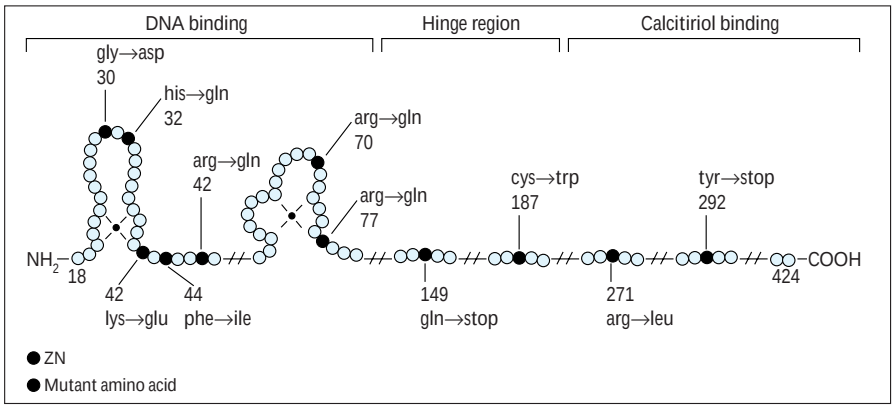


FIGURE 5-6

The vitamin D receptor (VDR). Within its target tissues, calcitriol binds to the VDR. The VDR is a 424 amino acid polypeptide. Its genomic information is encoded on the 12q12-14 chromosome, near the gene for the 1-α-hydroxylase enzyme. The VDR is found in the intestinal epithelium, parathyroid cells, kidney cells, osteoblasts, and thyroid cells. VDR also can be detected in keratinocytes, monocyte precursor cells, muscle cells, and numerous other tissues. The allele variations for the vitamin D receptor. Two allele variations exist for the vitamin D receptor (VDR): the b allele and the B allele. In general, normal persons with the b allele seem to have a higher bone mineral density [9]. Among patients on dialysis, those with the b allele may have higher levels of circulating parathyroid hormone (PTH) [7,9,10,11]. COOH—carboxy terminal; NH_2—amino terminal. (*From* Root [7]; with permission.)

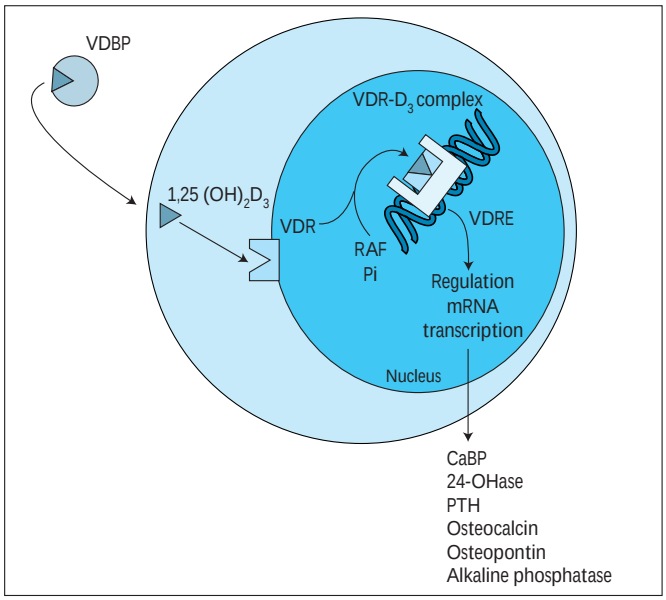


FIGURE 5-7

Mechanism of action of 1-25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$). $1,25(OH)_2D_3$ is transported to the target cell bound to the vitamin D–binding protein (VDBP). The free form of $1,25(OH)_2D_3$ enters the target cell and interacts with the vitamin D receptor (VDR) at the nucleus. This complex is phosphorylated and combined with the nuclear accessory factor (RAF). This forms a heterodimer, which then interacts with the vitamin D responsive element (VDRE). The VDRE then either promotes or inhibits the transcription of messenger RNA (mRNA) for proteins regulated by $1,25(OH)_2D_3$, such as Ca-binding proteins, the 25-hydroxy-vitamin D_3 24-hydroxylase enzyme, and parathyroid hormone. Pi—inorganic phosphate. (*Adapted from* Holick [8].)

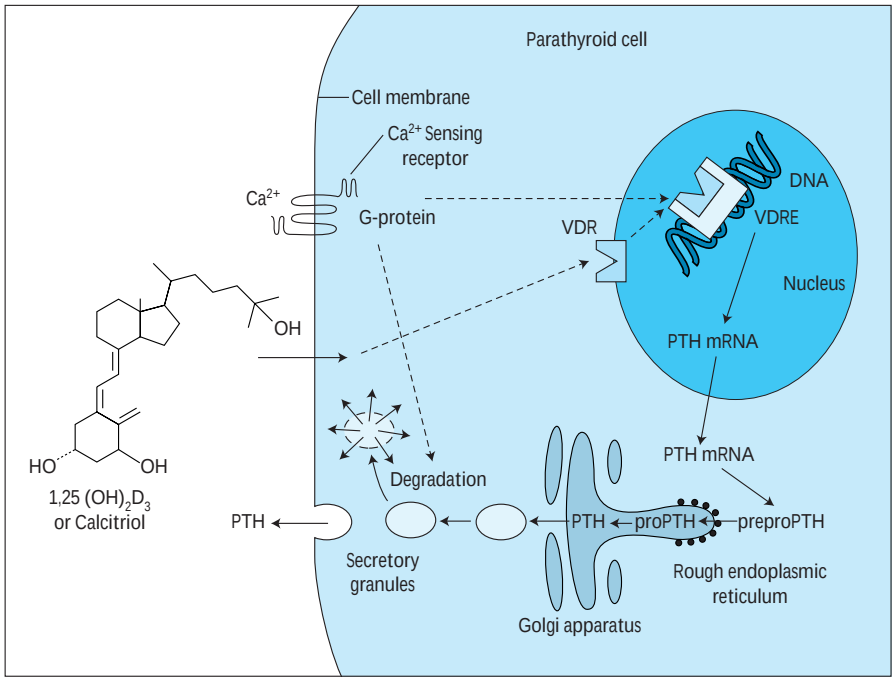


FIGURE 5-8

Metabolism of parathyroid hormone (PTH). The PTH gene is located on chromosome 11p15. PTH messenger RNA (mRNA) is transcribed from the DNA fragment and then translated into a 115 amino acid–containing molecule of prepro-PTH. In the rough endoplasmic reticulum, this undergoes hydrolysis to a 90 amino acid–containing molecule, pro-PTH, which undergoes further hydrolysis to the 84 amino acid–containing PTH molecule. PTH is then stored within secretory granules in the cytoplasm for release. PTH is metabolized by hepatic Kupffer cells and renal tubular cells. Transcription of the PTH gene is inhibited by 1,25-dihydroxy-vitamin D_3, calcitonin, and hypercalcemia. PTH gene transcription is increased by hypocalcemia, glucocorticoids, and estrogen. Hypercalcemia also can increase the intracellular degradation of PTH. PTH release is increased by hypocalcemia, β-adrenergic agonists, dopamine, and prostaglandin E_2. Hypomagnesemia blocks the secretion of PTH [7,12]. VDR—vitamin D receptor; VDRE—vitamin D responsive element. (*Adapted from* Tanaka and coworkers [12].)

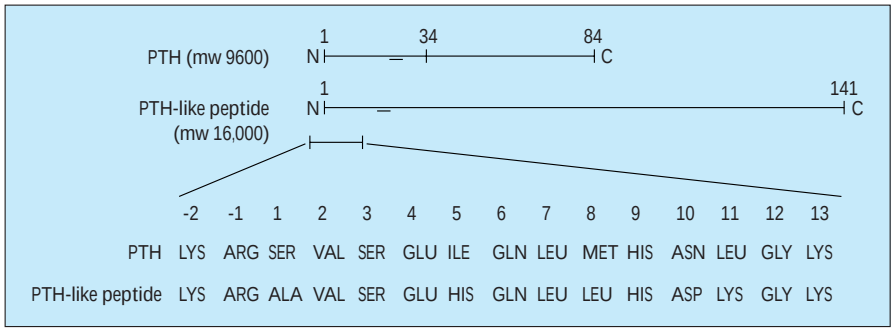


FIGURE 5-9

Parathyroid-hormone–related protein (PTHrP). PTHrP was initially described as the causative circulating factor in the humoral hypercalcemia of malignancy, particularly in breast cancer, squamous cell cancers of the lung, renal cell cancer, and other tumors. It is now clear that PTHrP can be expressed not only in cancer but also in many normal tissues. It may play an important role in the regulation of smooth muscle tone, transepithelial Ca transport (*eg*, in the mammary gland), and the differentiation of tissue and organ development [7,13]. Note the high degree of homology between PTHrP and PTH at the amino end of the polypeptides. MW—molecular weight; N—amino terminal; C—carboxy terminal. (*From* Root [7]; with permission.)

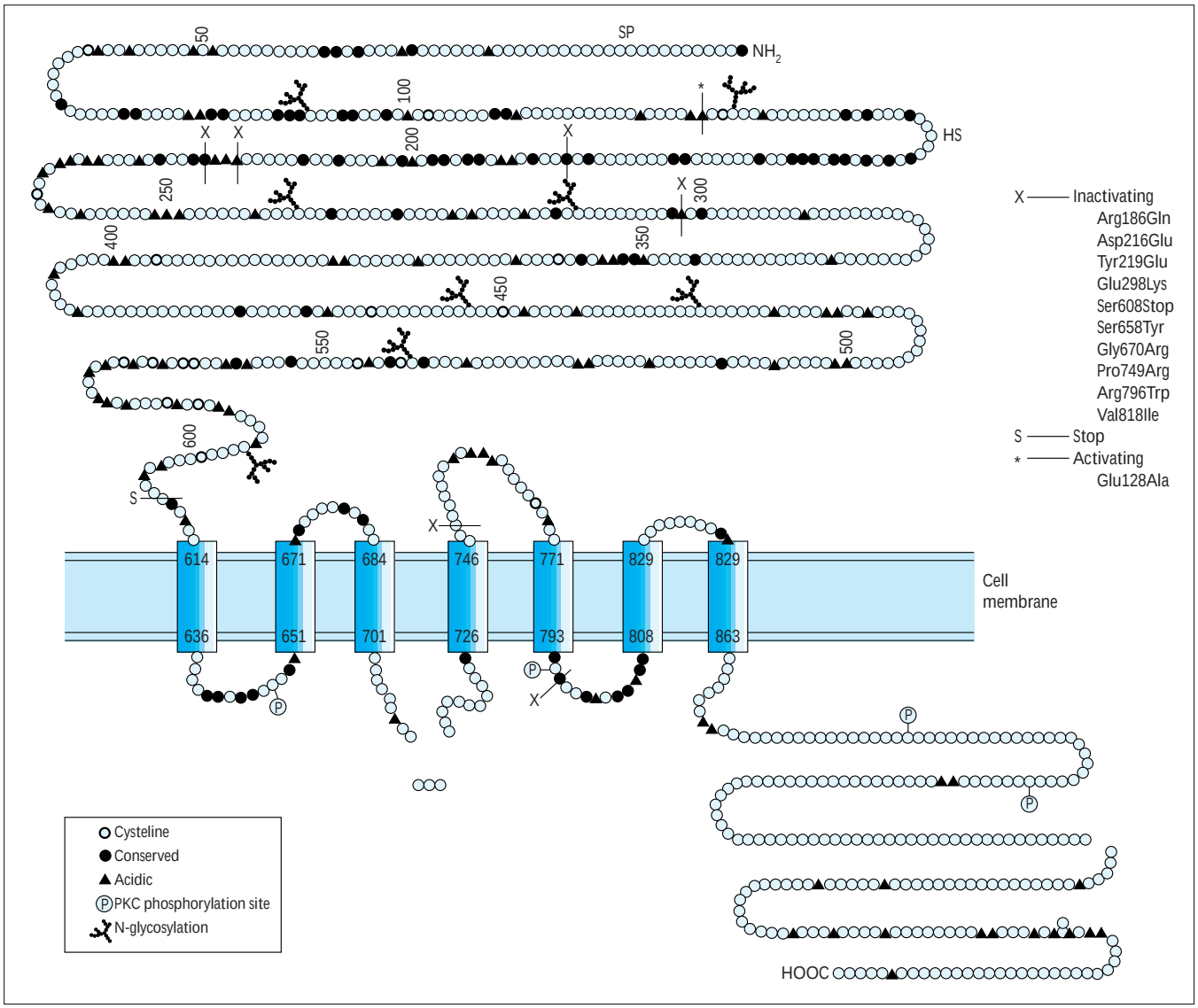
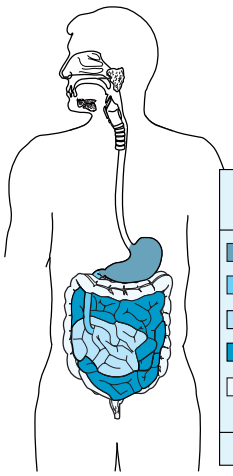


FIGURE 5-10

The calcium-ion sensing receptor (CaSR). The CaSR is a guanosine triphosphate (GTP) or G-protein–coupled polypeptide receptor. The human CaSR has approximately 1084 amino acid residues. The CaSR mediates the effects of Ca on parathyroid and renal tissues. CaSR also can be found in thyroidal C cells, brain cells, and in the gastrointestinal tract. The CaSR allows Ca to act as a first messenger on target tissues and then act by way of other second-messenger systems (*eg*, phospholipase enzymes and cyclic adenosine monophosphate). Within parathyroid cells, hypercalcemia increases CaSR-Ca binding, which activates the G-protein. The G-protein then activates the phospholipase C-β-1–phosphatidylinositol-4,5-biphosphate pathway to increase intracellular Ca, which then decreases translation of parathyroid hormone (PTH), decreases PTH secretion, and increases PTH degradation. The CaSR also is an integral part of Ca homeostasis within the kidney. The gene for CaSR is located on human chromosome 3q13 [3,4,7,14–16]. PKC—protein kinase C; HS—hydrophobic segment; NH_2—amino terminal. (*From* Hebert and Brown [4]; with permission.)

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].

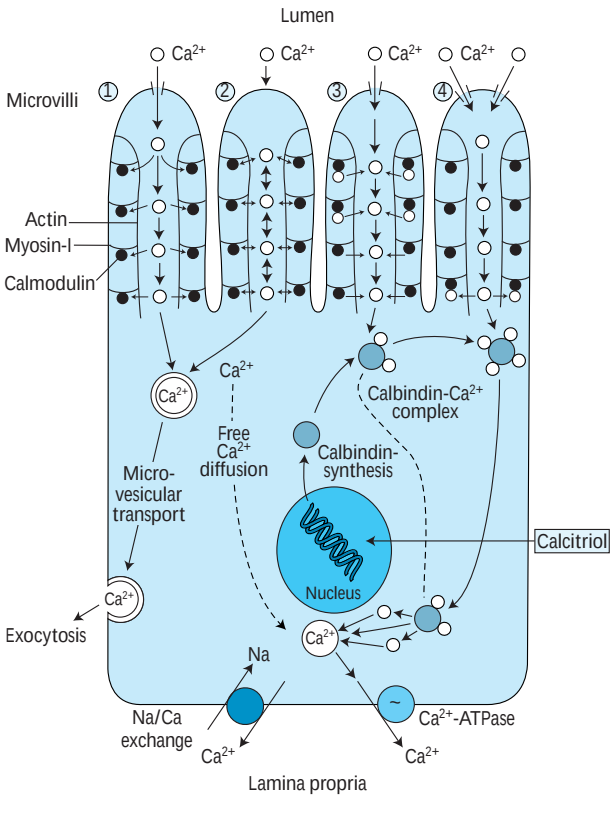


FIGURE 5-12

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

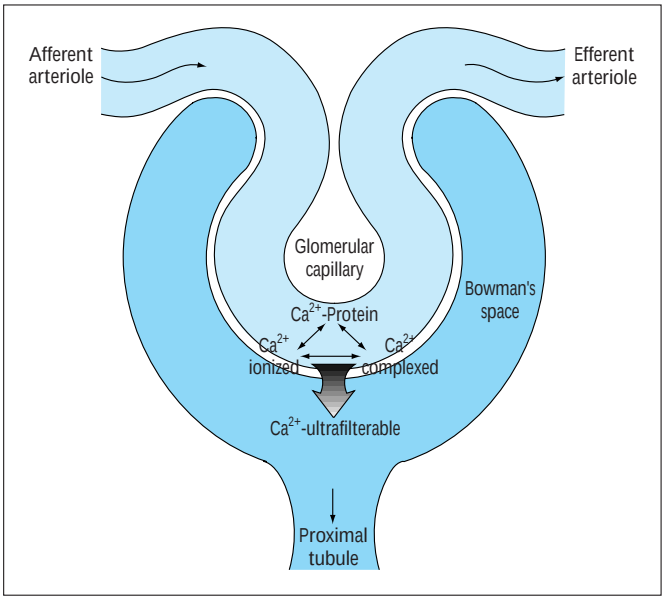


FIGURE 5-13

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].

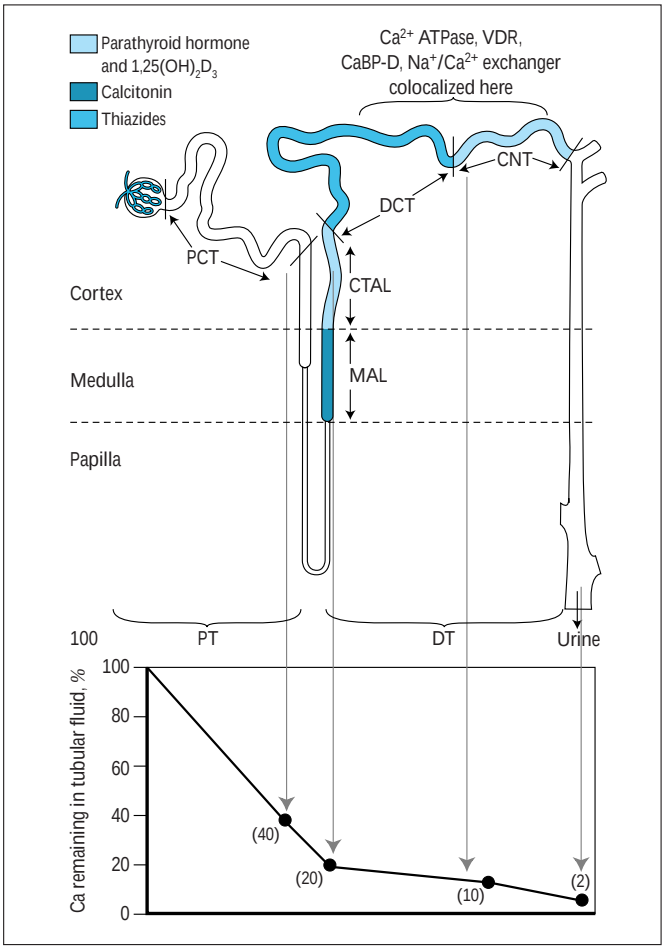


FIGURE 5-14

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].)

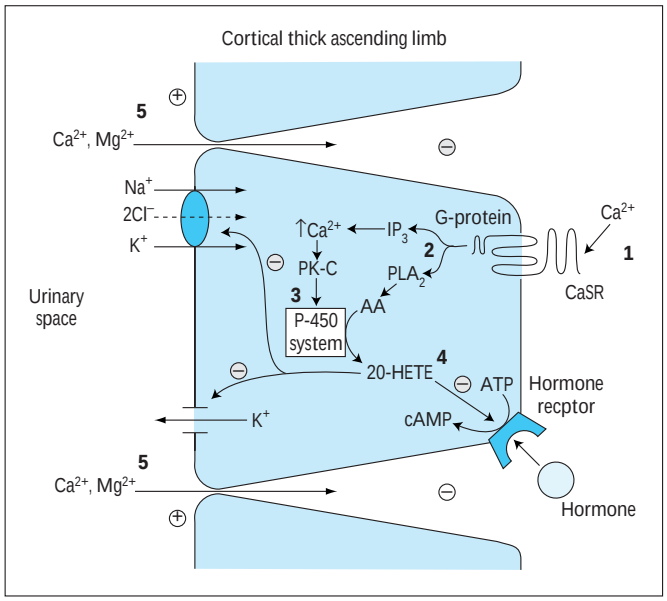


FIGURE 5-15

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.

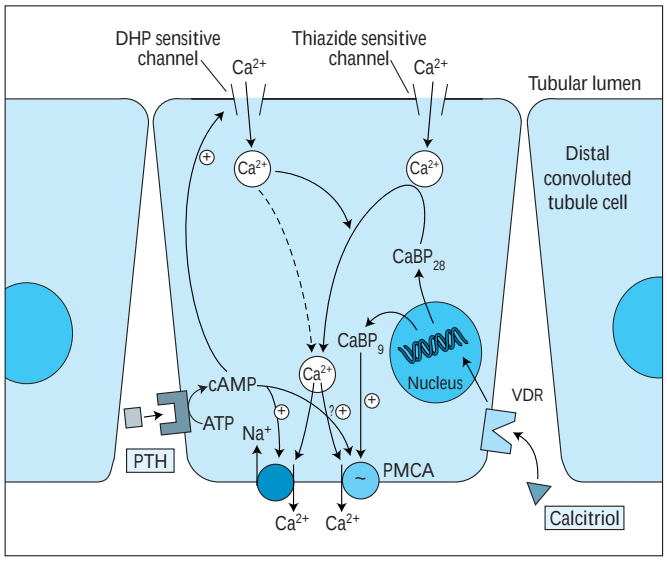


FIGURE 5-16

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.

Disturbances of Serum Calcium

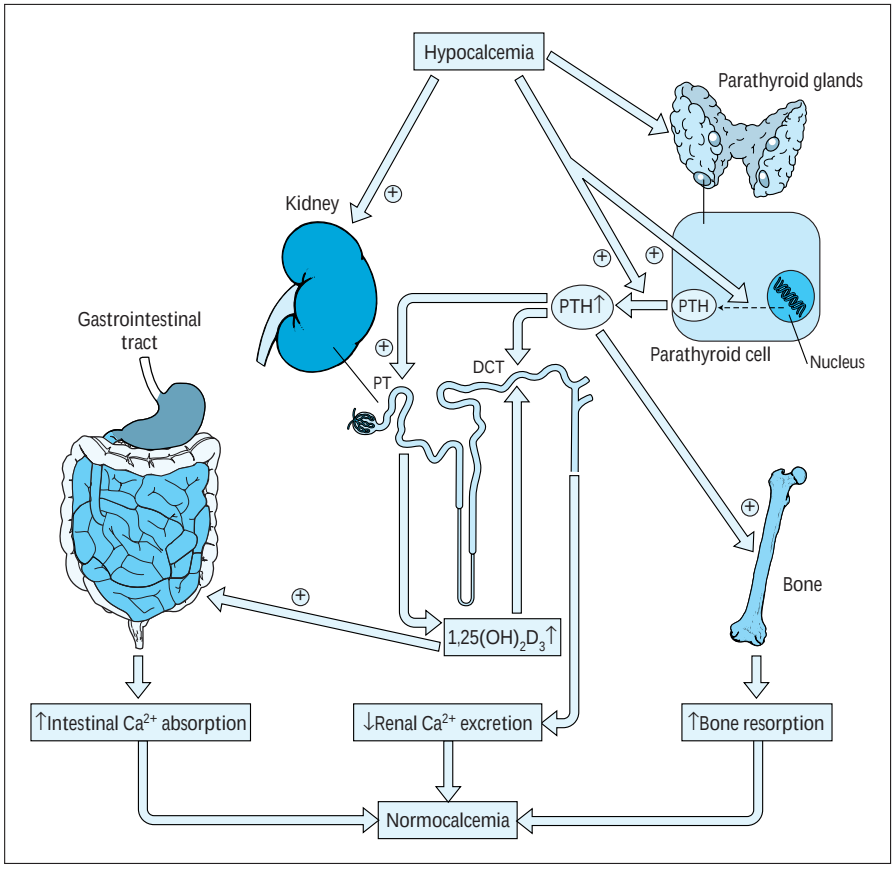


FIGURE 5-17

Physiologic response to hypocalcemia. Hypocalcemia stimulates both parathyroid hormone (PTH) release and PTH synthesis. Both hypocalcemia and PTH increase the activity of the 1-α-hydroxylase enzyme in the proximal tubular (PT) cells of the nephron, which increases the synthesis of 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$). PTH increases bone resorption by osteoclasts. PTH and $1,25(OH)_2D_3$ stimulate Ca reabsorption in the distal convoluted tubule (DCT). $1,25(OH)_2D_3$ increases the fractional absorption of dietary Ca by the gastrointestinal (GI) tract. All these mechanisms aid in returning the serum Ca to normal levels [1].

CAUSES OF HYPOCALCEMIA

Lack of parathyroid hormone (PTH)
- After thyroidectomy or parathyroidectomy
- Hereditary (congenital) hypoparathyroidism
- Pseudohypoparathyroidism (lack of effective PTH)
- Hypomagnesemia (blocks PTH secretion)

Lack of Vitamin D
- Dietary deficiency or malabsorption (osteomalacia)
- Inadequate sunlight
- Defective metabolism
  - Anticonvulsant therapy
  - Liver disease
  - Renal disease
  - Vitamin D–resistant rickets

Increased calcium complexation
- "Bone hunger" after parathyroidectomy
- Rhabdomyolysis
- Acute pancreatitis
- Tumor lysis syndrome (hyperphosphatemia)
- Malignancy (increased osteoblastic activity)

FIGURE 5-18

Causes of hypocalcemia (decrease in ionized plasma calcium).

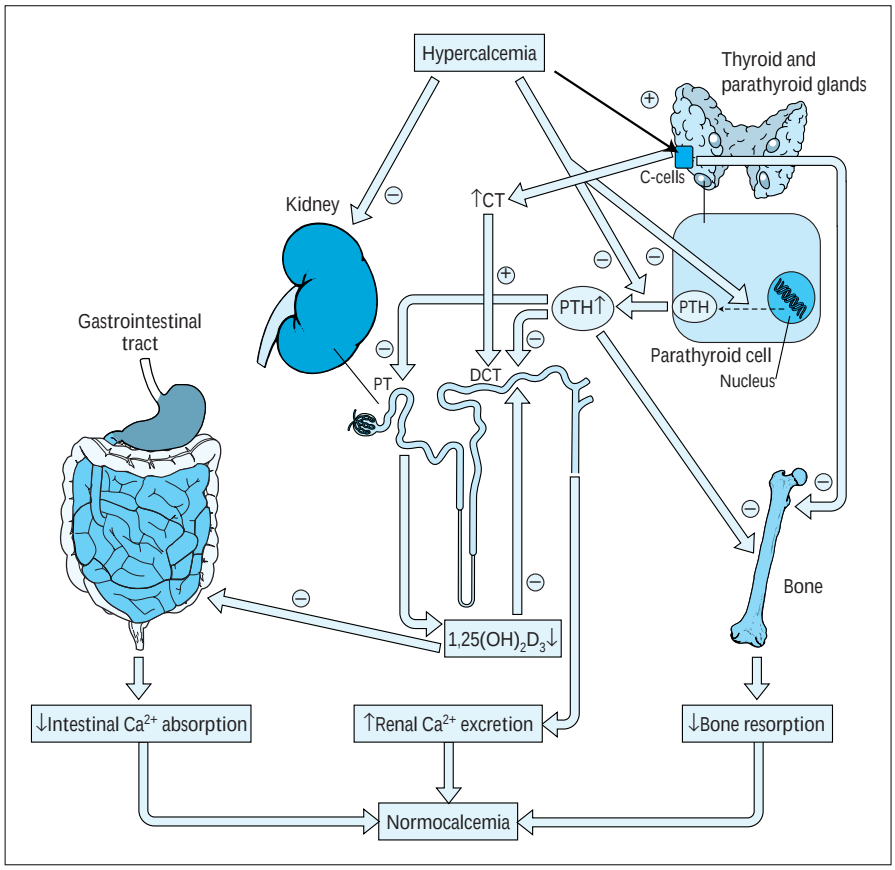


FIGURE 5-19

Physiologic response to hypercalcemia. Hypercalcemia directly inhibits both parathyroid hormone (PTH) release and synthesis. The decrease in PTH and hypercalcemia decrease the activity of the 1-α-hydroxylase enzyme located in the proximal tubular (PT) cells of the nephron, which in turn, decreases the synthesis of 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$). Hypercalcemia stimulates the C cells in the thyroid gland to increase synthesis of calcitonin (CT). Bone resorption by osteoclasts is blocked by the increased CT and decreased PTH. Decreased levels of PTH and $1,25(OH)_2D_3$ inhibit Ca reabsorption in the distal convoluted tubules (DCT) of the nephrons and overwhelm the effects of CT, which augment Ca reabsorption in the medullary thick ascending limb leading to an increase in renal Ca excretion. The decrease in $1,25(OH)_2D_3$ decreases gastrointestinal (GI) tract absorption of dietary Ca. All of these effects tend to return serum Ca to normal levels [1].

CAUSES OF HYPERCALCEMIA

Excess parathyroid hormone (PTH) production
- Primary hyperparathyroidism
- "Tertiary" hyperparathyroidism*

Excess 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$)
- Vitamin D intoxication
- Sarcoidosis and granulomatous diseases
- Severe hypophosphatemia
- Neoplastic production of $1,25(OH)_2D_3$ (lymphoma)

Increased bone resorption
- Metastatic (osteolytic) tumors (*eg*, breast, colon, prostate)
- Humoral hypercalcemia
  - PTH-related protein (*eg*, squamous cell lung, renal cell cancer)
  - Osteoclastic activating factor (myeloma)
  - $1,25\ (OH)_2D_3$ (lymphoma)
  - Prostaglandins
- Hyperthyroidism
- Immobilization
- Paget disease
- Vitamin A intoxication

Increased intestinal absorption of calcium
- Vitamin D intoxication
- Milk-alkali syndrome*

Decreased renal excretion of calcium
- Familial hypocalciuric hypercalcemia
- Thiazides

Impaired bone formation and incorporation of calcium
- Aluminum intoxication*
- Adynamic ("low-turnover") bone disease*
- Corticosteroids

*Occurs in renal failure.

FIGURE 5-20

Causes of hypercalcemia (increase in ionized plasma calcium).

AVAILABLE THERAPY FOR HYPERCALCEMIA*

Agent	Mechanism of action
Saline and loop diuretics	Increase renal excretion of calcium
Corticosteroids	Block 1,25-dihydroxy-vitamin D_3 synthesis and bone resorption
Ketoconazole	Blocks P450 system, decreases 1, 25-dihydroxy-vitamin D_3
Oral or intravenous phosphate	Complexes calcium
Calcitonin	Inhibits bone resorption
Mithramycin	Inhibits bone resorption
Bisphosphonates	Inhibit bone resorption

*Always identify and treat the primary cause of hypercalcemia.

FIGURE 5-21
Therapy available for the treatment of hypercalcemia.

Secondary Hyperparathyroidism

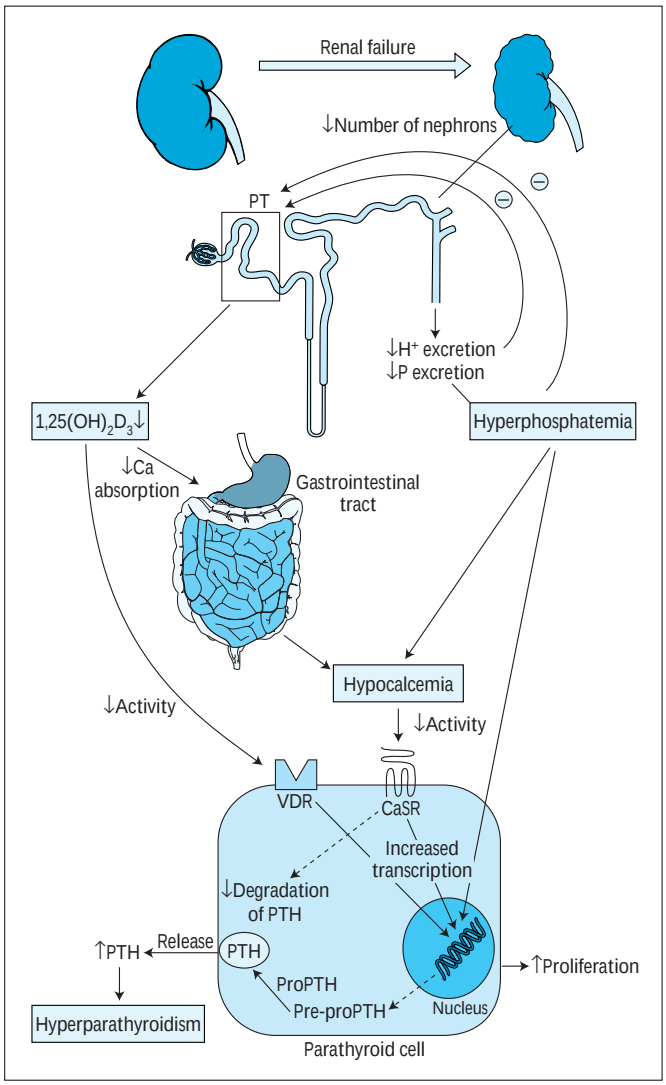


FIGURE 5-22
Pathogenesis of secondary hyperparathyroidism (HPT) in chronic renal failure (CRF). Decreased numbers of proximal tubular (PT) cells, owing to loss of renal mass, cause a quantitative decrease in synthesis of 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$). Loss of renal mass also impairs renal phosphate (P) and acid (H^+) excretion. These impairments further decrease the activity of the 1-α-hydroxylase enzyme in the remaining PT cells, further contributing to the decrease in levels of $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ deficiency decreases intestinal absorption of calcium (Ca), leading to hypocalcemia, which is augmented by the direct effect of hyperphosphatemia. Hypocalcemia and hyperphosphatemia stimulate PTH release and synthesis and can recruit inactive parathyroid cells into activity and PTH production. Hypocalcemia also may decrease intracellular degradation of PTH. The lack of $1,25(OH)_2D_3$, which would ordinarily feed back to inhibit the transcription of prepro-PTH and exert an antiproliferative effect on parathyroid cells, allows the increased PTH production to continue. In CRF there may be decreased expression of the Ca-sensing receptor (CaSR) in parathyroid cells, making them less sensitive to levels of plasma Ca. Patients with the b allele or the bb genotype vitamin D receptor (VDR) may be more susceptible to HPT, because the VDR-$1,25(OH)_2D_3$ complex is less effective at suppressing PTH production and cell proliferation. The deficiency of $1,25(OH)_2D_3$ may also decrease VDR synthesis, making parathyroid cells less sensitive to $1,25(OH)_2D_3$. Although the PTH receptor in bone cells is downregulated in CRF (*ie*, for any level of PTH, bone cell activity is lower in CRF patients than in normal persons), the increased plasma levels of PTH may have harmful effects on other systems (*eg*, cardiovascular system, nervous system, and integument) by way of alterations of intracellular Ca. Current therapeutic methods used to decrease PTH release in CRF include correction of hyperphosphatemia, maintenance of normal to high-normal levels of plasma Ca, administration of $1,25(OH)_2D_3$ orally or intravenously, and administration of a Ca-ion sensing receptor (CaSR) agonist [14–16,19–22].

Calcium and Vitamin D Preparations

CALCIUM CONTENT OF ORAL CALCIUM PREPARATIONS

Calcium (Ca) salt	Tablet size, mg	Elemental Ca, mg, %
Carbonate	1250	500 (40)
Acetate	667	169 (25)
Citrate	950	200 (21)
Lactate	325	42 (13)
Gluconate	500	4.5 (9)

Fractional intestinal absorption of Ca may differ between Ca salts.
Data from McCarthy and Kumar [19] and *Physicians' Desk Reference* [23].

FIGURE 5-23
Calcium (Ca) content of oral Ca preparations.

VITAMIN D PREPARATIONS AVAILABLE IN THE UNITED STATES

	Ergocalciferol (Vitamin D_2)	Calcifediol (25-hydroxy-vitamin D_3)	Dihydrotachysterol	Calcitriol (1,25-dihydroxy-vitamin D_3)
Commercial name	Calciferol	Calderol® (Organon, Inc, West Orange, NJ)	DHT Intensol® (Roxane Laboratories, Columbus, OH)	Rocaltrol® (Roche Laboratories, Nutley, NJ) Calcijex® (Abbott Laboratories, Abbott Park, NJ)
Oral preparations	50,000 IU tablets	20- and 50-µg capsules	0.125-, 0.2-, 0.4-mg tablets	0.25- and 0.50-µg capsules
Usual daily dose				
Hypoparathyroidism	50,000–500,000 IU	20–200 µg	0.2–1.0 mg	0.25–5.0 µg
Renal failure	Not used	20–40 µg*	0.2-0.4 mg*	0.25–0.50 µg
Time until increase in serum calcium†	4–8 wk	2–4 wk	1–2 wk	4–7 d
Time for reversal of toxic effects	17–60 d	7–30 d	3–14 d	2–10 d

*Not currently advised in patients with chronic renal failure.
†In patients with hypoparathyroidism who have normal renal function.
Data from McCarthy and Kumar [19] and *Physicians' Desk Reference* [23].

FIGURE 5-24
Vitamin D preparations.

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