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

		Ca Content*	
Location	Concentration	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

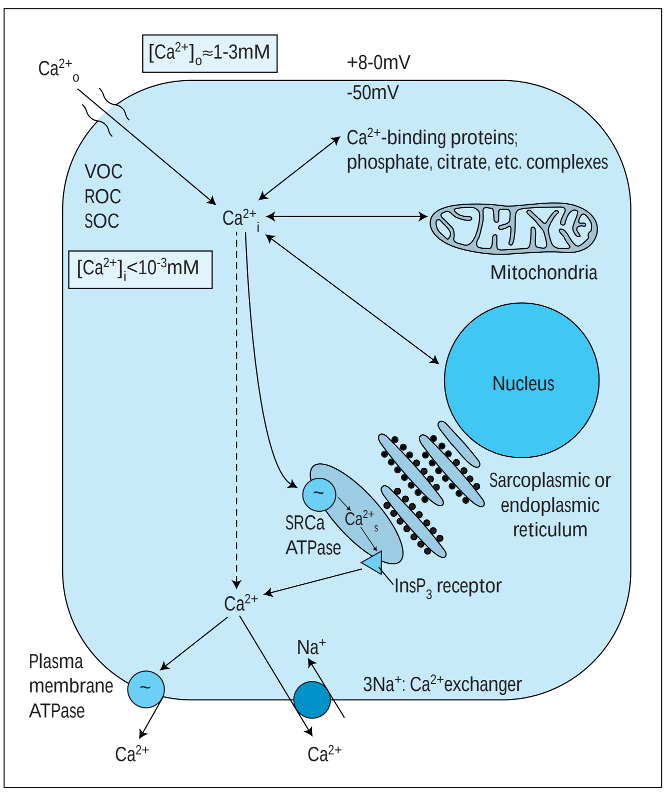

FIGURE 5-2

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

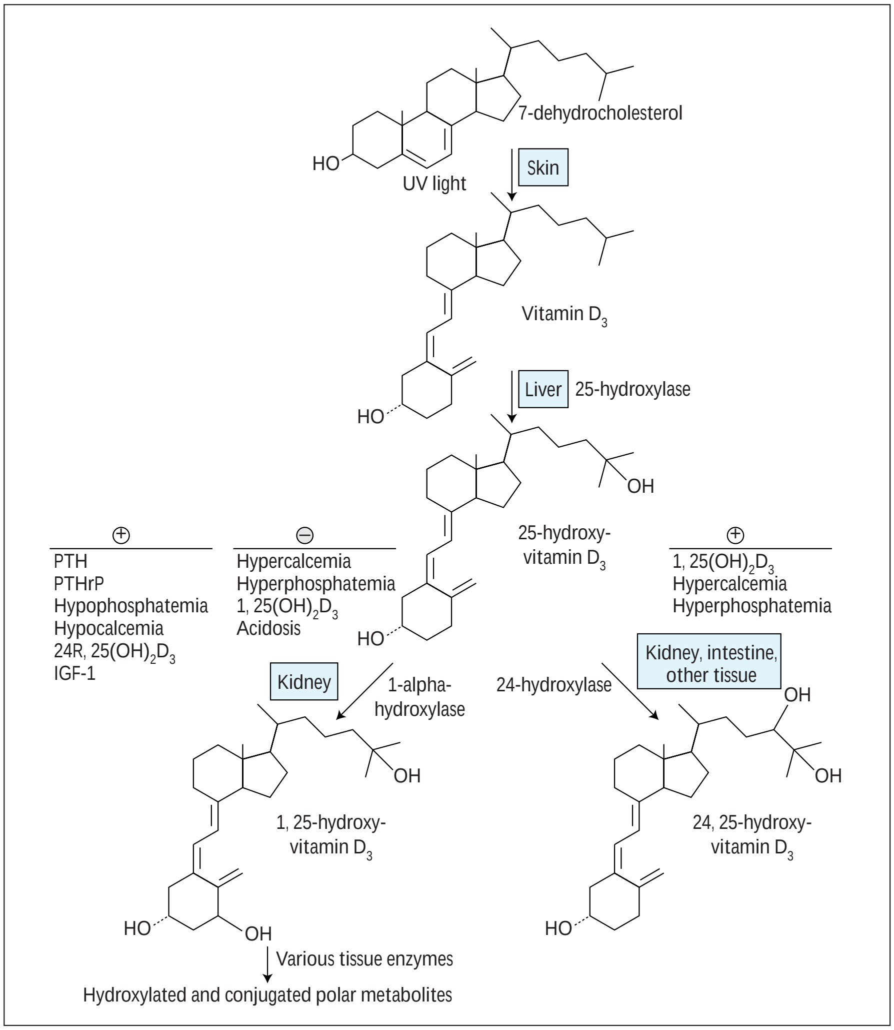

FIGURE 5-3

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].)

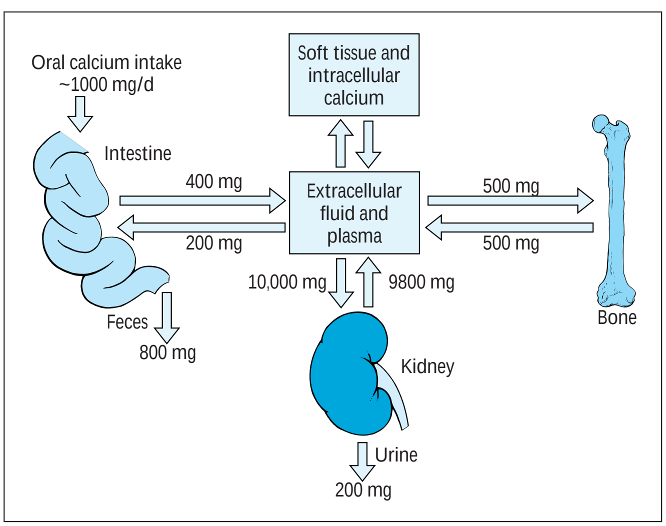

FIGURE 5-4

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.)