

FIGURE 5-5

Effects of 1,25-dihydroxy-vitamin D₃ (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.)

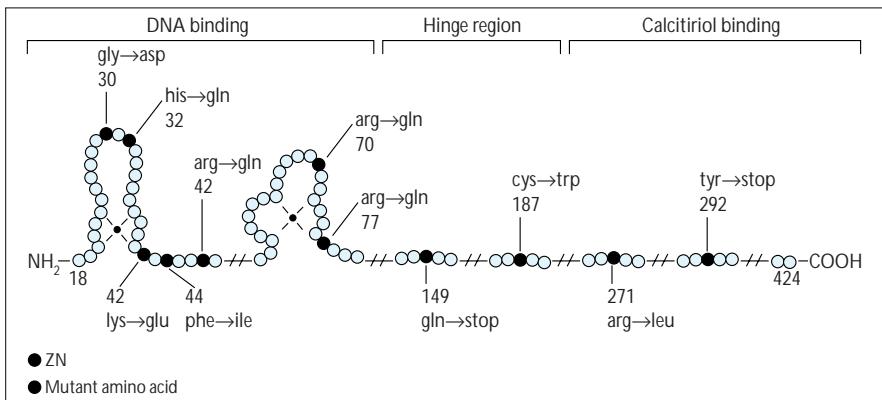


FIGURE 5-6

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; NH₂—amino terminal. (From Root [7]; with permission.)

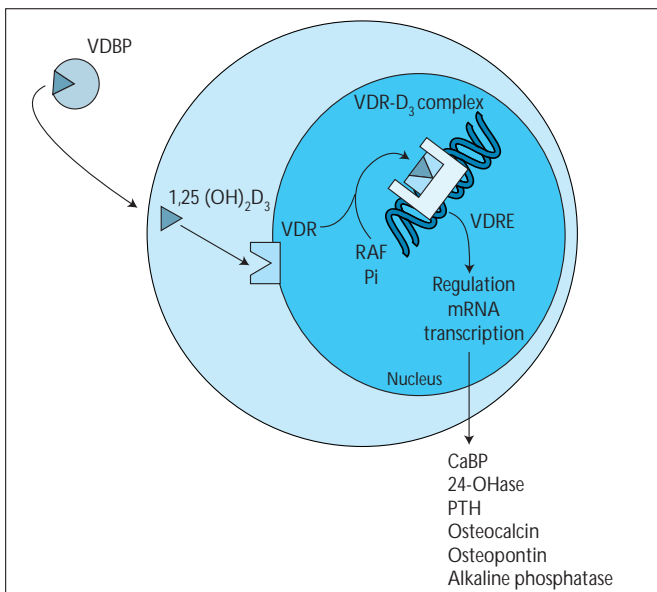


FIGURE 5-7

Mechanism of action of 1,25-dihydroxy-vitamin D₃ (1,25(OH)₂D₃). 1,25(OH)₂D₃ is transported to the target cell bound to the vitamin D-binding protein (VDBP). The free form of 1,25(OH)₂D₃ 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)₂D₃, such as Ca-binding proteins, the 25-hydroxy-vitamin D₃ 24-hydroxylase enzyme, and parathyroid hormone. Pi—inorganic phosphate. (Adapted from Holick [8].)

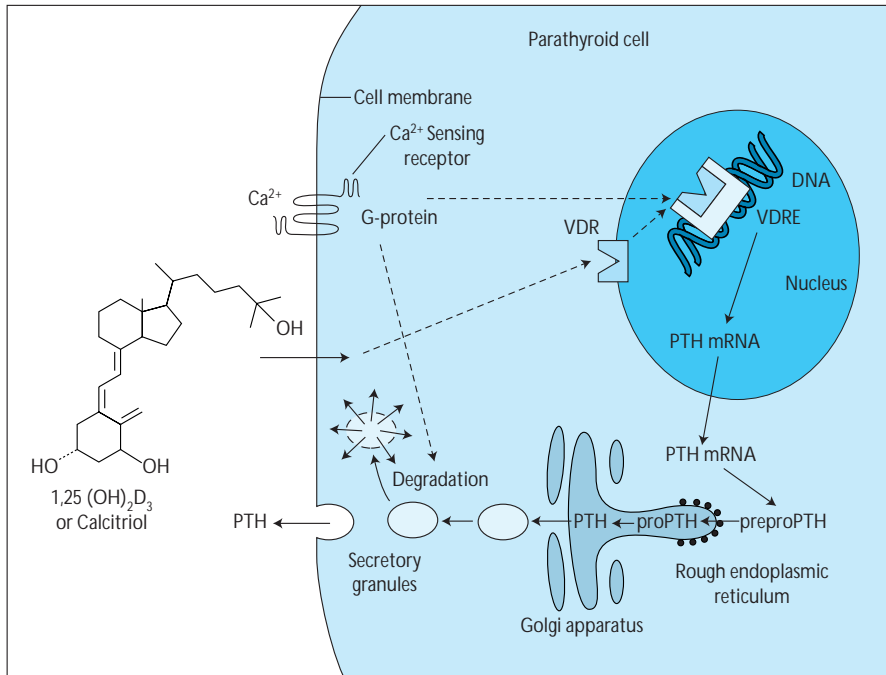


FIGURE 5-8

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 D₃, 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 E₂. Hypomagnesemia blocks the secretion of PTH [7,12]. VDR—vitamin D receptor; VDRE—vitamin D responsive element. (Adapted from Tanaka and coworkers [12].)

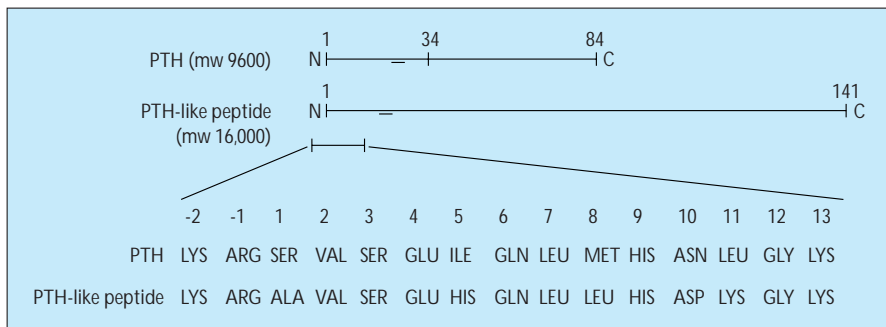
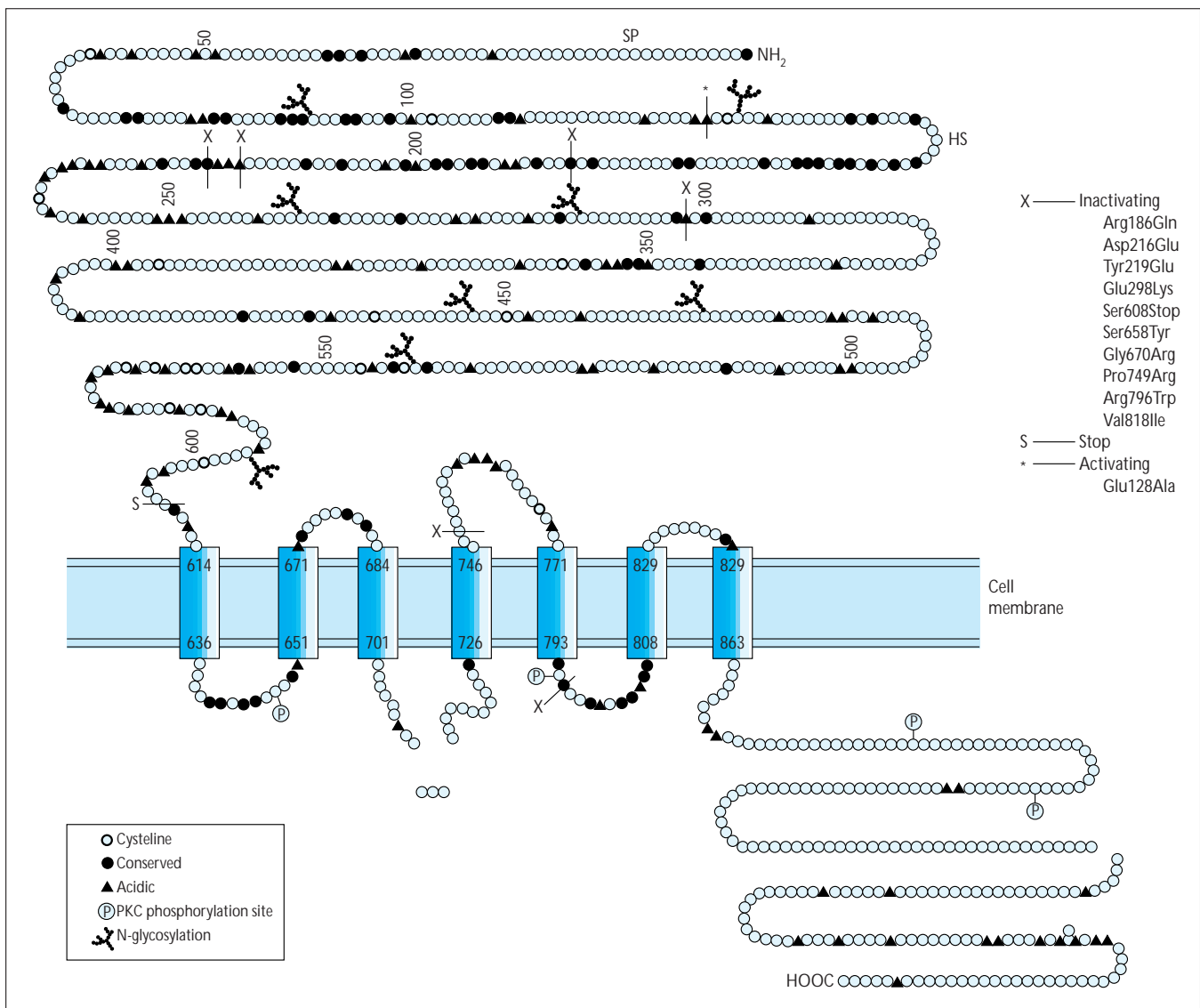


FIGURE 5-9

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 thyroïdal 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-bisphosphate 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; NH₂—amino terminal. (From Hebert and Brown [4]; with permission.)