integration of the calcium fluxes across the GI, skeletal, and renal compartments. The two key metabolic regulatory hormones that coordinate these activities are PTH and the active form of vitamin D, $1,25(OH)_2D$.

Regulatory Hormones

Parathyroid Hormone

PTH is a peptide hormone produced by the four parathyroid glands (Fig. 72-4). These glands are located behind the normal thyroid lobes, with two on the right and two on the left. Through the calcium sensor—a G protein–coupled receptor for calcium that is located on the surface of the parathyroid cell—the serum ionized calcium concentration is continuously monitored. In this exquisitely sensitive system, minor (e.g., 0.1 mg/dL) reductions in serum ionized calcium lead to PTH secretion, and minor increments in serum calcium lead to suppression of PTH secretion.

PTH is secreted as an 84-amino-acid peptide hormone that is rapidly (half-life of about 3 to 5 minutes) cleaved by the Kupffer cells in the liver into an active amino-terminal form; the carboxyl-terminal form is inactive. Continuous monitoring of the serum calcium concentration by the parathyroid glands, the immediate secretion of PTH in response to hypocalcemia, and the rapid clearance of PTH after secretion enable the parathyroid gland and PTH to regulate serum calcium with remarkable precision.

PTH targets three organs, two directly and one indirectly. The first directly targeted organ is the kidney, in which renal calcium excretion is inhibited by PTH. PTH also inhibits phosphate and bicarbonate reabsorption, which produces phosphaturia and hypophosphatemia and proximal renal tubular acidosis, respectively. The renal actions of PTH occur immediately. PTH also stimulates the production of the active form of vitamin D, $1,25(OH)_2D$.

PTH also directly targets the skeleton. PTH can mobilize calcium immediately from the skeleton through activation of osteoclastic bone resorption. Over days to weeks, PTH stimulates the activity of osteoblasts to produce new bone and thereby remove calcium from the circulation. The ability to stimulate osteoclasts acutely without activating bone formation is important for the rapid delivery of calcium to the ECF.

PTH has the indirect effect of increasing intestinal calcium absorption by increasing renal synthesis of $1,25(OH)_2D$. Seen in concert, PTH is secreted in response to hypocalcemia, and the actions of PTH combine to restore a low serum calcium concentration to normal by preventing renal calcium losses, by adding calcium to the ECF from the skeleton, and by indirectly stimulating (through $1,25(OH)_2D$) increases in intestinal calcium absorption.

Vitamin D Metabolism

Vitamin D is two compounds: ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) (Fig. 72-5). Both substances are inactive precursors. One (D_3) is derived principally from skin exposed to sunlight, and the other (D_2) is derived from plant sterols. Both D_2 and D_3 are found in multivitamins and commercial dietary supplements.

Both precursors are converted constitutively by the enzyme vitamin D 25-hydroxylase (CYP2R1) in the liver to their respective 25-hydroxyvitamin D (25[OH]D) derivatives. The derivatives also are inactive precursors, but they have two types of clinical significance. First, severe liver disease such as cirrhosis prevents this essential step and leads to vitamin D–deficient syndromes collectively called *hepatic osteodystrophy*. Second, 25(OH)D is the standard clinical laboratory measure of the vitamin D status (i.e., repletion or deficiency) of patients with hypocalcemia, osteomalacia or rickets, osteoporosis and intestinal malabsorption, and other similar conditions.

25(OH)D is converted, or activated, in the renal proximal tubule by the enzyme 25-hydroxyvitamin D_3 1α-hydroxylase (CYP27B1) to the active form of the vitamin, $1,25(OH)_2D$. This substance, which is also called *calcitriol*, is regulated by PTH. Increases in PTH stimulate $1,25(OH)_2D$ production, and decreases in PTH diminish $1,25(OH)_2D$ synthesis. The primary

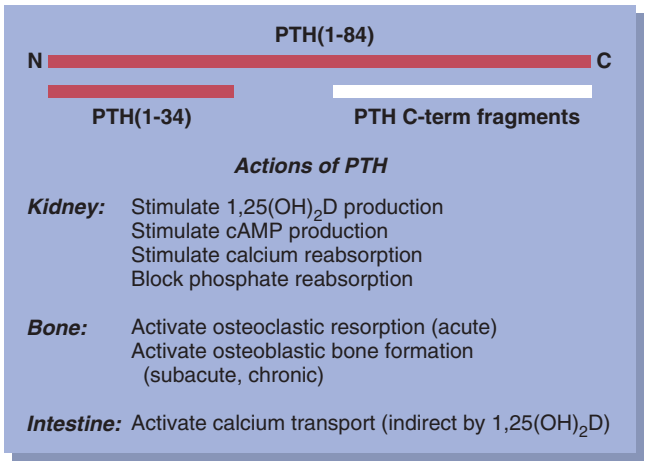

FIGURE 72-4 Structure and actions of parathyroid hormone (PTH). PTH is secreted as an 84-amino-acid protein, which is cleaved in the liver to derivative amino-terminal and carboxyl-terminal (C-term) forms. Actions of the amino-terminally intact forms of PTH are listed. cAMP, Cyclic adenosine monophosphate; $1,25(OH)_2D$, 1,25-dihydroxycholecalciferol.

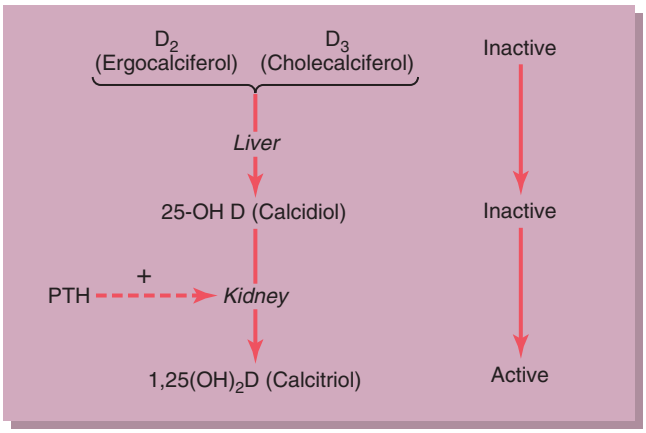

FIGURE 72-5 The vitamin D metabolic pathway. Biologically inactive vitamin D exists in two forms, D_2 and D_3, which are hydroxylated in the liver and kidney to yield the biologically active form of vitamin D: 1,25-dihydroxycholecalciferol ($1,25[OH]_2D$), also called *calcitriol*. PTH, Parathyroid hormone.