PTH and Vitamin D

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ABSTRACT

PTH and Vitamin D are two major regulators of mineral metabolism. They play critical roles in the maintenance of calcium and phosphate homeostasis as well as the development and maintenance of bone health. PTH and Vitamin D form a tightly controlled feedback cycle, PTH being a major stimulator of vitamin D synthesis in the kidney while vitamin D exerts negative feedback on PTH secretion. The major function of PTH and major physiologic regulator is circulating ionized calcium. The effects of PTH on gut, kidney, and bone serve to maintain serum calcium within a tight range. PTH has a reciprocal effect on phosphate metabolism. In contrast, vitamin D has a stimulatory effect on both calcium and phosphate homeostasis, playing a key role in providing adequate mineral for normal bone formation. Both hormones act in concert with the more recently discovered FGF23 and klotho, hormones involved predominantly in phosphate metabolism, which also participate in this closely knit feedback circuit. Of great interest are recent studies demonstrating effects of both PTH and vitamin D on the cardiovascular system. Hyperparathyroidism and vitamin D deficiency have been implicated in a variety of cardiovascular disorders including hypertension, atherosclerosis, vascular calcification, and kidney failure. Both hormones have direct effects on the endothelium, heart, and other vascular structures. How these effects of PTH and vitamin D interface with the regulation of bone formation are the subject of intense investigation. Published 2016. *Compr Physiol* 6:561-601, 2016.

Parathyroid Hormone

Introduction

Parathyroid hormone (PTH), a product of the parathyroid glands, embedded in the thyroid (in rodents) or located behind the thyroid (in humans), is a key regulator of calcium and phosphorus homeostasis through its effects on bone, kidney and intestine, and by regulating 1α, 25-dihydroxyvitamin D (372). The serum concentration of PTH is derived both from the release of PTH stored in secretory granules and from de novo synthesis of PTH in response to alterations in the serum levels of calcium, phosphorus, and vitamin D (277). Acute regulation of PTH is accomplished by the release of stored PTH in response to ambient calcium level through the calcium sensing receptor expressed on the chief cells of the parathyroid glands while long-term synthesis and release is dependent upon de novo synthesis through transcription and translation of mRNA encoding pre-pro-PTH (520, 521). PTH restores serum calcium by three different mechanisms: (i) release of calcium and phosphorus from the bones through stimulation of osteoclastic activity; (ii) decrease in calcium excretion and a concomitant decrease in phosphate reabsorption in the kidney; and (iii) increase dietary absorption of calcium and phosphorus in the gut (271) (Fig. 1).

Substantial advances made in the late 1970s and early 1980s to understand the biochemical and cellular regulation of PTH metabolism and mechanisms of action (278-282) led to the development of assays for the detection of PTH in the blood of humans and animals. These efforts uncovered the presence of multiple forms of immunoreactive PTH molecules in circulation adding a previously unappreciated complexity to PTH metabolism. Evidence suggests that the hormone is subjected to proteolysis both in the parathyroid gland and in end organs including liver and kidney. This review will focus on the structure, synthesis, secretion, and functions of the hormone and consider the pathophysiological, pharmacological, and treatment of abnormalities of biosynthesis and secretion of PTH.

History

Although evidence of pathologies now associated with the parathyroid glands can be documented as far back as ancient Egypt (164, 332), the existence of the parathyroid glands was not discovered until the second half of the nineteenth century, and their function not definitively explored until well into the twentieth century. The parathyroid glands went through numerous cycles of naming and discovery, and took several decades to gain traction in the scientific field. It was during

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Published online, April 2016 (*comprehensivephysiology.com*)

DOI: 10.1002/cphy.c140071

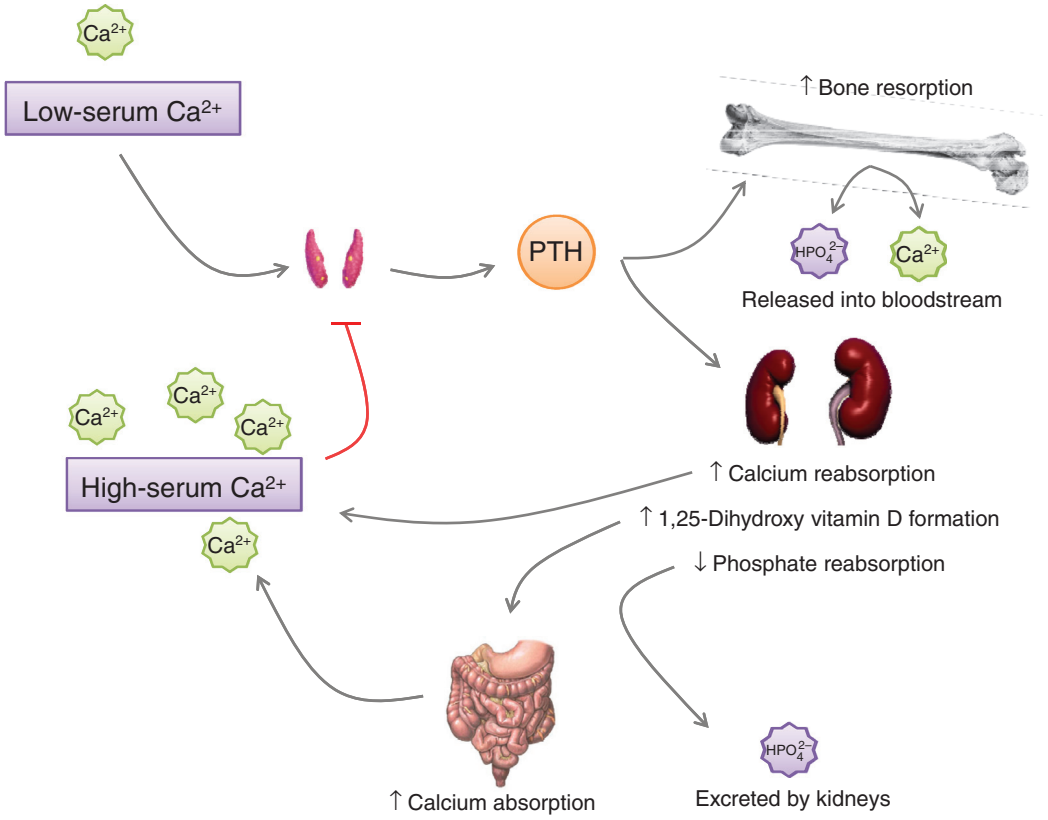

Figure 1 Regulation of serum Ca^{2+} by PTH. Low serum Ca^{2+} stimulates the release of PTH from the parathyroid gland. PTH acts on the bone to increase bone resorption, releasing Ca^{2+} and HPO_4^{2-} into the bloodstream. At the kidney, PTH increases Ca^{2+} reabsorption and decreases HPO_4^{2-} reabsorption, maintaining the elevated serum Ca^{2+} from the resorption of bone. Vitamin D becomes activated in the kidney by 1α-hydroxylase, leading to increased Ca^{2+} absorption from the gut. The restored serum Ca^{2+} provides a negative feedback signal to the parathyroid glands, discontinuing the release of PTH.

the necropsy of a Great Indian Rhinoceros in 1852 that Sir Richard Owen of the Royal College of Surgeons first described the parathyroid glands (219, 497). Remak (544) and Wirchow (690) found the parathyroid glands in humans. Although it had been well established by the beginning of the twentieth century that removal of the glands from humans and animals caused death from tetany, intense debate still existed as to the function of the glands. It was even suggested that the parathyroid glands serve a detoxification purpose, much akin to the liver (409-411). At the turn of the twentieth century, the German pathologist Erdheim determined that patients undergoing thyroid surgery who developed tetany had undergone simultaneous accidental removal of the parathyroid glands (201, 655). In 1915, Schlagenhaufer, a Viennese physician, was the first to draw the conclusion that the osteitis fibrosa cystica observed in his patient was in fact due to an enlarged parathyroid, and not the other way around (332). While previous researchers had implicated a role of the parathyroid in calcium homeostasis, injection of parathyroid extract into animals with tetany failed to relieve the symptoms; thus, the precise relationship between parathyroid glands and calcium homeostasis remained unclear. It was not until Collip developed a method for extracting biologically active parathyroid hormone that the role of the parathyroid glands in calcium homeostasis began to emerge. Collip used a hot acid extraction method to purify potent parathyroid extracts that when injected back into parathyroidectomized animals restored muscle excitability to normal levels (160-162, 522, 524). Although effective, the hot acid extraction was also harsh, and yielded fragmented portions of parathyroid hormone, which frustrated efforts to sequence the polypeptide in the 1950s. In 1954, Handler et al. (284) summarized the frustrations of several scientists in a report by stating that "(i) the active material in the gland may be large protein which in the course of isolation is degraded into fractions of varying size, each of which still has activity; (ii) the active molecule may not be a large molecule at all, but instead a small molecule which adheres to each one of these fractions." In 1959, Aurbach (35) and Rasmussen and Craig (534) independently isolated the polypeptide and individual fragments without degradation using organic solvent extraction methods. Using standard protein sequencing techniques, they were able to determine the structure of bovine and human PTH. In the 1970s with the development of molecular techniques, it became possible to determine the mechanisms for hormone synthesis, processing, and metabolism.

PTH gene regulation

Several proteins play a critical role in parathyroid gland development. These include glial cells missing (GCM), eyes absent (Eya1), and *Hoxa3/Pax1* compound genes. However, there is very limited information available identifying activating and repressing factors that control the transcription of the *PTH* gene. Early studies suggested that extracellular calcium inhibited *PTH* gene transcription through a conserved negative calcium-response element (371, 487-489). More recent studies have elucidated an additional role for calcium in regulation of PTH through posttranscriptional repression. Rats that were fed low calcium diets were found to have increased levels of PTH mRNA, whereas rats that were fed low phosphate diets had decreased PTH mRNA expression (457). Low serum calcium and high serum phosphorus are signals that both increase PTH secretion by increasing PTH gene expression posttranscriptionally (60, 61). Additionally, 1,25-dihydroxyvitamin D decreases PTH expression by decreasing PTH mRNA (471, 472). Vitamin D deficiency increases the PTH mRNA expression through two processes, (i) impaired calcium absorption leading to decreased extracellular calcium and (ii) removal of a known repressor of PTH gene transcription (369). Initial experiments determined that specific sequences in the 3′ UTR of PTH mRNA determine its rate of degradation (646). Calcium and phosphate were identified as regulating PTH posttranscriptionally, through alteration in the interaction of RNA binding protein with the 3′-UTR of the PTH transcript. Two of these proteins are AU-rich element binding factor 1 (AUF1) and KSRP (372). AUF1, an RNA-binding protein, enhances the PTH transcript stability by binding to the 3′UTR region in response to phosphate and calcium concentrations in the serum (61). KSRP destabilizes the PTH transcript through KSRP's interactions with the 3'-UTR of PTH mRNA (239). Other proteins involved in *PTH* gene expression include hepatocyte nuclear factor 1β (HNF1β), which binds to the PTH promoter and acts as a translational repressor, as patients with a mutated HNF1β display hyperparathyroidism (223).

Several consensus sequences have been identified in PTH promoter region that regulate its gene expression. A cyclic AMP response element was identified at the transcription start site of the human, bovine, and murine PTH genes. A unique DNA repressor element that binds to the vitamin D receptor has also been identified in the human PTH gene promoter. Alimov et al. (19, 20) identified a highly conserved Sp1 element and a Sp3 element in the human and bovine PTH promoter. Sp1 strongly stimulates the transcription of wild-type bovine and human PTH promoters. The role of Sp3 promoter is not known.

Structure and biochemical properties of PTH

The biosynthetic pathways involved in the synthesis, cellular transport, and metabolism of PTH has been extensively studied. These studies demonstrated that the mRNA encoding the PTH is translated as a 115 amino acid pre-pro-PTH on the rough endoplasmic reticulum (277, 343-346) (Fig. 2).

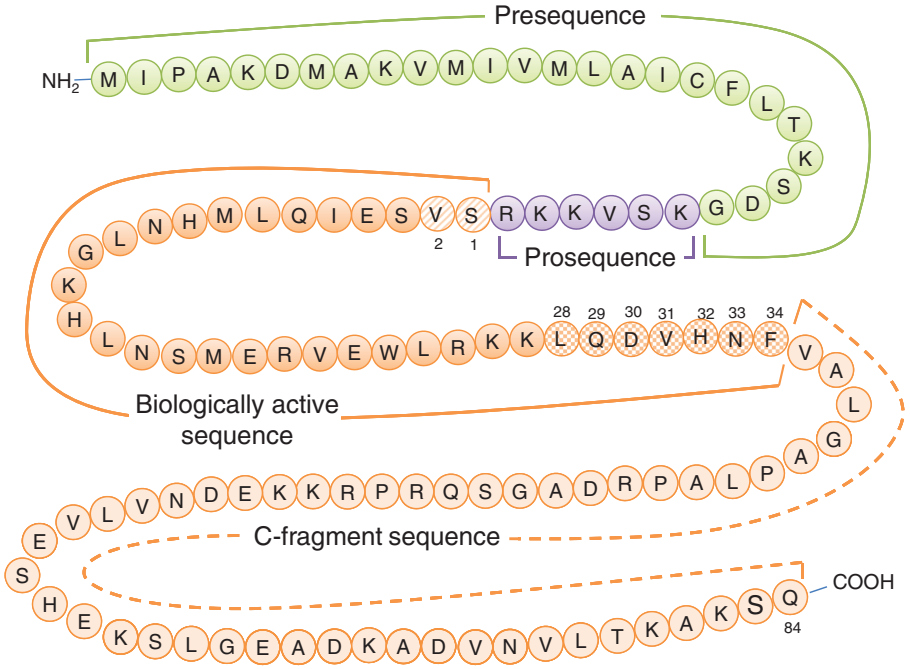

Figure 2 Primary sequence of human parathyroid hormone (sequence from Ensembl.org). The pre- and prosequences are cleaved prior to secretion into the bloodstream. Residues 1 and 2 (diagonally striped) are required for PTH receptor activation. Residues 28-34 (checkered pattern) interact with the extracellular amino domain of the PTH receptor. The C-fragment may be cleaved either prior to or after release from the parathyroid gland.

The first two methionines are cleaved during translation by a methionyl amino peptidase releasing the signal peptide such that the protein is directed to a membrane vesicle. During the transit to the Golgi, the N-terminal signal sequence of 23 amino acids is cleaved at the glycyl-lysyl bond to form an intermediate protein of 90 amino acids called the pro-PTH, which is an inactive precursor. The N-terminal six amino acids of the pro-PTH are proteolytically cleaved in the Golgi yielding the mature 84 amino acid PTH which is stored in granules to be released into the circulation by exocytosis after appropriate stimulus (282, 371, 598). Analysis of the region-specific radioimmunoassays demonstrated that pro-PTH constitutes only 7% of the total PTH in normal parathyroid glands and the rest is mostly mature PTH (283). The protein is further cleaved into smaller fragments by cathepsin-B in the parathyroid glands (227, 412, 413). The hormone and its fragments are removed from circulation by receptors predominantly in kidney but also in the bone (282).

The naturally occurring PTH 1-37 and 1-34 fragments of PTH maintain full activity of the intact PTH 1-84. Osteoporosis patients treated with PTH1-34 have increased bone density suggesting that this fragment of PTH has all the anabolic activities of the intact 1-84 PTH. Mutation analyses of the PTH molecule have identified amino acids critical for receptor signaling. Truncation of the first two amino acids (PTH 3-34) results in a partially active PTH while removal of the first six amino acids (PTH 7-34) results in a low-affinity antagonist. Further studies have demonstrated that the 17 to 34 amino acid residues are critical for high affinity receptor binding (468).

The structure of PTH has been partially defined through X-ray crystallography and NMR spectroscopy techniques (323). The secondary structure of PTH 1-34 differs depending upon whether it is in aqueous solutions, lipid solutions, or in the presence of secondary structure-inducing solvents such as trifluorethanol (47, 91, 357, 478, 505, 614). X-ray crystallography studies have identified critical amino acids associated with specific structural qualities of PTH. PTH 1-34 has a multihelical structure with a bend between amino acid residues 12 and 21 (323). Mutation analysis demonstrated that the helical structure around Gly12 is important for biological activity and binding of the peptide to its receptor (149, 150). NMR studies have shown three helices between Ser3-Asn10, Ser17 to Lys27, and Asp30 to Leu37 in the N-terminal. An additional poorly defined helix between Asn57 and Ser62 was observed in the C-terminal with evidence of interaction between helix 1 and helix 2. The NMR studies also demonstrated a "U" or "V" shaped tertiary structure formed by the interaction between the N- and C-terminal helices which form a hydrophobic core (47, 141, 270, 699).

Regulation of PTH synthesis, secretion, and metabolism

Mature PTH is stored in granules close to the plasma membrane. Electron microscopy of the parathyroid gland demonstrated that the granules containing mature PTH are limited while there are abundant immature vesicles present near the Golgi. These vesicles are transported to the cell surface without incorporation into mature granules. Extracellular ionized calcium concentration is the major physiologic regulator of the synthesis and secretion of PTH (Fig. 3A and B). Decreasing ionized calcium concentration by infusion of the calcium chelator, EGTA, in cows increases the synthesis and secretion of PTH within 20 s of infusion. The initial response to a 0.1 mg/dL decrease in calcium concentration is to release the preformed vesicles from the parathyroid gland (100). Chronic decreases in serum calcium will increase the rate of synthesis and release of PTH (101). Apart from serum calcium, epinephrine, calcitonin, vitamin D, magnesium, and phosphate regulate the synthesis and release of PTH in humans (105,226). (Fig. 3C) An extracellular calcium receptor (CaSR) acting as a sensor for ionized calcium levels provides the critical link between circulating ionized calcium concentration and PTH secretion, maintaining calcium within a narrow range. High extracellular calcium levels sensed by the CaSR results in decreased PTH secretion and increased Ca^{++} excretion by the kidney (148, 474). Conversely, lower levels of plasma calcium stimulate PTH secretion and Ca^{++} reabsorption by the kidney (474-477, 671).

Plasma PTH levels exhibit significant fluctuations during the course of the day and about 20% to 30% of its secretion is pulsatile (565). The circadian rhythm of PTH reaches a maximum at late morning, followed by two prominent peaks one in the afternoon and another in early morning (569). However, the maximum PTH secretion occurs at nighttime when the bone resorption activity is highest (202). Both nocturnal increases in PTH secretion and bone resorption can be prevented by administration of calcium in the evening (426). PTH concentration time profiles have revealed a rhythm of secretion consisting of seven secretory pulses per hour, accounting for approximately 30% of spontaneous PTH secretion and regulated by extracellular calcium (572). The mechanisms for the pulsatile secretion of PTH are not very well understood, nor are the functional consequences. It is proposed that the dense autonomic innervation of the parathyroid gland acts as neuronal pacemaker for PTH secretion (123, 208, 613). Acute disruption of sympathetic input by β-adrenergic receptor blockers increases the PTH pulse two fold and increases plasma PTH levels but does not eliminate the pulsatile oscillations (570,571). It has been suggested that this cyclic release of PTH may be critical for the anabolic effects of bone mass by activating the cyclic AMP pathway while chronically elevated levels of PTH lead to bone destruction through PKC and RGS2-dependent pathways (312,342). This is based, at least in part, on the observation that daily recombinant PTH injections, which results in exaggerated peaks of serum PTH levels, are an effective treatment for osteoporosis and bone repair, stimulating new bone production in postmenopausal women (75, 209). In contrast, sustained high levels of PTH seen in primary and secondary hyperparathyroidism tend to result in bone destruction. PTH secretion also is dependent upon seasonal fluctuations. It decreases by about

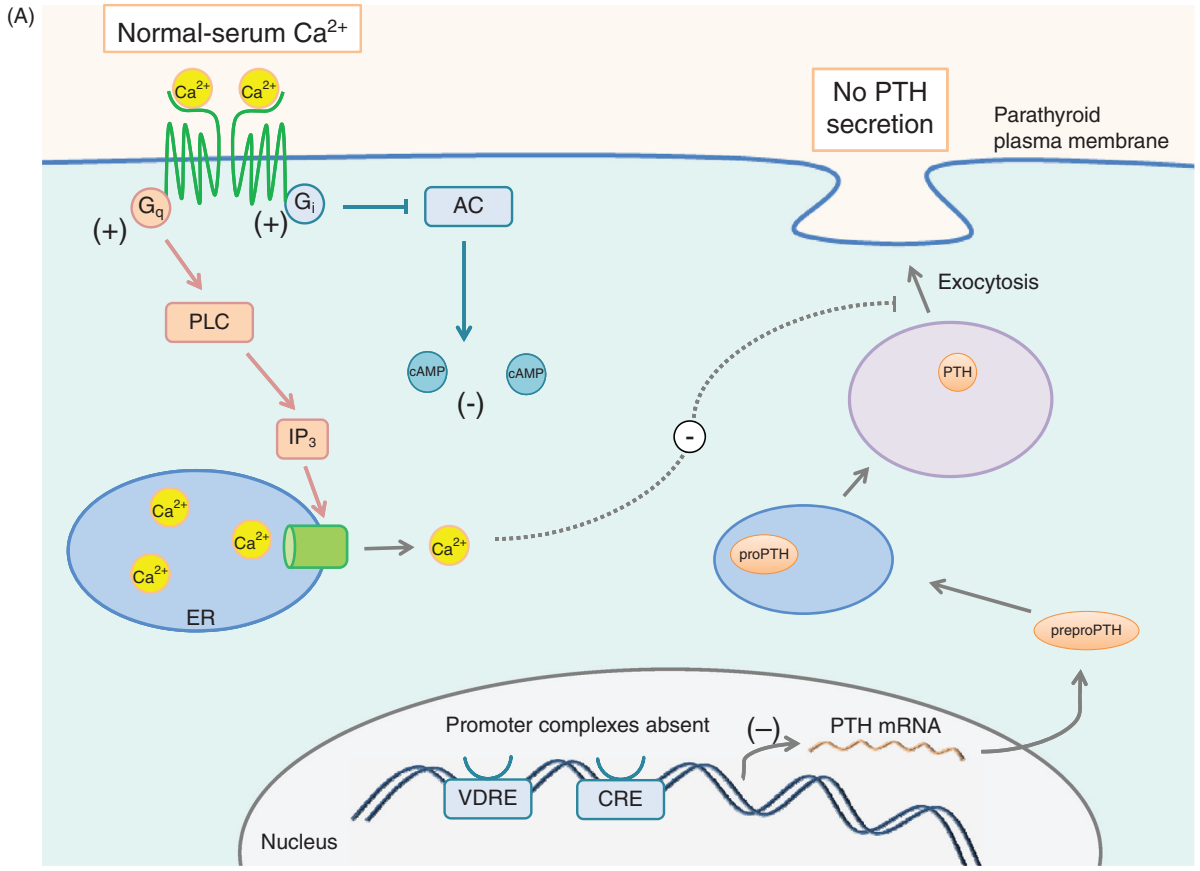

Figure 3 (A) Effect of serum $[Ca^{2+}]$ on PTH synthesis and secretion. Ca^{2+} binds to the CaSR and activates G_q and G_i. G_q activation leads to increased $[Ca^{2+}]_i$ via PLC signaling and IP_3 formation. Increased $[Ca^{2+}]_i$ inhibits exocytosis of PTH secretory vesicles. G_i activation inhibits adenylyl cyclase, leading to less cAMP, and therefore less transcription of the PTH gene as well as decreased stimulus for secretory vesicle exocytosis. (B) Effect of low serum $[Ca^{2+}]$ on PTH synthesis and secretion. In the absence of serum Ca^{2+}, CaSR signaling terminates, allowing $[cAMP]_i$ to increase, which drives transcription of PTH and secretory vesicle exocytosis, leading to increased serum PTH levels. (C) Effect of Vitamin D on PTH secretion. Vitamin D enters the cell through diffusion across the plasma membrane. Once inside, Vitamin D is bound by the vitamin D receptor (VDR). In the nucleus, the Vit D-VDR complex binds to RXR and the vitamin D response element (VDRE) within the PTH promoter. This promoter complex inhibits transcription of the PTH gene, leading to less preproPTH production. The Vit D-VDR complex also binds to the VDRE within the promoter of p21, activating the transcription of the p21 gene. Increased p21 expression inhibits parathyroid cell proliferation.

20% in summer and increases by about 20% in winter season (693).

Berson and Yalow demonstrated immunochemical heterogeneity of plasma PTH for the first time and suggested that this may be due to postsecretory modifications of the hormone (70-72). Later studies confirmed the observations of Berson and Yalow and by using RIA demonstrated that the majority of fractions are C-terminal fragments of the hormone (468). Habener et al. demonstrated that direct intravenous injection of intact bovine PTH into calves led to the accumulation of C-terminal fragments generated by peripheral metabolism of the administered hormone (278). In 1973 Canterbury et al. identified N-terminal fragments of PTH that were biologically active (117). This observation was later confirmed by several studies. The N-terminal fragments were found to be more short-lived than the C-terminal fragments. The discovery of biologically active N-terminal fragments led to the hypothesis that peripheral metabolism of secreted PTH is required for biological activity (503). However, this was disproved by the observations of Glotzman et al. who demonstrated that intact PTH could activate adenylate cyclase (260, 507). Fang and Tashjian (215) were the first to demonstrate the contribution of liver in clearance of intact PTH from circulation. This was later confirmed by several studies [reviewed in (468)]. Recent studies demonstrated that the Kupffer cells take up intact PTH, a process that is dependent on amino acids 28-48, and generate C-terminal fragments by proteolysis of the intact hormone (173, 174). Daugaard et al. (183, 184) demonstrated that only C-terminal biologically inactive fragments were generated during liver perfusion. Bringhurst et al. (110-112) demonstrated that the N-terminal fragments are degraded in the Kupffer cells. The demonstration that both intact and fragmented circulating forms of PTH are increased in patients with renal disease (71, 179, 443) and nephrectomized animals (118, 313, 431, 432) suggests that kidneys play a major role in PTH clearance. A portion of PTH is cleared independent of

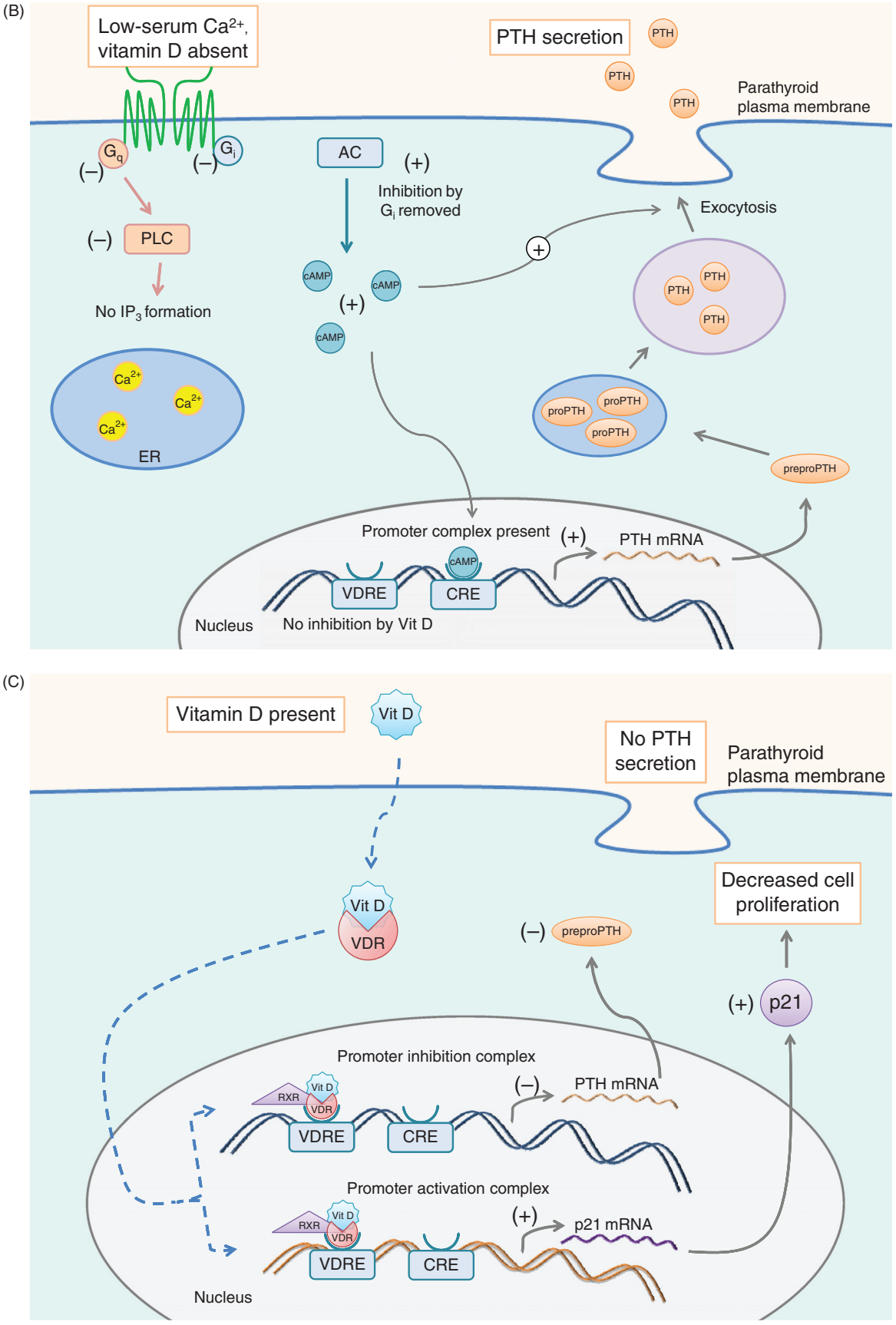

Figure 3 (*Continued*)

glomerular filtration, through peritubular uptake by binding to PTH1R and involve receptor-mediated endocytosis at the basolateral membrane of the tubule cells (185, 432). Recent studies suggest that megalin/cubulin-dependent endocytosis plays an important role in PTH clearance from urine independent of PTH1R (273, 298).

PTH receptors

Three distinct receptors for PTH viz., PTH1R, PTH2R, and PTH3R have been described in literature. The most common and the classical receptor, the PTH1R, a type II G-protein coupled receptor, is expressed widely, both in the classic PTH target tissues, bone and kidney, as well as many others. PTH1R is activated by both PTH and the PTH-related peptide, a protein that shares the name with PTH but is not derived from the same gene. PTH2R is expressed in very low levels in most tissues, except for the limbic system and the hypothalamus (148). PTH2R is activated by PTH and an unrelated protein, the tuberoinfundibular peptide of 39 amino acids (TIP39). The PTH3R was cloned from zebrafish and is activated 20 times more potently by PTHrP than PTH. The mammalian homologues of PTH3R have not yet been discovered.

The PTH1R is the best studied PTH receptor. Jüppner et al. in 1991 identified a 585 amino acids protein from COS7 and opossum kidney (OK) cells using 125I-[Tyr36]hPTHrP (1-35)NH2 binding (329). This protein was characterized as type II G-protein-coupled receptor, characterized by the presence of an ~150 amino acid N-terminal extracellular domain with four N-glycosylation sites, eight conserved extracellular cysteine residues forming four disulfide bridges, seven transmembrane regions, and a large (150-190 amino acid) intracellular C-terminal tail (148, 362, 578) (Fig. 4A). The *PTH1R* gene resides on the short (p) arm of chromosome 3 between positions 22 and 21.1 (3p22-p21.1). The PTH1R is encoded by a rather large 22 kb gene that contains 15 exons

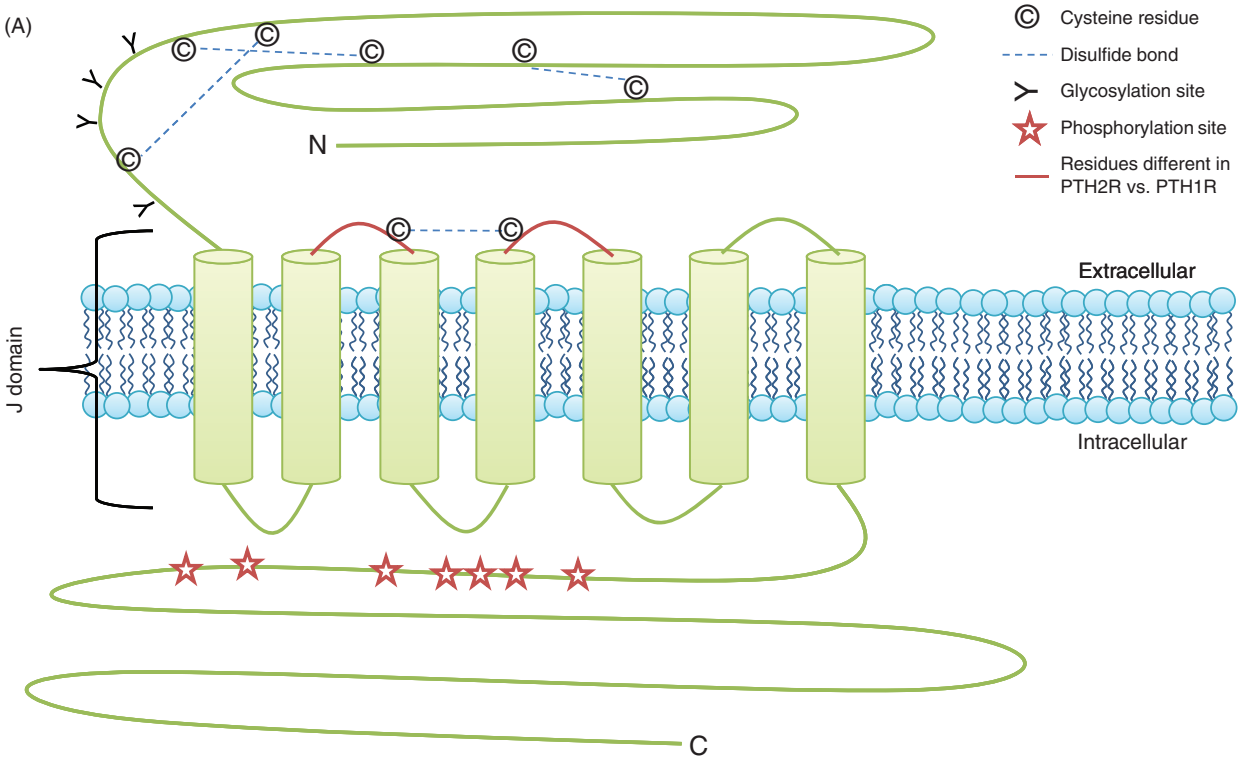

Figure 4 (A) PTH receptor topology and ligand binding. (A)The PTH1R consists of an extracellular amino terminus, a J domain consisting of transmembrane domains as well as intra- and extracellular loops, and an intracellular carboxy terminus. The extracellular amino terminus is 150 residues long, with 4 N-glycosylation sites and 4 disulfide bridges. Less is known regarding PTH2R topology as compared to PTH1R topology. Importantly, residue variations in two of the extracellular loops (highlighted in red) decrease the affinity of the receptor for PTHrP while maintaining specificity for PTH. (B) PTH receptor topology and ligand binding. (B) PTH(1-34) (rainbow structure) interacts with both the extracellular amino terminus of the PTH1R as well as the J domain. Docking of PTH to the PTH1R is thought to occur through initial binding of the C-terminus of PTH (residues 15-34) to the N-terminus (blue regions) of the PTH1R. This interaction is closely followed by the binding of the N-terminus of PTH (residues 1-14) to the J domain (red regions) of the PTH1R, initiating G protein recruitment and intracellular signaling cascade activation. (C) PTH-receptor binding and intracellular signaling. (1) Two-site model of PTH-receptor docking. (2) The N-domain of the PTH receptor (PTHR1) binds the C-domain of PTH. (3) The J-domain binds the amino-terminal region of PTH. (4) Binding of the ligand to the receptor increases the association with the J-domain, while also increasing the affinity of the intracellular beta-gamma binding region of the C-terminal region of the PTH receptor for G proteins, resulting in their subsequent activation and initiation of downstream signaling cascades. $G_{\alpha}s$ activates adenylate cyclase (AC), which increases intracellular [cAMP], resulting in activation of Epac and PKA. G_q activates phospholipase C (PLC), forming diacylglycerol (DAG) and inositol triphosphate (IP_3). DAG directly activates PKC, whereas IP_3 indirectly activates PKC by releasing Ca^{2+} from the ER.

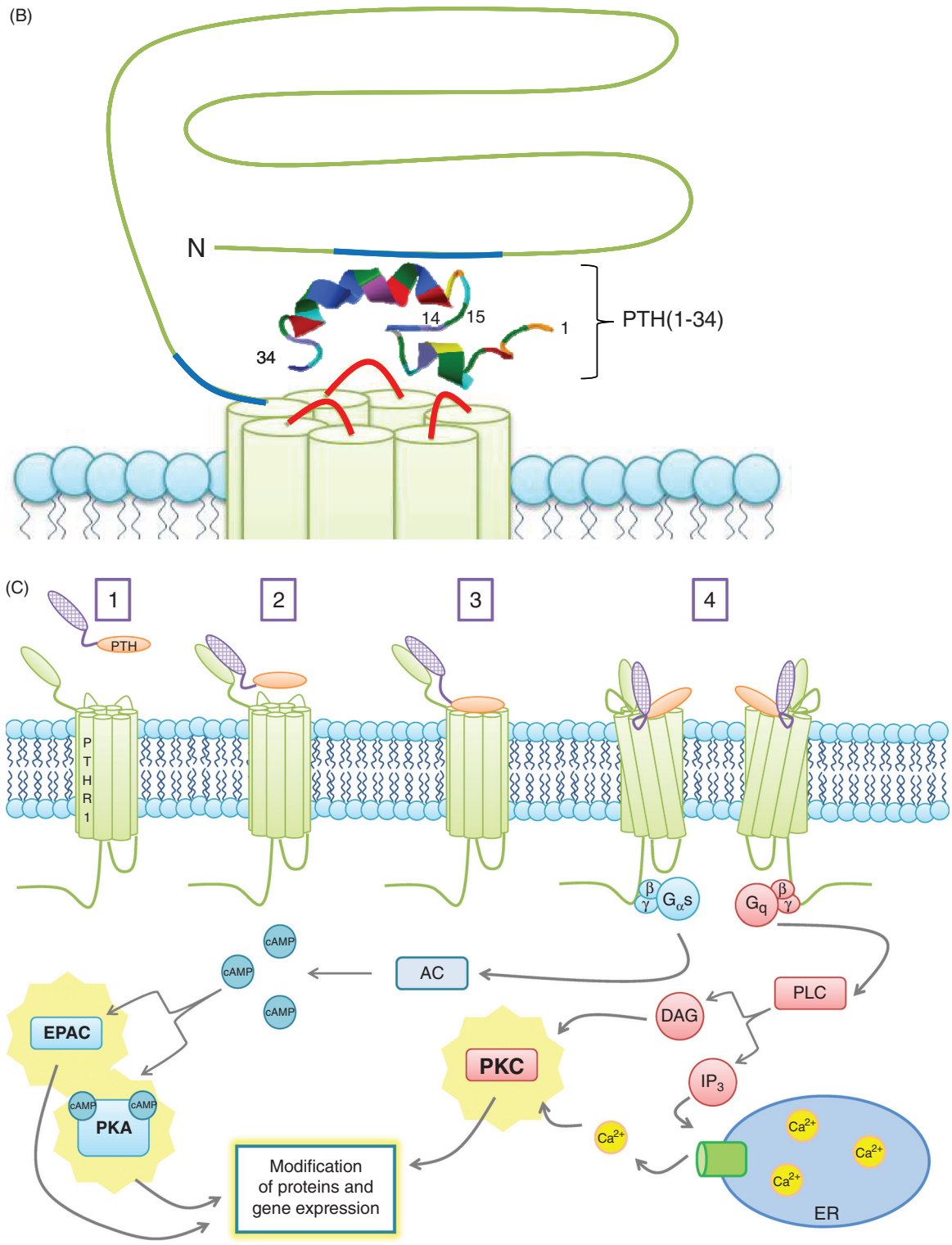

Figure 4 (*Continued*)

and 14 introns. The mature transcripts exhibit an extensive poly A tail at the 3′ end (366). Examination of the genomic map of the *PTH1R* gene has led to the identification of potential splice donor and acceptor sequences (148, 327, 366), and multiple promoters in the 5′ regulatory regions of the mouse, rat, human, and porcine PTH1R resulting in the production of multiple transcripts which show regulation at the developmental and tissue level (327, 441, 442, 595). The mouse, rat, and porcine transcripts have two promoter regions (P1 and P2) while the human transcript has three promoter regions (P1, P2,

and P3) (75,148,327,442,604). They all lack the conventional TATA box homology. However, they contain the GC rich Sp1 motifs and are regulated by ubiquitously expressed transcription factors Sp1, myc-associated zinc-finger protein, and embryonic TEA domain-containing factor (34,442,450). The P1 and P3 promoter regions are methylated in a tissue specific manner and the differential methylation patterns are important during development (74). Transcription of the PTH1R is regulated by vitamin D, retinoic acid, and glucocorticoids (23, 335, 643, 701). Vitamin D downregulates the transcription of PTH1R in osteoblasts by inhibiting the activity of P2 promoter while retinoic acid and dexamethasone increases the transcription in mouse embryonal carcinoma P19 cells and ROS 17/2.8 cells respectively but not in OK cells. Glycosylation is an important posttranslational modification of GPCR that regulates the intracellular folding, stabilization, intracellular trafficking, and function (23,335,643,644,701). The four N-glycosylation sites (N-151, 160, 165, and 175) are located in the putative ligand-binding extracellular amino terminal domain of the PTH1R. Initial studies using inhibition of glycosylation by tunicamycin or by treatment with endoglycosidase F in OK and HEK 293 cells suggested that glycosylation is not required for proper folding, expression, and ligand binding (91, 93, 382, 722). However, more recent data using site-directed mutagenesis of the Asn to Gln showed decreased membrane expression and ligand binding in transiently transfected COS-7 cells suggesting that glycosylation plays an important role in intracellular trafficking, membrane expression, and function of PTH1R (721). Mutations in the six extracellular amino terminal cysteine residues also showed decreased membrane expression and ligand binding of the PTH1R. Two amino acid residues, R233 in the second and Q451 in the seventh transmembrane domain, are highly conserved in type II GPCR, and critical for effective PTH interaction and signaling as mutations in these two sites reduce ligand binding and transmembrane signaling by PTH1R (148, 381) (Fig. 4B).

The PTH2R was identified by homology screening based on conserved sequences from calcitonin, secretin, and PTH1R from a cerebral cortex cDNA library. The gene for PTH2R, an 88kb gene with 13 exons and several large introns, has been located on chromosome 2q33. Like the PTH1R, the PTH2R is a class II GPCR and 51% identical to PTH1R. Similar to PTH1R, PTH2R has a large hydrophilic amino-terminal domain containing 120 amino acid residues containing four glycosylation sites and six extracellular cysteine residues, seven transmembrane domains, and a large intracellular C-terminal domain. The PTH2R is highly expressed in brain particularly in the limbic system and parts of hypothalamus. Peripherally, the PTH2R is also expressed in pancreatic islet D cells, parafollicular C cells of the thyroid, cells that produce gastrointestinal peptide, cartilage, and heart muscle cells (148). In contrast to the PTH1R, PTH2R selectively binds to PTH but not to PTHrP. The natural ligand of PTH2R in the CNS is the 39 amino acid tubero-infundibular peptide (TIP-39) in the bovine hypothalamus, described for human, rat, and zebrafish PTH2R. PTH also activates human PTH2R but not the rat and zebrafish PTH2R. TIP-39 and PTH do not share sequence homology. Only five residues of bovine PTH and TIP-39 are similar and align with each other. However, NMR studies have demonstrated that the two peptides are structurally very similar with regard to the orientation of polar and nonpolar amino acid residues in the amino-terminal region (57, 245, 300, 645).

The third and the most recently identified PTH receptor, the PTH3R was cloned using genomic PCR from zebrafish DNA. PTH3R is 69% similar and 61% identical to the PTH1R and shares only 48% similarity with PTH2R. PTH3R is almost exclusively activated by PTHrP and is the least studied of the three PTH receptors. The mammalian ortholog of PTH3R has not yet been identified. Similar to PTH1R and PTH2R, PTH3R has been classified as a class II GPCR but little else about its structure-function relationships is known (557, 702, 703).

Recent evidence suggests the presence of PTH receptors specific for the C-terminal of PTH which may play a role in gluconeogenesis, leukocyte migration, and pancreatic secretions [reviewed in (468)].

PTH-PTH1R interactions

Photo-affinity cross-linking studies of the interactions between a modified PTH 1-34 and its cognate receptor (PTH1R) suggest that the position 13 of the PTH (1-34) docks at the positions 169-198 in the N-terminal region of the PTH1R (3,91,722) and position 27 of PTH1-34 docks at position 241-285 of the receptor (267, 512). The 1, 3, 23, and 27 positions of the PTH interact with the receptor residues M425, R186, T33/Q87, and L261 (91, 148). Molecular modeling demonstrated that the N-terminal region of hPTH1-34 binds to an invagination of the PTH receptor formed between TM3, TM4, and TM6. (Fig. 4B) Mutation analysis revealed that the residues Trp23, Leu24, and Leu28 of PTH1-34 interact with Phe173 and Leu174 of the PTH receptor through hydrophobic interactions. Hydrophilic interactions are formed between Arg20 of PTH1-34 and residues Glu177, Glu180 of the receptor, and between Lys27 of PTH1-34 and Glu169 of the receptor (250). Mutation of Leu24 and Leu28 results in 4000- and 1600-fold decrease in binding affinity, respectively, while mutation of Asp30 to Lys has no effect on receptor binding (246). The hydrophilic interactions are less important for binding as compared to hydrophobic interactions (246). The human PTH1-37 and 1-34 fragments retain full activity of the intact PTH1-84 and activate both adenylyl cyclase and phospholipase C activity. However, PTH1-31 is nearly equipotent but predominantly stimulates adenylyl cyclase activity, while removal of 2 N-terminal amino acids (PTH3-34) results in loss of adenylyl cyclase activity but activation of phospholipase C activity is retained (45, 46, 231, 685).

Based on molecular modeling, Hoare et al. (299) described a "two-site" dynamic model of interaction between PTH and PTH1R. According to their model, the extracellular

N-terminal domain of PTH1R is the docking site for the C-terminal portion of PTH 1-34. The N-terminal of PTH 1-34 interacts with the J domain of the PTH1R which includes extra and intracellular loops and the transmembrane domains. The PTH1R N-domain provides the binding interactions between PTH and PTH1R while the J domain provides a stabilization function involved in receptor activation, G-protein coupling, and signal transduction (65, 330). Residues 15-34 of PTH function primarily as the binding domain (131) while residues 1-14 domain are responsible for the initiation of intracellular signaling through adenylate cyclase and PKC (65, 242, 246, 521). The binding of the N- and C-termini of PTH to the N- and J-domains of the receptor leads to increased affinity of the ligand-receptor complex, G protein complex formation, and activation of the downstream signaling pathways (65, 243, 244, 330). The current data suggest that the PTH receptor and PTH complex is present in an intermediate preactive R^0 confirmation where G proteins are not coupled to the receptor ligand complex. The PTH-PTHR1 interaction stimulates the binding of heteromeric G proteins and the complex switches to an active confirmation (RG). Competition binding assays suggest that PTH1-34 binds with greater affinity to the R^0 state than the RG state (299).

Signaling mechanisms of PTH1R

When PTH binds to the PTHR, the PTHR undergoes conformational change that promotes binding of G proteins (Gαβγ) to the receptor, followed by exchange of GDP for GTP on the α-subunit, and dissociation of the Gα from Gβγ subunits. (Fig. 4C) Gαs activates adenylyl cyclases to synthesize cyclic-AMP resulting in activation of protein kinase A (PKA). Gαq activates phospholipase C (PLC) which converts PIP2 to diacyl glycerol (DAG) and inositol (1,4,5)-triphosphate (IP3). IP3 stimulates calcium release from the endoplasmic reticulum to the cytosol. Increased Ca^{++} allows translocation of protein kinase C to the plasma membrane where it is activated by DAG (658, 660). Identification of signal selective peptides has led to better understanding of the PTH-PTHR interactions and downstream signaling mechanisms. For example, PTH1-28 is a cAMP-selective agonist that stimulates PKA activation but does not activate PLC-dependent and -independent PKC activation. This agonist also does not cause receptor internalization or recruitment of β-arrestin. Removal of the first two amino acids of PTH results in loss of cAMP signaling (92). Mutation analysis has demonstrated that the conserved valine at position 2 is critical for signaling through both arms (589). PTH 7-34 acts as a weak antagonist of PTHR, does not stimulate either Gs or Gq-mediated signaling pathways but does cause receptor internalization. The N-terminal truncated PTH fragments like PTH7-34 and PTH39-84 may have inhibitory effects (479). The C-terminal fragments of PTH blunt bone resorption and vitamin-D dependent osteoclastogenesis (196). These actions of PTH are thought to be independent of PTHR but are dependent upon yet an elusive carboxy-terminal PTH fragment receptor and stimulate alkaline phosphatase activity and induce expression of mRNA for both alkaline phosphatase and osteocalcin (195,617). It is important to note that the ability of PTH to activate cAMP and/or PLC/PKC pathways is cell specific. For example, PTH stimulates cAMP-PKA pathway but not the PLC/PKC pathway in vascular smooth muscle cells (415) while in keratinocytes (495,684), cardiac myocytes (531, 568), and lymphocytes (359), PTH activates PLC/PKC pathway but not the cAMP/PKA pathway. The development of FRET based assays allowed kinetic studies of binding of PTH to its receptor and signaling in live cells. These studies demonstrated that binding of PTH to its receptor involves two steps. The first step, rapid binding of PTH to the N-terminus of the receptor, requires 150 ms at saturating concentrations of PTH. The second step where the C-terminal of PTH binds to the J-domain of the receptor is considerably slower, requiring about 1 s. The subsequent interaction between PTHR and Gs depends upon the expression levels of Gs and can be completed in about 0.96 s. In about 10 s following receptor coupling with Gs, cAMP production is initiated (130, 222, 656).

The actions of PTH on bone are very well documented and have been the subject of recent excellent reviews (62, 135, 165, 209, 459, 528, 543, 591, 691, 719). PTH interacts directly with osteoblasts and osteocytes through PTH1R to stimulate a number of different pathways including cAMP/PKA, PLC/PKC, β arrestin translocation, and ERK1/2. In bone, the downstream signaling from these pathways is heavily regulated by RGS2 (regulator of G protein signaling 2), one of a family of proteins that modulates G protein activity stimulated by G protein-coupled receptors. Depending on whether the hormone presence is continuous or pulsatile, the overall effect of PTH signaling on bone metabolism will be catabolic or anabolic, respectively. Key to determining which effect predominates is the differential control of the osteoprotegerin-receptor activator of NFκB ligand-receptor activator of NFκB (OPG-RANKL-RANK) pathway. OPG, which is a bone-derived cytokine, and RANK, which is a receptor located on the preosteoclast, compete for binding with RANKL, another bone derived cytokine. Interaction between RANK and RANKL stimulates osteoclastogenesis while OPG prevents that interaction by binding itself to RANKL. It is this pathway that controls the PTH-stimulated interaction with the osteoclast precursor cell, which can mature into a functional osteoclast and mediate bone resorption. Continuous presence of PTH leads to an increase in the mRNA for RANKL and a decrease in the mRNA for OPG through PKA dependent pathways, the result of which is enhanced binding of RANKL to RANK and enhanced osteoclast maturation. PTH stimulates osteoblast differentiation, decreases osteoblast apoptosis, and activates lining cells. The effects of PTH to stimulate osteoblastogenesis can be seen in bone progenitor cells, mediated through changes in the transcriptional program that result in the expression of characteristic bone proteins such as alkaline phosphatase, type I collagen, RUNX2, and others. Recently, several downstream mediators of PTH action on bone have been identified including monocyte chemoattractant protein-1, sclerostin, dickkopf1, and EphrinB2/EphB4

(591) Investigation into the mechanisms of PTH regulation of bone is a dynamic area of inquiry as witnessed by the recent explosion of findings highlighting the intricacies of the process.

The other major target for PTH is the kidney. In human kidneys, the PTH receptors are expressed in proximal tubules, cortical ascending limbs of the Loop of Henle, and distal tubules. The receptors are expressed on both the apical and basolateral membranes of proximal tubules (291, 340, 353, 546,633). Activation of the receptors on the basolateral membranes activates the PLC/PKC pathway while activation of the receptors on the apical membranes activates cAMP-PKA pathway (546, 633). Both pathways contribute to endocytosis of the type IIa sodium-phosphate cotransporter, leading to inhibition of phosphate reabsorption (350,351,380,467). The differences in the activation of PLC/PKC pathway or cAMP-PKA pathway has been attributed to the binding of PTHR to sodium-hydrogen exchanger regulatory factor-1 (NHERF1), a scaffolding protein that exhibits two internal PDZ domains and an ezrin binding domain at the C terminal (677). Mahon and Segre recognized that the intracellular C-terminal domain of PTHR expresses a PDZ recognition motif D/E-S/T-X-ϕ that preferentially binds to PDZ1 domain of NHERF1 and PDZ2 domain of NHERF2 (418), and confirmed that PTHR binds to both proteins, NHERF1 and NHERF2. NHERF1 and NHERF2, through binding with ezrin, link membrane proteins with the actin cytoskeleton and recruit several proteins including receptors, ion transporters, and signaling proteins to the plasma membrane (97,167,676,677). Using heterologous expression of NHERF2 and PTHR in PS120 fibroblast cells, Mahon and Segre identified that PTH activates PLC/PKC pathway. In the absence of NHERF2, PTH activated cAMP-PKA without affecting PLC/PKC pathway (418,419). These studies suggest that NHERF provides signaling switch that could explain cell specific functions of PTHR independent of PTHR expression levels and expression of splice variants of PTHR (237). The expression patterns of NHERF1 and PTHR have important physiological consequences for renal phosphate and calcium handling. NHERF1 null mice exhibit phosphaturia and hypophosphatemia in part due to decreased apical membrane expression of type IIa sodium phosphate cotransporter without any changes in serum calcium (121, 167-170, 583, 584, 663, 675, 678-681). Phosphate wasting without changes in serum calcium has also been seen in patients who express NHERF1 polymorphisms or mutations (64, 166, 334, 545). The absence of NHERF1 expression in distal nephrons may explain the differences in the renal regulation of phosphate and calcium by PTH (237).

PTH1R trafficking and desensitization

Following binding and activation, the PTHR undergoes internalization and desensitization similar to most GPCRs (251, 252, 386). PTHR is phosphorylated in the C-terminus by G-protein-coupled receptor kinases (GRKs), resulting in increased association with β-arrestin and internalization through clathrin-coated pit dependent pathways (129, 606, 618, 624, 625, 659). Some of the receptors undergo rapid recycling while the rest are degraded in the lysosomes. The PTHR desensitization is more complex due to its associations with cytoplasmic adapter proteins NHERF1, NHERF2, and disheveled (Dvl2) (552, 607). Binding of these adapter proteins to the C-terminal domain of PTHR alters the selectivity and specificity of PTHR signaling through cell and ligand-dependent effects (273,416,417,420). The laboratory of Peter Friedman extensively studied the internalization of PTHR in kidney cells. Using EGFP tagged PTH1R they demonstrated that GRK2-dependent phosphorylation of PTH1R is required for endocytosis in mouse proximal and distal tubule cells (92, 657). Their studies revealed that the PTH fragments that do not activate the receptor like PTH7-34 cause endocytosis in distal convoluted tubules but not in proximal tubules (237, 660). When they stimulated NHERF1- transfected distal tubule cells with PTH 7-34, they demonstrated blunting of internalization of PTH1R. Similarly, proximal tubule cells expressing dominant negative NHERF1 showed increased internalization of the PTHR in response to PTH7-34. These data suggest that interaction of PTHR with NHERF1 plays an important role in receptor internalization (237,660). Mutations in the PDZ binding motif of PTHR prevented binding of NHERF1 to the PTHR but did not interfere with signaling or internalization of the receptor. These results suggest that the intact PDZ motif is required for association with NHERF1, but additional studies will be needed to define the nature of association and the impact on receptor internalization. Mutations in the NHERF1 ezrin binding domain prevented NHERF1-PTHR-actin interaction but failed to prevent internalization in response to PTH7-34. Similar results were shown in the presence of actin destabilizing agent, cytochalasin-D. Together these studies suggest that degradation of any component of the interaction between NHERF1-PTHR-actin cytoskeleton allows internalization of the PTHR in response to PTH7-34 (237).

Recent studies from Friedman laboratory suggest that PTHR also associates with the PDZ adaptor protein disheveled 2 (Dvl2). Unlike, the interaction with NHERF1, association with Dvl2 occurs between residues 470 and 480 of the PTHR. Using immunoprecipitation, they demonstrated that PTH1-34 increases interaction between PTHR and Dvl2 transiently. Binding of PTHR with Dvl2 increases its association with AP2 and β-arrestins resulting in internalization of the receptor (140, 552, 710).

Recent studies suggest that internalization of the PTHR in response to PTH1-34 does not completely blunt cAMP-PKA pathway. These observations led to the hypothesis that persistent calcemic responses in animals, prolonged increases in serum 1,25-dihydroxyvitamin D, bone resorption and prolonged cAMP-PKA activation results from signaling through intracellular PTH bound to PTHR in the early endocytic compartment. These provocative studies suggest that GPCR stimulated signaling is not confined to the plasma membrane (116,192,222,360). Further studies are required to determine

the physiological consequences of intracellular signaling through endocytosed GPCRs.

Functions of PTH

Several very careful cellular, molecular, and *in vivo* studies helped to understand the physiological roles of PTH. PTH plays diverse roles in the body from maintaining whole body calcium homeostasis to maintaining bone density. In the kidney, PTH regulates phosphate homeostasis by decreasing expression of sodium-phosphate cotransporters NpT2a (38, 39, 96, 121, 188, 203, 294, 348, 350, 351, 467) and NpT2c (109, 274, 377, 379, 454, 455, 576, 577), thus inhibiting reabsorption of filtered phosphate by the proximal tubules. PTH may also decrease phosphate absorption in the intestine by decreasing membrane expression of NpT2b (115, 255, 562). These two actions that tend to decrease total body phosphate content contrast with the pro-absorptive effects of PTH on calcium and ensure that maintenance of adequate calcium stores is not accompanied by accumulation of excessive phosphate. PTH increases ammoniagenesis (146) and gluconeogenesis (347, 573, 664) in the kidney. In the proximal tubules PTH induces inhibition of bicarbonate partly through inhibition of Na^+/H^+ exchanger activity (235). The actions of PTH on Na^+/H^+ exchanger are complex and different from the actions of Na-Pi cotransporters. PTH inhibits the activity of Na^+/H^+ exchanger but does not decrease the number of transporters whereas it causes endocytosis and degradation of Na-Pi cotransporters (390, 707, 720). The activity of Na^+/H^+ exchanger returns quickly to normal levels once PTH is removed unlike the activity of Na-Pi cotransporters which requires de novo synthesis (292, 462). PTH activates 25 vitamin D 1α-hydroxylase, thus stimulating conversion of 25-hydroxy vitamin D to its active form, 1, 25-dihydroxy vitamin D (373, 586). The active vitamin D increases calcium reabsorption in the intestine. In the thick ascending limb of the Loop of Henle PTH increases transepithelial transport of sodium, calcium, and magnesium. PTH stimulates distal renal tubular calcium reabsorption by regulating the expression of proteins involved in calcium reabsorption, viz; sodium calcium exchanger, Ca-ATPase, calbindin, TRPV5, and TRPV6 (187, 235, 321, 651). PTH promotes apical calcium entry through dihydropyridine-sensitive calcium channels. Apical calcium entry in this segment of the nephron is favored due to basolateral increase in chloride conductance resulting in increased chloride efflux and fall of intracellular chloride concentrations. Calbindin also plays a crucial role in calcium homeostasis by binding to reabsorbed calcium inside the cells and therefore prevents increases in free intracellular calcium. Expression of calbindin is regulated by PTH-dependent calcitriol synthesis (321). However, the most important function of PTH is to regulate bone mineralization. PTH affects all bone cells; stimulation of osteoblasts enhances bone formation while stimulation of osteoclast maturation increases bone resorption. The stimulatory effects of PTH on bone turnover have been successfully and effectively used pharmacologically to treat osteoporosis (520).

Interaction of PTH with other hormones

The most well studied interaction of PTH with other hormones is the interaction with fibroblast growth factor 23 (FGF23)/klotho complex (328). FGF23 is produced by osteocytes and osteoblasts (68, 429, 525, 527, 588, 597, 704). Both PTH and FGF23 are phosphaturic hormones and regulate phosphate homeostasis by inhibiting phosphate absorption in the intestines and reabsorption in the kidneys through decreasing membrane expression of sodium-phosphate cotransporters NpT2a (26, 247, 248) and NpT2c (66, 247, 248). PTH increases 1α-hydroxylase activity, active vitamin D, and calcium absorption in the intestines and reabsorption in the kidneys whereas FGF23 decreases 1α hydroxylase activity, active vitamin D thereby decreasing the absorption of calcium (289). PTH and FGF23 regulate the synthesis of each other. Higher serum phosphate increases the synthesis of FGF23 and lowers serum calcium, which will trigger synthesis of PTH. While PTH increases calcium reabsorption and indirectly increases FGF23 synthesis. Both of these mechanisms will eventually result in bone disease (328).

In recent years, an association between PTH and aldosterone has been described. New data demonstrate the expression of PTH in the aldosterone secreting zona glomerulosa cells of the adrenal glands and the expression of the mineralocorticoid receptor in parathyroid cells (632). Studies suggest that PTH directly regulate the secretion of aldosterone from the zona glomerulosa cells of adrenal glands and aldosterone in turn regulates PTH secretion from the parathyroid cells (631, 632). Isales et al. (316) and Olgaard et al (490) demonstrated that PTH stimulated aldosterone secretion in a dose dependent manner and potentiated angiotensin 2 stimulated aldosterone secretion. Rosenberg et al confirmed that adrenal glands are a novel target of PTH (554, 555). The effects of PTH on aldosterone secretion were mediated through PTH1R activation of cAMP/PKA and PLC/PKC pathways (213, 214). In patients with primary hyperparathyroidism (pHPT), elevated levels of aldosterone have been demonstrated (249), and parathyroidectomy has resulted in decreased aldosterone levels, decreased blood pressure, decreased risk of metabolic syndrome, and improvement in several parameters of vascular function (21, 216, 217, 407, 496). A prospective study in 226 patients with essential hypertension demonstrated a positive correlation between aldosterone and PTH levels (631, 632). Primary aldosteronism (PA) has been associated with higher PTH and lower calcium. Treatment with spironolactone decreased PTH levels in PA patients (556). Taken together these data suggest aldosterone and PTH cooperatively would cause vascular damage to multiple organs and support the hypothesis that regulation of PTH and aldosterone are associated, though whether these are linked or separate pathways remains unclear. These primarily epidemiologic and associative studies require more investigation to confirm a true

cause and effect relationship and to identify the prevalence of these combined disorders.

Pathophysiology

Once it was recognized that parathyroid glands secrete a hormone, PTH, in response to changes in ionized calcium levels, studies were conducted to understand the consequences of hyper- or hyposecretion of PTH. Even in the absence of reliable imaging techniques or assays for the measurement of mineral ions in the early twentieth century, pioneering work of several investigators identified clinical sequelae of excessive (hyperparathyroidism) or insufficient (hypoparathyroidism) PTH.

Hyperparathyroidism

The insights gained from pathological and mechanism-based studies identified and defined the clinical features of hyperparathyroidism (16, 17). Hyperparathyroidism may be primary or secondary (448). pHPT can result from an adenoma, multigland hyperplasia, or carcinoma. In most (about 90%) adults a single adenoma causes pHPT while others (about 5%) may have double or multiple adenomas of the parathyroid glands. About 5% of patients present with glandular hyperplasia and 1% with carcinoma (558). Mechanisms for the development and growth of parathyroid adenomas in the setting of primary and secondary hyperparathyroidism have been investigated extensively. The size of the adenomas is inversely proportional to the nutritional status of vitamin D (532), suggesting a role for vitamin D in regulating the growth of these adenomas, presumably through the VDR. On the other hand, studies of the expression of vitamin D receptor in the adenomas have not demonstrated a consistent pattern (368, 616, 654). Similarly, expression of the CaSR in adenomas has been described as increased, decreased, or unchanged; however, recently Koh and colleagues identified RGS5 as highly expressed in parathyroid adenomas and have suggested that the increased expression of this protein could alter CaSR signaling to decrease its effect on PTH secretion (361). Proteomic analysis comparing normal and adenomatous tissue suggests that proteins involved in apoptosis are decreased in parathyroid adenomas compared to normal parathyroid glands (653). The genetic basis for the development of sporadic hyperparathyroidism has not been fully established. In some circumstances, mutations in the *MEN1* gene, the *RET* gene, or the *CaSR* gene which are associated with familial forms of hyperparathyroidism have been identified, but not universally (630). Clearly, multiple different mechanisms appear to result in the clinical syndrome of hyperparathyroidism, suggesting that identification of these mechanisms in the individual patient could lead to more directed and effective therapy, perhaps even nonsurgical therapy (585).

Clinically, most patients present with asymptomatic hypercalcemia on routine lab work and a high circulating PTH level. Older literature classically refers to the manifestations of hyperparathyroidism as "stones, bones, abdominal groans, and moans" (58). Stones are due to nephrocalcinosis, hypercalcuria, and renal tubular reabsorption disturbances. Bone pain can be experienced due to fractures resulting from enhanced bone resorption leading to osteoporosis and osteitis fibrosa cystica. Abdominal groans are due to nausea, constipation, anorexia, and pain. Moans refer to both neuromuscular and neuropsychiatric symptoms including depression, anxiety, cognitive dysfunction, and fatigue. Other symptoms include headache, emesis, polydipsia, diarrhea, and joint pains (58). Symptoms are frequently more severe in children than in adults but this may be due in part to delay in diagnosis as serum calcium is not monitored regularly in children (364). Recent data suggest that cyclin D1 mutations also cause pHPT (32, 33, 422, 423).

pHPT can be normocalcemic, asymptomatic, or hereditary (533). Normocalcemic hyperparathyroidism is a fairly newly recognized condition wherein patients present with normal calcium (including ionized calcium) levels and high serum PTH levels with no secondary causes like renal disease, medications, gastrointestinal illness, idiopathic hypercalciuria, or vitamin D deficiency (592). A percentage of these individuals later develop hypercalcemia. It is often diagnosed in patients found to have low bone mass or nephrolithiasis. This two-phase process for the development of full-blown hyperparathyroidism is incompletely understood. One theory holds that initial target organ resistance to the actions of PTH, as would be seen perhaps in premenopausal women with higher circulating estrogen levels, mask the hypercalcemic response to PTH, which then becomes apparent after menopause when estrogen levels decline precipitously. However, most patients with normocalcemic hyperparathyroidism actually are postmenopausal, somewhat negating this theory (18). The epidemiology and natural history of this disorder are not well understood as yet [reviewed in (172)].

Asymptomatic hyperparathyroidism is characterized by mild hypercalcemia, low to deficient vitamin D, and normal serum phosphate levels. It is more prevalent in women than in men and manifests within the first decade after menopause. In asymptomatic patients, densitometric and histomorphometric analyses demonstrate reduced bone mineral density in the distal one-third radius while lumbar region is often preserved and the hip region is intermediate between distal and lumbar regions. PTH levels are high with low 25-hydroxyvitamin D levels [reviewed in (593)].

Familial hyperparathyroidism is a group of inherited autosomal dominant parathyroid disorders (256). These include multiple endocrine neoplasia (MEN) type I MEN1, type 2 MEN2a, type 4 MEN4, familial hypocalciuric hypercalcemia (FHH), neonatal severe hyperparathyroidism (NSHPT), autosomal dominant moderate hyperparathyroidism (ADMH), hyperparathyroidism-jaw tumor syndrome (HPT-JT), and familial isolated hyperparathyroidism (FIHPT). MEN1 is caused by mutations in the *MEN1* gene on chromosome 11q13 (388, 389). Patients develop parathyroid adenomas but

carcinomas are rare. Patients show multiglandular parathyroid disease with asynchronously and asymmetrically enlarged parathyroid glands (211, 212, 236, 424). MEN2a syndrome is an autosomal dominant condition with high risk of developing medullary thyroid carcinoma. The average onset of PHPT is 38 years of age (256). MEN2 is caused by mutations in *RET* gene localized to chromosome 10 that encodes a tyrosine kinase (286, 458, 463-465). MEN2 is characterized by parathyroid adenoma or hyperplasia (256). MEN4 is a rare disorder, the result of mutations in *CDKN1B* gene leading to dysfunctional cell cycle inhibitor p27 (383, 384, 425, 504). Little is known about this illness.

FHH and NSHPT are associated with inactivating mutations in *CaSR* gene. FHH patients express a mutation in one allele and have hypercalcemia, mild hypermagnesemia, and hypophosphatemia. Generally, these individuals are completely asymptomatic; however, parathyroid glands may be moderately enlarged. This condition is differentiated from the usual sporadic pHPT by very low urine calcium, generally less than 100 mg/day, and requires no treatment. NSHPT is a homozygous form of FHH, resulting in the very rapid development of PHPT at birth or shortly thereafter. Patients have severe hypercalcemia, bone demineralization, and neurodevelopmental disorders. In this disorder, parathyroid glands should be surgically removed within first few days of life to prevent fatal outcome (434-437).

ADMH is caused by mutations in cytoplasmic C-terminal tail of CaSR and is characterized by parathyroid hyperplasia or adenoma. The treatment of choice is surgical removal of the parathyroid gland (126, 127).

HPT-JT is an autosomal dominant disorder caused by mutations in the HRPT2 gene encoding parafibromin, a critical protein for cell growth (128). HPT-JT is associated with a variety of manifestations including fibrous-osseous tumors of the jaw, Wilm's tumor, papillary renal carcinoma, polycystic kidney disease, renal cysts, and pHPT (132, 133, 136, 582). Sporadic parathyroid carcinomas are very common in the HPT-JT patients (256).

FIHPT is another rare autosomal dominant disorder associated with mutations in CaSR, MEN1, and HRPT2 genes. The disease is characterized by uni- or multiglandular lesions of parathyroid glands, treated by simple surgical removal of adenomas (285, 449, 626, 672).

Secondary hyperparathyroidism is quite common and is caused by decreased levels of vitamin D, hypocalcemia, or in chronic renal disease (233). Patients may present with low bone density, osteoporosis, or fragility fractures. Hypocalcemia of any cause can result in increased PTH secretion. Common clinical situations include intestinal malabsorption or poor diet, which limit calcium intake; pancreatitis or rhabdomyolysis, which sequester calcium; or vitamin D deficiency due to poor diet, lack of sun exposure, nephrotic syndrome, or liver failure. In contrast to pHPT, correction of the underlying disorder will normalize PTH levels. Individuals with secondary hyperparathyroidism more commonly have diffusely hyperplastic glands than those with sporadic pHPT, who more likely will have an adenoma. Secondary hyperparathyroidism complicates the clinical course of nearly all patients with chronic kidney disease, although it is generally not manifest until late in the course. The etiology of secondary hyperparathyroidism associated with chronic kidney disease is complex (210, 275). Early in the development of chronic kidney disease, levels of FGF23 begin to rise, a phenomenon attributed at least in part to the loss of renal expression of klotho and to a diminished ability of the kidney to excrete phosphorus. The rise in FGF23 is mirrored by a decrease in 1,25-dihydroxyvitamin D, resulting in decreased intestinal calcium absorption and hypocalcemia. Clinically, this hypocalcemia may be subtle, asymptomatic, and not recognized. As kidney failure progresses, frank hyperphosphatemia becomes more prominent. The combination of hypocalcemia, decreased active vitamin D, and hyperphosphatemia results in progressive secondary hyperparathyroidism, which is not easily reversible. These individuals may exhibit parathyroid gland hyperplasia or multiple adenomas composed of monoclonal or polyclonal clusters of parathyroid cells. The secondary hyperparathyroidism of chronic kidney disease is implicated in a variety of complications of kidney disease including accelerated vascular disease, vascular calcification, and fractures.

Hypoparathyroidism

Patients with hypoparathyroidism present with severe hypocalcemia, hyperphosphatemia, tetany, hypomagnesemia, and lower levels of vitamin D. Basal ganglia calcifications are another very common feature of this syndrome. The most common cause of hypoparathyroidism is damage or removal of parathyroid glands during neck surgery, especially complicated thyroid surgery. However, hypoparathyroidism may occur as a congenital disorder or as an autoimmune condition, in isolation or in conjunction with other organ failure. The reader is referred to several recent excellent clinical reviews of this rare condition (73, 89, 590). A number of parathyroid-specific autoantibodies have been identified and implicated in the development of hypoparathyroidism in the autoimmune polyendocrinopathy syndrome type I, including antibodies directed against the calcium sensing receptor, tryptophan hydroxylase, interferon omega, and the NACHT leucine rich repeat protein 5 (NALP5) to name a few. However, the autoantibodies responsible for isolated autoimmune hypoparathyroidism and for other forms of autoimmune polyendocrinopathy syndromes are still in question. Standard treatment for symptomatic patients has been high-dose active vitamin D and calcium, but recently, clinical trials of recombinant parathyroid hormone have been initiated (171). Another rare syndrome is pseudohypoparathyroidism where there is resistance to PTH hormone action, either globally or confined to the proximal tubule of the kidney. This condition is caused by mutations in the gene for the Gsα subunit, resulting in abnormal Gsα function or in abnormal Gsα transcription (448, 629).

Human chondrodysplasias

Two devastating forms of chondrodysplasia, Blomstrand's lethal chondrodysplasia (BLC) and Jansen's metaphyseal chondrodysplasia (JMC), resulting from mutations in PTH1R gene have been described (567).

BLC was first described by Blomstrand et al in 1985 (99) and is prenatally lethal due to premature bone mineralization, ossification, shortened limbs, and abnormal tooth and mammary gland development (567, 700). Three different inactivating PTH1R mutations have been identified in patients with BLC, which result in failure of PTH to bind to the receptor, diminished PTH1R expression, or impaired signal transduction [reviewed in (567)].

JMC is a rare autosomal dominant disorder associated with severe abnormalities of the growth plate. Clinically, the patients have short stature, disproportionate limbs, and micrognathia. Patients have severe asymptomatic hypercalcemia, hypophosphatemia, increased phosphate and cAMP excretion in urine, and elevated levels of vitamin D with normal or undetectable PTH. JMC is caused by gain of activity single point mutations in PTH1R including H223R, T410P, and I458R that result in PTH-independent activation of cAMP/PKA pathway [reviewed in (567)].

Enchondromatosis is caused due to common solitary or multiple benign tumors of bone. Recently, missense mutation (R150C) in PTH1R has been identified in two patients with enchondromatosis. The mutation results in a constitutively active receptor leading to increased cAMP levels. This mutation is less severe than the mutations observed in JMC [reviewed in (567)].

Conclusions

PTH is a hormone critical for many cell processes, primarily focused on mineral metabolism. This tightly regulated hormone is critical for regulation of calcium and phosphate homeostasis as well as bone metabolism. Dysfunction in the regulation results in dramatic clinical pictures characterized by poor bone mineralization and increased soft tissue mineralization. These abnormalities in turn lead to cardiovascular disease and kidney failure. Key gaps in our understanding of PTH include the role of intracellular signaling, the interaction of PTH with other hormones involved in mineral metabolism, and the mechanisms by which PTH can influence cardiovascular health.

Vitamin D

Introduction

Vitamin D is a steroid hormone, synthesized through conversion of metabolites supplied by skin or intestinal absorption and involved in multiple critical processes for living organisms (Fig. 5). Functioning as a circulating hormone produced by the kidney, active vitamin D's most prominent role is as a critical regulator of bone mineralization. Vitamin D deficiency results in severe metabolic bone disease both in children and adults. Osteomalacia, a defect in bone mineralization detected by bone biopsy, occurs in both children and adults whereas rickets occurs only in children. Increasingly, vitamin D is recognized as a mediator of multiple other processes in the body including immune function, the renin-angiotensin axis, insulin metabolism, and cell proliferation, to name a few.

History of discovery

Vitamin D was discovered early in the twentieth century but the fact that there was an active substance in milk apart from the carbohydrate, fat, and protein content that was critical for life was reported first in 1880 by N. Lunin, a Russian scientist who noted that newborn mice fed a diet composed of casein, carbohydrate, fat, and salts died while those fed milk lived (440). In 1922, McCollum reported that cod liver oil, which had been used for a century to treat rickets, contained a fat soluble substance that prevented rickets in rats and named it vitamin D (440). Ensuing work by a number of investigators established the existence of a compound similar but not identical to cholesterol which could be activated by irradiation of skin, liver, and multiple food substances which similarly had antirachitic properties. The compound in food was identified as ergosterol by Windaus and Hess in 1931 and the compound in animal tissue was identified as 7-dehydrocholesterol by Windaus and Bocke in 1937 (697). The full biosynthetic pathway was finally delineated by Holick et al. (189, 309) in 1980.

Structure: Biochemical properties

The vitamin D family compounds are secosteroids, exhibiting a tetracyclic structure with a cleaved ring (153,307,309,311). They differ from conventional steroids in that the B ring is open, lacking a sixth carbon atom. Vitamin D2 or ergocalciferol is synthesized from ergosterol (311, 325), a naturally occurring substance in yeast and plants while vitamin D3 or cholecalciferol is synthesized from 7-dehydrocholesterol, a cholesterol precursor (153, 232, 258, 309). Throughout the metabolic pathway of vitamin D, multiple compounds can be generated, most of which are thought to be inert or which have not been studied (102, 153, 232, 265, 307, 308, 310, 311). Ergocalciferol, cholecalciferol, 25-, and 1,25 vitamin D are fat soluble. The terminal step in vitamin D degradation is calcitroic acid (1α-hydroxy-23-carboxy-24,25,26,27-tetranorvitamin D), which is water soluble and excreted primarily in the urine (537).

Vitamin D synthesis, metabolism, and regulation

Vitamin D metabolism

Vitamin D is a family of steroids originating from ultraviolet light conversion of precursor compounds in the skin (5,309) or through ingestion of precursor substances in food. In skin, ultraviolet light effects a conformational change in

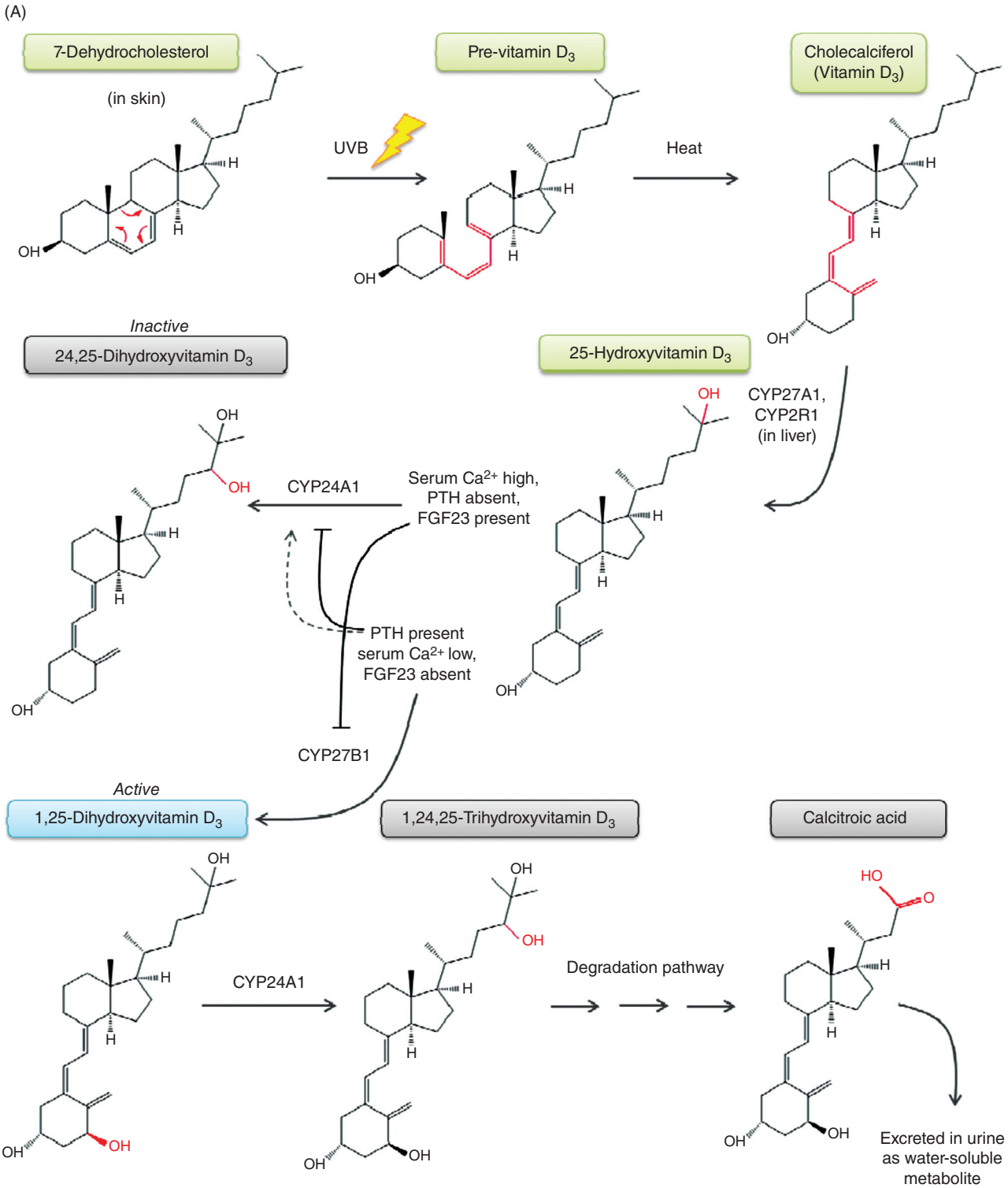

Figure 5 (A) Metabolic pathway of vitamin D. (A) The production of 1,25-dihydroxyvitamin D begins in the skin with the precursor 7-dehydrocholesterol. UVB light catalyzes the conversion of 7-DHC to pre-Vitamin D (structural changes denoted in red), which is further converted to Vitamin D by heat through the process of thermal isomerization. Vitamin D enters the bloodstream, and in the liver undergoes hydroxylation by either CYP27A1 or CYP2R1 to form 25-hydroxyvitamin D. Depending on serum Ca^{2+} levels and hormones present, in the kidney, 25-hydroxyvitamin D will either be converted to its active form, 1,25-dihydroxyvitamin D, by the enzyme CYP27B1, or be converted to its inactive form, 24,25-dihydroxyvitamin D, by the enzyme CYP24A1. FGF23 upregulates CYP24A1 expression and downregulates CYP27B1. PTH stimulates CYP27B1 expression, and depending on the circumstances, either downregulates CYP24A1 or slightly upregulates its expression. 1,25-dihydroxyvitamin D_3 is degraded first by hydroxylation at the 24^{th} position to form 1,24,25-trihydroxyvitamin D, then through a series of steps form the end product calcitroic acid, which is water-soluble and is excreted in the urine. (*continued*)

(B)

Classic effects: Mineral metabolism	Nonclassic effects: All other
↓ PTH release	↓ Insulin resistance
↑ Bone resorption	↓ Circulating renin and angiotensin II activity
↑ Ca^{2+} and HPO_4^{2-} absorption	Epidermal proliferation and differentiation
↑ Ca^{2+} and Mg^{2+} reabsorption	↑ T cell differentiation

Figure 5 (*Continued*) (B) 1,25-Dihydroxyvitamin D_3 promotes both classic effects on mineral metabolism as well as nonclassic effects on immune function, cardiovascular protection, and others as listed. (B) Metabolic pathway of vitamin D. (A) The production of 1,25-dihydroxyvitamin D begins in the skin with the precursor 7-dehydrocholesterol. UVB light catalyzes the conversion of 7-DHC to previtamin D, which is further converted to vitamin D by heat. Vitamin D enters the bloodstream, and in the liver undergoes hydroxylation by either CYP27A1 or CYP2R1 to form 25-hydroxyvitamin D. Depending on serum Ca^{2+} levels and hormones present, in the kidney, 25-hydroxyvitamin D will either be converted to its active form, 1,25-dihydroxyvitamin D, by the enzyme CYP27B1, or be converted to its inactive form, 24,25-dihydroxyvitamin D, by the enzyme CYP24A1. 1,25-dihydroxy-D_3 is degraded through a series of steps to the water-soluble product calcitroic acid, which is excreted in the urine. (B) 1,25-Dihydroxy-D_3 promotes both classic effects on mineral metabolism as well as nonclassic effects on immune function, cardiovascular protection, and others.

the steroid 7-dehydrocholesterol to produce previtamin D which then is converted to cholecalciferol (vitamin D), a process that requires up to three days (309). The origin of 7-dehydrocholesterol in the skin has been debated, with some arguing for an intestine derived origin; however, more recent studies suggest that 7-dehydrocholesterol is formed *de novo* by numerous skin cell types (258, 599). Factors regulating this initial step include age, skin pigmentation, degree and duration of skin exposure, and intensity of sunrays (104, 158, 306, 309). Aging and darker skin pigment will limit this process as does, predictably, lesser surface area of skin exposure, lesser time of skin exposure, higher latitude, and the angle of the sun during winter season. A recent study suggested, however, that the degree of conversion correlated more with baseline 25-hydroxy vitamin D25-hydroxy vitamin D levels and total cholesterol levels than with degree of pigmentation (104, 266). The production of cholecalciferol by sun exposure is self-limited as excessive sun results in degradation of previtamin D and vitamin D (574). In addition, sunlight also converts 7 dehydrocholesterol to some inactive metabolites such as tachysterol and lumisterol (190, 266, 306). Cholecalciferol diffuses into the skin capillaries, and circulates as either the free compound or bound to vitamin D binding protein (DBP) (153, 156, 190, 311, 314). Cholecalciferol has no documented direct activity and a relatively short half-life (12-24 h). The free compound enters cells relatively easily and the degree of binding to DBP largely determines the rate of uptake by adipose tissue, muscle, or liver. Cholecalciferol can also be obtained through ingestion of foods containing naturally occurring vitamin D such as egg yolks, fatty fish, and liver, or through foods fortified with vitamin D such as milk, breads, infant formula, and orange juice (95, 686). Absorption of cholecalciferol is dependent on bile acid-mediated formation of micelles. While some of the absorbed vitamin D is transported through the portal system to the liver, the majority of absorbed vitamin D is taken up through chylomicrons into the lymphatics (686). A significant amount of the absorbed vitamin D is taken up into fat tissue and muscle (314). How or whether vitamin D sequestered into these tissues is regulated is unknown. The propensity for adipose tissue absorption of vitamin D may explain the higher vitamin D requirement and/or the lower circulating vitamin D levels in obese individuals. Of note, high bolus ingestions of vitamin D are rapidly cleared by fat and muscle and not released subsequently into the circulation (311). Thus smaller daily doses of cholecalciferol (1000-2000 IU) are preferred to infrequent large doses for maintenance of stable daily serum concentrations of cholecalciferol (306, 311).

Cholecalciferol undergoes 25-hydroxylation to form 25-hydroxyvitamin D, a metabolite that also is considered inactive (27, 293, 724). Several tissues express 25-hydroxylase activity including kidney, intestine, and liver, but the majority of cholecalciferol hydroxylation appears to occur in the liver (77-81, 326, 491, 513). Many 25-hydroxylases capable of performing this function have been identified but most interest has focused on the mitochondrial enzyme CYP27A1 and the microsomal enzyme CYP2R1 (326). Liver exhibits a high expression of the mRNA for 25-hydroxylase, CYP27A1, but, interestingly, mutations in the gene encoding *CYP27A1* do not result in significant abnormalities in vitamin D metabolism (315, 398). In contrast, mutations in cytochrome p450 2R1 or vitamin D 25-hydroxylase (*CYP2R1)* have been reported in individuals with very low vitamin D levels, suggesting that this enzyme is essential for 25-hydroxylation (142). Moreover, CYP2R1 but not CYP27A1 25-hydroxylates both vitamin D2 and vitamin D, while CYP27A1 hydroxylates only D (325, 326). CYP2R1 has a high affinity for vitamin D and is quite specific for the 25 position on vitamin D but not other steroid compounds (615). Thus, CYP2R1 is currently the leading contender for the physiologically relevant

CYP governing this aspect of vitamin D metabolism. A very recent study demonstrated that neither *Cyp27a1* nor *Cyp2r1* is essential for 25-hydroxylation as mice lacking both enzymes, showed only a 50% reduction in 25-hydroxy-vitamin D and exhibited normal 1,25 vitamin D levels (724), suggesting considerable redundancy in this metabolic step. CYP27A1 is regulated by multiple hormones, particularly insulin, glucocorticoids, sex hormones and by 1,25 dihydroxyvitamin D itself (27). Hormonal regulation of CYP2R1 has not been studied. The activity of the 25-hydroxylase enzymes is largely driven by substrate availability; thus this step in vitamin D metabolism is not considered a site of significant regulation. Despite the fact that 25-hydroxy vitamin D25-hydroxy vitamin D is not the active form of vitamin D, it is preferentially measured in clinical medicine to establish vitamin D status because of its long half-life of about 2 to 3 weeks (156, 159, 311). However, concerns about the reproducibility and reliability of the assays raise questions about using 25-hydroxy vitamin D25-hydroxy vitamin D measurement to define vitamin D deficiency (207). 25-Hydroxyvitamin D circulates in three forms: 85% with DBP, 15% albumin-bound, and 0.03% free. The current assays measure total, not free 25-hydroxy vitamin D25-hydroxy vitamin D, and vitamin D-binding protein levels can vary considerably on an individual basis. Nonetheless, at this time, the standard of care is to measure 25-hydroxy vitamin D25-hydroxy vitamin D to evaluate vitamin D status. The presence of 25-hydroxylases capable of cholecalciferol hydroxylation in other tissues has only recently been recognized and potential roles for cholecalciferol in these tissues are currently under investigation (24, 87, 98, 102, 103, 326).

The 25-hydroxy vitamin D25-hydroxy vitamin D-vitamin D-binding protein complex binds to the megalin receptor complex of proximal renal tubule cells and undergoes endocytosis. Once internalized, 25-hydroxy vitamin D25-hydroxy vitamin D is metabolized through one of two pathways: 1α hydroxylation by CYP27B1 to form the active metabolite 1,25-dihydroxyvitamin D or 24-hydroxylation by CYP24A1 to form an inactive metabolite 24,25-dihydroxyvitamin D (6, 11, 29, 98, 153, 337, 367, 492). The balance of the activities of these two enzymes is what determines the ultimate level of active vitamin D. Much of the regulation of these two enzymes is accomplished at the gene level. PTH, a major stimulator of active vitamin D production, increases the level of *CYP27B1* activity (12, 29, 42, 228, 241). The effect on the level of *CYP24A1* has been variably reported as slightly increased, insufficient to blunt the effect on *Cyp27b1*, or as decreased with the result being an increase in 1,25 vitamin D synthesis (725, 726). 1,25-dihydroxyvitamin D itself activates *CYP24A1*, limiting active vitamin D formation. FGF23, a major inhibitor of vitamin D formation, increases CYP24A1 activity, shunting 25-hydroxy vitamin D25-hydroxy vitamin D into the inactive metabolite pathway (290, 293, 427, 523, 526). In addition, FGF23 inhibits *CYP27B1*. Other factors influencing vitamin D conversion include aging, metabolic acidosis, chronic kidney disease, and a variety of other hormones (28, 30, 31, 153, 275, 385, 514-519, 635-637). Because of its short half-life of hours, 1,25 dihydroxyvitamin D is not considered a useful indicator of vitamin D status (88, 153, 718).

Inactivation of active vitamin D begins with 24-hydroxylation of 1,25 dihydroxyvitamin D, followed by oxidation at carbon 24 and sequential modification of the steroid culminating in the production of calcitroic acid (153, 326, 537). A carbon 23 oxidation pathway has also been described but its significance is unclear. Urinary excretion of the water-soluble calcitroic acid is the major mechanism for vitamin D disposal though a small amount is excreted through the gastrointestinal tract.

The other major source of vitamin D is the plant sterol, ergocalciferol or vitamin D2, which is present in the diet. Intestinal absorption and disposition are very similar to what is seen with vitamin D, although as discussed below, its interaction with DBP is weaker, a property that some investigators believe plays a significant role in their differential clinical efficacies (257).

Vitamin D-binding protein

DBP is central to the metabolism of vitamin D. Originally identified as a member of the albumin family and named GC globulin (group-specific component of serum) in 1959, this abundant serum protein was relabeled DBP after the discovery of this specific property in 1976 by Daiger and colleagues (154, 156, 178, 311, 461). Over 100 isoforms of the protein have been isolated by immunoelectrophoresis, divided into three major isoforms—GC1F, GC1S, and GC2, classified by amino acids at positions 416 and 420—and multiple minor isoforms, grouped around the major isoforms (9, 69, 154, 156, 575). These changes in amino acid sequence result in measurable differences in the glycosylation patterns, especially between the GC1 and GC2 isoforms. Genetic analysis has uncovered an even greater degree of variability with over 1000 variants identified in both major and minor isoforms. Specific patterns of isoform expression are associated with specific ethnicities, allowing the study of population migrations and genetics (69, 134, 175, 176, 575). Many of the genetic variations translate into differences in DBP binding to both 25 and 1,25 vitamin D. Interestingly, GC2 isoforms are very uncommon in the equatorial African populations, while GC1F is the most common. GC1S is seen most frequently in individuals of European ancestry while Asians exhibit both GC1S and GC1F. Binding efficiencies to vitamin D are GC1F>GC1S>GC2, correlating with skin pigmentation and leading to the hypothesis that the different isoforms arose in concert with changes in skin color to facilitate sun-stimulated vitamin D formation and metabolism (461, 470).

DBP is composed of three domains, one which expresses 10 α-helices forming a vitamin D binding cleft, a second which expresses nine α helices and one coil, while the third expresses four α helices (154, 156, 262). Circulating DBP vastly exceeds its vitamin D binding capacity and the protein

also binds free actin, which limits actin polymerization and endothelial damage. DBP can also be modified to form DBP-MAF, macrophage-activating factor, which stimulates macrophage and osteoclast activation, thus serving roles in immune function and bone metabolism independent of vitamin D.

The major site of DBP production is the liver, lesser production measured in kidney, testis, and adipose tissue. The human gene exhibits 13 exons and 12 introns and its promoter expresses three binding sites for hepatocyte nuclear factor.

As indicated previously, DBP binds both 25 and 1,25 vitamin D as well as the parent compound, cholecalciferol, in the circulation, transporting the substrates to their intended targets. However, whether DBP is required for vitamin D activity remains an unanswered question. The mouse lacking DBP does not exhibit any discernible defects in bone and mineral metabolism; however, on a vitamin D deficient diet develops metabolic bone defects at an earlier time point than the normal controls (63, 563, 718). DBP appears to play a role in limiting active vitamin D formation, as injection of radiolabeled cholecalciferol into the DBP null mice resulted in a more rapid and enhanced liver uptake. Also, the addition of DBP to cell cultures of monocytes or culture of monocytes in serum derived from DBP-replete mice (when compared to monocytes cultured in serum derived from DBP-deficient mice) inhibited vitamin D-stimulated cathelicidin induction, the high affinity isoforms showing a greater effect than the lower affinity isoforms. These findings suggested that DBP was blunting the uptake of vitamin D into those cells, resulting in diminished responses (155). DBP may also serve as a storage mechanism for vitamin D. Vitamin D bound to DBP is endocytosed into renal proximal tubule cells through a megalin-cubulin-dependent process, allowing the body to recapture filtered 25-hydroxy vitamin D (336, 403, 473, 564). Interestingly, however, DBP null mice exhibit a less extreme phenotype than lrp2 (megalin)-deficient animals (336,387,403,473,484,564), suggesting that vitamin D can gain entry into these cells through megalin-independent mechanisms. Likewise, DBP can enter cells that do not express megalin, highlighting the possibility of alternative mechanisms for vitamin D entry into cells.

Gene and its regulation

The gene encoding 25-hydroxy vitamin D 1α hydroxylase (*CYP27B1)* in humans is located on chromosome 12, 12q14.1, flanked by the genes for *METTL21B*, methyltransferase 21b; *METTL1* methyltransferase like 1; *MARCH9*, a member of the E3 ubiquitin ligase family; *CKD4*, cyclin D kinase isoform 4; and mir6759, a microRNA. The gene contains nine exons, including a very large exon 9. The promoter region expresses sequences consistent with three cAMP response elements but no sequence corresponding to a vitamin D response element (108). Consistent with this structure, PTH and direct activators of cAMP such as forskolin increase transcription of the gene but vitamin D has no effect. These findings suggest that PTH stimulates vitamin D production through increased transcription of the *CYP27B1* but the well described self-inhibition by 1,25 vitamin D is not mediated through an effect on gene transcription. In contrast, Murayama and colleagues (466) were able to identify a sequence that could serve as a negative regulatory site for 1,25 vitamin D. A recent study found that 1,25 vitamin D could bind to VDR in the proximal tubule brush border and translocate to the nucleus, accompanied by a decrease in CYP27B1 activity and an increase in CYP24A1 activity and suggesting that VDR functions as a sensor for active vitamin D status. Using transfected promoter constructs, Armbrecht et al. (29) reproduced the stimulatory effect of PTH and forskolin on *CYP27B1* promoter activity, concluding that these effects were sufficient to explain the stimulation of 25-hydroxy vitamin D25-hydroxy vitamin D activation by PTH. They also showed that PTH and 1,25 vitamin D had a stimulatory effect on *CYP24* (25-hydroxy vitamin D 24 hydroxylase) but had an interactive effect. The magnitude of the increase in CYP24 activity was not felt to be sufficient to explain the effect of these hormones on CYP24 mRNA levels. Although several cell types are capable of converting 25-hydroxy to 1,25-dihydroxyvitamin D, only kidney produces sufficient quantity to contribute to circulating levels under typical physiologic conditions. Yoshida et al. (708) have identified an enhancer in the promoter region of the gene specific to proximal tubule which may explain this observation.

Several other factors have been identified that regulate cyp24 and cyp27b1 expression. In mice, absence of the Npt2a (*Slc34a1*) results in increased cyp27b1 mRNA expression and decreased cyp24 mRNA expression, predictably leading to marked increases in active circulating 1,25 vitamin D (56). These animals have hypercalcemia, hypercalciuria, and nephrocalcinosis as well as hypophosphatemia. Whether this is a direct effect, a result of suppression of FGF23 by hypophosphatemia, or both, is not known. Absence of the other major type II sodium phosphate cotransport Npt2c (Slc34a3) has minimal effect on the mRNA expression of cyp27b1 but does result in significant suppression of cyp24 mRNA (331, 352, 577); thus, 1,25 vitamin D levels are increased as well. However, these animals present a phenotype that differs little from wild-type mice. Interestingly, kidney-specific inducible Npt2c deletion has no effect on phosphate, calcium, or vitamin D homeostasis, suggesting that the phenotype seen in the whole organism constitutive deletion model results from nonrenal phosphate transport mechanisms (469). The differential effects of the sodium phosphate cotransporters on vitamin D metabolism in humans have not been investigated at a molecular level. Unlike mice, humans lacking functional Npt2c exhibit a dramatic clinical phenotype characterized by rickets, hypophosphatemia, hypercalcemia, hypercalciuria, and high vitamin D levels while mutations in Npt2a present a rather mild phenotype of a tendency toward osteopenia and kidney stones (67, 166, 181, 317, 324, 379, 402, 530, 650, 713). The basis for these differences and their

implications for regulation of vitamin D metabolism have not been determined. Dietary phosphate deficiency stimulates renal cyp27b1 activity through a growth hormone-dependent mechanism; the sensor for this response remains unknown but may be one of the proximal tubular phosphate transporters (708).

Multiple environmental factors determine the level of vitamin D, including season of the year, vitamin D intake, adiposity, and hormonal status, especially for women (159, 306, 399, 444, 559, 673, 688). Stimulation of renal cyp27B1 by estrogens (433, 510, 511, 536, 621) and the increase in circulating 1,25 vitamin D in pregnancy (536) were demonstrated over 30 years ago. Subsequent studies suggest that the increase in circulating vitamin D levels during pregnancy are of maternal kidney origin as an anephric pregnant woman failed to show the predicted increase (640). However, as this report predated the discovery of FGF23 which is capable of inhibiting extra-renal as well as renal conversion of 25 to 1,25 vitamin D, an exclusive role of the kidney in providing the increase in vitamin D during pregnancy cannot be claimed (37). Exogenous estrogens increase both 25 and 24,25 vitamin D in postmenopausal women, associated with an increase in serum calcium and a decrease in serum phosphorus (44). Cyp27b1 activity is increased by estrogens in extra-renal tissues as well including vascular smooth muscle cells (608); however, it is unlikely that the amount of 1,25 vitamin D produced would alter serum levels.

The level of vitamin D is also subject to significant genetic regulation (51, 482). Twin studies suggest a 43% to 70% heritability for 25-hydroxy vitamin D and a 65% heritability for the active vitamin D (205, 206, 692, 709). These studies have been supported by family studies as well. The few studies of African Americans and Hispanics suggest that heritability may also be influenced by ethnicity, as the estimates of heritability for both forms of vitamin D in these populations are significantly lower. These investigations, however, involve at most approximately 1000 individuals and frequently have been derived from studies of human illnesses such as asthma or multiple sclerosis. Thus, the applicability to the general population could be questioned. Linkage analysis, genome wide association studies, and candidate gene approaches to identify genes important in determining vitamin D levels have uncovered a number of potential candidates including *CYP27B1*; *CYP2R1*; *CYP24A1*; *VDR*; and *DHCR7*, the gene encoding the reductase that catalyzes the 7-dehydrocholesterol to cholesterol reaction in the skin; and *GC*, the gene encoding the DBP (9, 69, 114, 182, 665, 692). CYP27B1 is a member of the cytochrome P450 family most strongly associated with vitamin D levels, but multiple studies support potential contributions from each of the other candidate genes. The reasons for the discrepancies are not known but likely result from differences in study population, small sample sizes, and differences in analytic methods. The reader is referred to a recent review of this topic by Dastani et al. for a more in depth discussion (182).

Receptors

The vitamin D receptor, a member of the steroid hormone receptor superfamily, is expressed in a broad variety of tissues and exhibits significant fluidity in expression dependent on age, underlying pathophysiologic conditions, and even vitamin D status (83, 84, 98, 106, 151, 191). One interesting aspect of VDR is the radical change in expression pattern during development (259, 670). In the mature animal, the receptor is most abundant in the small and large intestine, distal tubule of the kidney nephron, and the parathyroid gland. Other tissues with significant expression include the pancreas, renal proximal tubule, bronchial cells, osteoblasts, thymus, pituitary gland, prostate, and mammary gland. Specifically, the receptor is minimal or not identified in liver, muscle, thyroid, adrenal gland, or nervous tissue, including the central nervous system. It is notable that tissue expression of 1αhydroxylase and the vitamin D receptor show significant overlap, setting the stage for autocrine function and feedback.

Upon interaction with 1,25 vitamin D, the VDR heterodimerizes with the retinoid X receptor (RXR), the complex migrating to the nucleus where it interacts with the nuclear chromatin through VDRE, vitamin D response elements (83, 331) (Figs. 3C and 6). This step also involves two additional layers of regulation (4, 83). First, the transfer of the vitamin D complex to the nucleus is performed by proteins of the Hsc70 chaperone family. Second, the VDRE may be occupied by RNA-binding proteins that compete with the vitamin D complex for occupancy (428). Investigation into the regulation of these two steps is in its infancy. Interaction of the vitamin D receptor complex with the VDRE in some tissues requires the presence of the Williams Syndrome Transcription Factor (WTSF) (49, 238), functioning as one of the subunits of the ATP-dependent chromatin remodeling complex known as WINAC, the WTSF including nucleosome assembly complex. The essential requirement for this interaction has been demonstrated *in vitro* in knockdown experiments as well as in the skin fibroblasts of Williams Syndrome patients (49, 177, 338, 339, 354, 355). WINAC downregulates VDR-stimulated activation of 1αhydroxylase and activates 24-hydroxylase, thus serving to limit active vitamin D formation (49, 338, 339).

Classically, the VDR-RXR complex has been thought to interact with DNA at specific motifs designated VDRE (vitamin D response elements), thus influencing transcription of its target genes (163, 414, 486, 498). The classic motif is a triple repeat of the PuGG/TTCA sequence separated by three base pairs. In fact, however, the number of gene sites occupied by VDR-RXR has been estimated to be between 2000 and 8000, and many of these genes do not express classic VDRE (124, 125, 561, 581, 639, 641, 667, 687). VDR-RXR bound to active 1,25 vitamin D binds DNA sites that differ from the unbound VDR. Furthermore, the VDR is capable of interacting with other transcription factors to influence their effects. Thus, failure to identify a VDRE motif in the gene of a protein of interest does not exclude the possibility that the gene may be regulated by vitamin D.

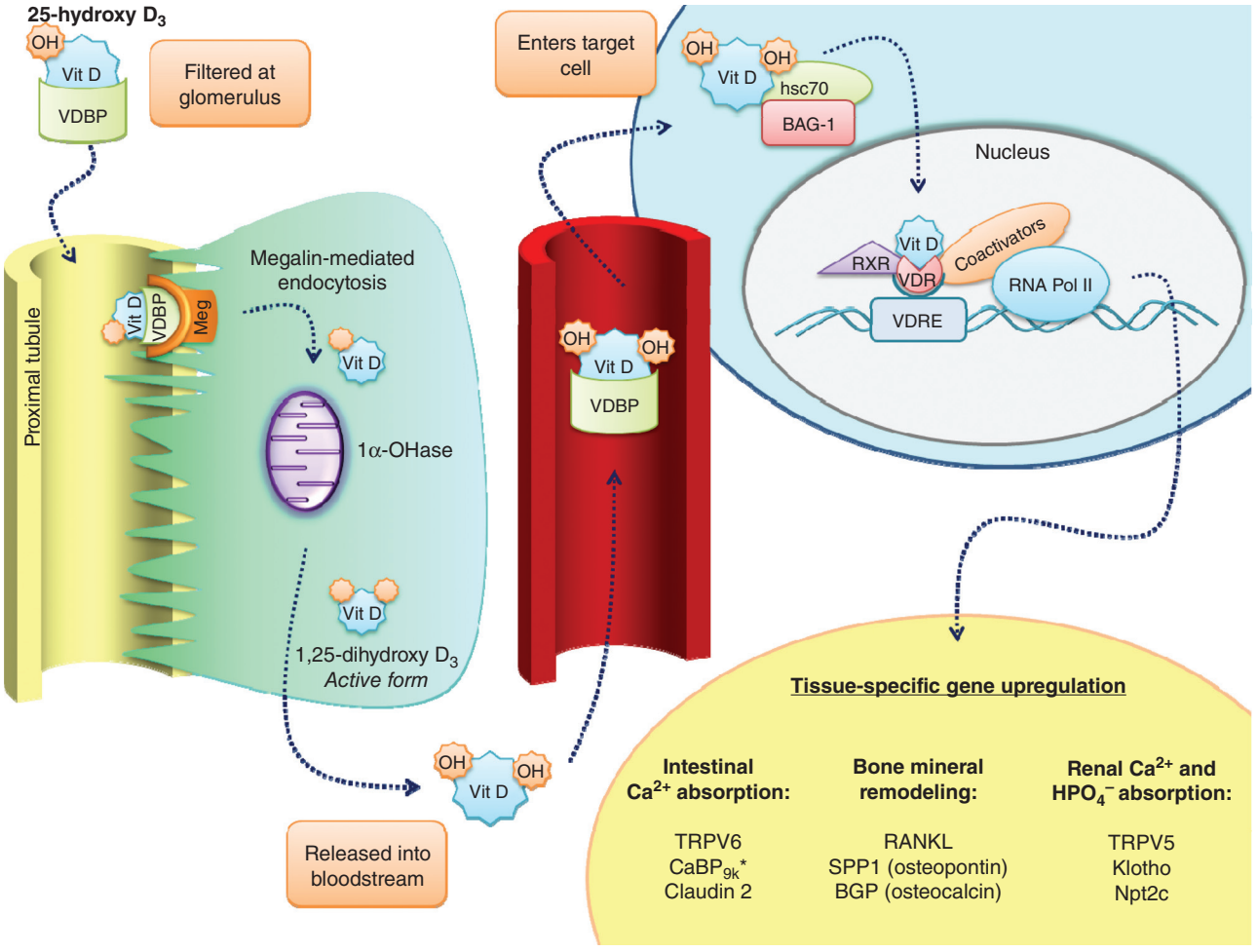

Figure 6 Vitamin D effector mechanisms. 25-Hydroxy-vitamin D bound to DBP is filtered, binds to the megalin complex and is endocytosed into the renal proximal tubule cell where it undergoes 1 α hydroxylation. Activated vitamin D bound to cofactors and chaperones (BAG-1 and hsc70) enter the nucleus and interacts with the VDR in concert with the RXR. This complex interacts with specific genomic regions including the VDRE to influence gene transcription.

There is also evidence that vitamin D may have signaling mechanisms that are nongenomic, specifically activation of protein kinase C and MAP kinases. These pathways have not been studied as intensively as the classic pathway described earlier, but likely contribute substantively to vitamin D actions [reviewed in (456)].

Functions

Classical actions: Mineral metabolism intestine

The major recognized functions of vitamin D revolve around the regulation of mineral metabolism (Fig. 5). The most straightforward and accepted effect of vitamin D is enhanced intestinal absorption of both calcium and phosphate through the stimulation of increased expression of the transporters TRPV6 and Npt2b, respectively (43, 48, 107, 138, 139). Activated vitamin D increases the expression of the calcium channel, TRPV6, in the apical membrane of small intestine, enhancing intestinal cell calcium entry. Predictably, VDREs have been identified on the promoter region for the gene for TRPV6 that play a role in vitamin D stimulation of TRPV6 expression (43, 331, 446, 447). Vitamin D is also important for calbindin D expression but whether this occurs through a classic VDRE has not been established. Vitamin D regulation of the plasma membrane calcium ATPase, the pump responsible for the egress of calcium from the intestinal cell into the blood compartment, has been demonstrated in rats. Lack of significant homology in the VDREs of different species has cast doubt on the applicability of findings in animal models to humans. A recent study using culture explants from endoscopic samples of human duodenum confirmed enhanced expression of TRPV6 mRNA after 6h treatment with either 25 or 1,25 vitamin D (43). Interestingly, treatment with 25-hydroxyvitamin D resulted in increased protein expression of CYP27B1, identified predominantly in the crypt cells, and the increase in TRPV6 correlated strongly with the increase in CYP27B1 expression. These remarkable findings suggest that vitamin D regulation of intestinal calcium absorption may be a function of both autocrine and endocrine actions

of vitamin D. How the two systems interact and why and/or when one system or the other will predominate are important questions to be addressed. 1,25-Dihydroxycholecalciferol also significantly increased the mRNA expression of PMCA1 and CYP24 but not calbindin-D9k.

Vitamin D also enhances intestinal phosphate absorption, though the mechanisms and proteins involved are unknown. Studies have shown that 1,25-dihydroxycholecalciferol does not increase the expression of Npt2b, the type IIb sodium dependent phosphate cotransporter, and that the increase in phosphate absorption is sodium-independent (352). A recent study did identify an active vitamin D analog, ED-71, that strongly increased Npt2b expression at the mRNA and protein level through a VDR-dependent mechanism, but had no effect on either Pit-1 or Pit-2, two other sodium-dependent phosphate transporters identified in intestinal epithelium (113). Interestingly, ED-71 also exhibited a profound stimulatory effect on CYP24, increasing levels ten thousand fold over active vitamin D. The authors also noted that serum concentrations of ED-71 level remained constant over greater than 24 h, whereas serum concentrations of active vitamin D levels promptly decreased to baseline within 6 h and suggested that the dramatic differences in pharmacokinetics accounted for the differences in phosphate stimulating potency. This study underscores the role of the rapid counterregulatory processes stimulated by active vitamin D in limiting its actions.

Kidney

1,25-Dihydroxyvitamin D enhances renal calcium reabsorption through stimulation of the expression of virtually all of the proteins involved in calcium transport in the distal nephron (42, 98). Mice lacking expression of CYP27B1 show decreased renal epithelial mRNA and protein expression of TRPV5, calbindin-D28k, calbindin-D9k, and NCX1, the basolateral Na-Ca exchanger responsible for transfer of reabsorbed calcium from the cell to the blood space (194, 301-305, 481). Treatment with calcitriol corrects all of these deficiencies while a high dietary calcium corrects all except for calbindin-D9k. Interestingly, while PTH has a similar effect on the same proteins, it may not be through a vitamin D-dependent mechanism. The coordinated increase in the expression of the calcium transport proteins is dependent on the increase in TRPV5 expression, TRPV5 deficient animals fail to respond to vitamin D with an increase in the additional calcium transport proteins. TRPV5 deficiency results in hypercalciuria, hypocalcemia, and compensatory elevations in 1,25 vitamin D. Thus, stimulation of TRPV5 expression is the key effect of vitamin D on renal calcium absorption (698).

The effect of vitamin D on renal phosphate transport remains very poorly understood (352). Mice-deficient in the VDR fail to express Npt2a and Npt2c but expression can be stimulated by feeding a high calcium diet suggesting that the expression of these two transporters is not dependent on vitamin D (333). The genes for both Npt2a and Npt2c exhibit potential VDRE but an effect of vitamin D on expression of the two proteins has not been specifically demonstrated.

Bone

The effect of vitamin D on bone has been extensively studied but remains somewhat enigmatic. Mice lacking VDR develop rickets; however, a diet providing high calcium and phosphate can rescue the bone phenotype, suggesting that the major contribution of vitamin D to bone health is provision of adequate mineral through stimulation of intestinal absorption (563). However, vitamin D clearly has direct effects on bone cells. Osteoblasts express VDR, which upon stimulation by vitamin D leads to the production of receptor activator of NFκB ligand (RANKL) which interacts with RANK on osteoclast precursors, resulting in osteoclast maturation (52, 612, 652). Vitamin D also inhibits the expression of the competing decoy receptor for RANKL, osteoprotegerin, contributing to osteoclast maturation. Another Vitamin D-responsive gene in osteoblasts is LRP5, the Wnt coreceptor that stimulates bone cell proliferation (52, 234, 331, 509). Vitamin D stimulation of osteoblasts and osteoblast precursors enhances the expression of osteoblast specific transcription factors such as RUNX2 and subsequently proteins such as osteocalcin, osteopontin, and alkaline phosphatase. The simultaneous activation of both osteoblasts and osteoclasts would result in an increase in bone turnover but whether the result is predominantly bone formation, bone resorption, or a neutral effect is somewhat unclear. The anti-rachitic effect, although thought to be primarily mediated by the effect of vitamin D on mineral homeostasis, may also result from direct effects on bone. Transgenic mice overexpressing VDR in osteoblasts show an increase in bone formation (376, 452). CYP27B1/VDR double knockout mice fed a rescue diet exhibit fewer osteoblasts, a lower mineralization rate, and decreased bone volume, when compared to control animals (500, 501). These studies are consistent with the hypothesis that the major effect of vitamin D on bone is formative and are consistent with much older studies showing that neither vitamin D deficiency nor vitamin D excess altered bone resorption rate as determined by increases in inner marrow diameter in growing chicks prelabeled with injections of radiolabeled calcium, tetracycline, and proline (358). In this study, chicks given excess vitamin D showed a decrease in bone radiolabeled calcium while the vitamin D-deficient animals showed no change in bone label. Under both conditions, bone mass decreased. The decrease in the bone mineral mass seen in vitamin D deficiency was attributed to lack of intestinal absorption of mineral whereas the decrease seen in vitamin D excess was attributed to failure of calcium reutilization. While these observations suggest a role for vitamin D on the formative arm of bone metabolism, the fact that vitamin D stimulates RANKL, leading to activation of osteoclasts would argue for a physiologic role in bone resorption as well. However, a recent study suggests vitamin D deficiency causes PTH elevation, which leads to cortical thinning and in some cases cause marrow fibrosis (13). An important

unanswered question regarding vitamin D effect on bone is whether its effects change with organism age. In human studies, vitamin D administration prevents rickets in children and treats osteomalacia in adults (269, 306); however, the effect of vitamin D in the treatment of osteoporosis—whether vitamin D can prevent or reverse the bone loss associated with aging—remains a controversial topic (36, 542, 560).

Nonclassical actions

Kidney A variety of other effects of vitamin D on kidney function apart from regulation of mineral metabolism has been described. VDR polymorphisms have been associated with differences in proximal tubule citrate handling, specifically, the presence of the bb genotype of BsmI and the TT genotype of TaqI are associated with hypocitraturia in stone formers when compared to nonstone formers or normocitraturic stone formers(460, 642, 723). Great interest has emerged from studies showing that vitamin D can have an antiproteinuric effect (186, 404, 609, 706), even in patients already on inhibitors of the renin angiotensin aldosterone system. Glomerular epithelial cells, podocytes, expresses VDR and activation of VDR increases podocyte synthesis and expression of nephrin, a key slit-membrane protein important for the integrity of the glomerular filtration apparatus (396, 609, 668). In diabetic animals or in podocytes exposed to high glucose, stimulation or overexpression of the VDR blocked podocyte apoptosis through inhibition of ERK1/2 and caspase 3 activation and blocked activation of the renin angiotensin axis (669).

Vasculature Several studies support a role for activated vitamin D in maintenance of vascular health (14, 25, 253). VDR deficient mice fed a rescue diet to maintain mineral homeostasis show increased pulse pressure, stiffness of their blood vessels, and a higher heart weight/body weight ratio. Interestingly, blood pressure was not affected. The investigators demonstrated deficient nitric oxide synthesis in endothelial cells (480). Vitamin D blocks vascular plaque formation by inhibiting the ability of macrophages to take up cholesterol (204, 682). Interestingly, both vitamin D deficiency and excess reportedly accelerate atherosclerotic plaque formation (727). VDR deficiency enhances macrophage production of renin and angiotensin, important mediators of atherosclerosis (25, 144, 221, 263, 395, 594). Vitamin D deficiency has also been implicated in the development of preeclampsia (401, 408, 547).

Skin In addition to being a major contributor to circulating vitamin D, the skin is another site of significant autocrine vitamin D production, active 1,25 vitamin D and a variety of unique vitamin D metabolites, some of which have demonstrable activities (599-602, 638). Epidermal CYP27B1 is required during differentiation of keratinocytes and is associated with the expression of important differentiation markers such as involucrin (84-86). However, the expression of CYP27B1, the VDR, and other components of vitamin D metabolism decrease as differentiation is completed. Interestingly, a variety of skin cancers show increased expression of the vitamin D metabolic pathway and in vitro studies suggest that active vitamin D may be a useful adjunctive therapy by virtue of its prodifferentiation, antiproliferative effects (320, 391-393, 453, 538-541, 600, 622). Vitamin D signaling may also play a role in the development and maintenance of the barrier function of the epithelium, through maintenance of the production of lamellar bodies and antimicrobial peptides (15, 502, 550, 566).

VDR null mice and humans with VDR mutations suffer from alopecia (191, 218, 421). The mechanism is thought to be the loss of dermal stem cells responsible for hair follicle recycling. However, vitamin D deficiency is not accompanied by alopecia. This apparent contradiction suggests alternative roles for the VDR and in fact the mechanism for this phenomenon appears to be a vitamin D independent interaction of VDR with the cWnt and hedgehog target genes (157, 400, 405, 406, 627).

Pancreas Vitamin D has multiple effects on the pancreatic beta cells that express VDR including protection against cytokine damage (254, 276, 548, 694-696), suppression of the islet renin-angiotensin system (143), and regulation of genes encoding proteins that regulate including neuropeptide production, membrane trafficking, tight junction formation, and ion channels (147, 695). Vitamin D increases beta cell insulin production (717). Vitamin D may also indirectly protect islet cell function through provision of adequate calcium, as calcium deficiency has been demonstrated in some animal models to accelerate the development of diabetes (197, 529, 535, 610).

Immune system Vitamin D has well-established immunomodulatory capabilities (40, 119, 120, 287, 296, 297). Macrophages are capable of producing significant quantities of active vitamin D from 25-hydroxy vitamin D, described by Adams et al in 1983 in studies utilizing alveolar macrophages from patients with sarcoidosis (7, 8). This phenomenon explains the occurrence of hypercalcemia in patients with sarcoidosis; however, the more physiologically relevant consequence of vitamin D production by macrophages is the significant contribution to the antibacterial activity against certain organisms as first reported by Rook in 1986 (553). Vitamin D enhances the production of cathelicidin, which in turn is responsible for the elaboration of antimicrobial peptides (261, 502, 566, 666, 674). VDR is present on activated but not quiescent lymphocytes and vitamin D exerts an antiproliferative effect on these cells. In addition, vitamin D blunts immunoglobulin and cytokine production by T cells. It is these immunomodulatory properties of vitamin D that have been invoked to explain the effects of vitamin D and/or vitamin D status on autoimmune disorders (2, 120, 224, 225, 397, 493, 494, 551, 605, 619, 705),

progression of renal disease (263, 404), response to infections (268, 349, 711), obesity (661), and some cancers (55, 84, 240, 634).

Interaction with other hormones

Effect on other hormones involved in mineral metabolism

Parathyroid gland cells express VDR (52,151,180,318). Stimulation of VDR in this tissue decreases PTH synthesis and secretion, inhibits PTH cell proliferation, and an increases the expression of the calcium sensing receptor. These diverse functions all contribute to a decrease in circulating PTH, thus preventing overcorrection of low calcium levels, the major stimulus to PTH secretion. The PTH gene expresses a VDRE which, when occupied by the VDR-RXR complex, exerts an inhibitory effect on PTH gene transcription, at least in part by displacing another regulatory factor, nuclear factor-Y. Notably, parathyroid gland cells express CYP27B1, thus are capable of generating active vitamin D from circulating vitamin D (82, 151, 241). How circulating and locally produced vitamin D interact to regulate PTH synthesis is not entirely clear; however, the secondary hyperparathyroidism seen with mild vitamin D deficiency may be explained by a deficiency in the autocrine production of active vitamin D (341). PTH, on the other hand, leads to enhanced renal production of 1,25 vitamin D through increasing Cyp27B1 expression and decreasing Cyp24 expression.

Vitamin D stimulates production of FGF23 from bone (52, 331, 363), while it represses the production of PHEX (phosphate-regulating endopeptidase homology, X-linked), an enzyme linked to the degradation and inactivation of FGF23. As would be predicted from both of these actions, treatment with 1,25 vitamin D increases serum FGF23, leading to phosphaturia. Bone cells themselves express CYP27B1; thus, vitamin D regulation of FGF23 production likely results from both circulating and autocrine vitamin D(622, 623). Animals lacking expression of the VDR have suppressed FGF23 levels, even when serum phosphate is corrected by diet, suggesting that vitamin D-stimulated FGF23 is, in fact, mediated through VDR (712). Interestingly, chondrocyte expression of VDR appears to play a key role as chondrocyte-specific VDR deletion results in reduced osteoblast FGF23 expression and enhanced renal 1,25 vitamin D production (438). FGF23 decreases 1,25 vitamin D expression through increasing the renal expression of cyp24, leading to enhanced vitamin D inactivation, and decreased renal expression of cyp27b1, leading to decreased vitamin D production (41). Animals lacking expression of FGF23 have remarkably elevated vitamin D levels associated with elevated cyp27b1 activity (295,587,596,714). FGF23 inhibits vitamin D activation in nonrenal tissues including parathyroid gland (37, 153, 297, 370, 485, 536, 612), monocytes, and placenta.

Effect on hormones not specifically involved in regulation of mineral metabolism

Vitamin D interacts with the renin-angiotensin-aldosterone system at many levels (10, 76, 122, 144). Animals lacking expression of VDR or CYP27B1 show increased renin activity associated with the development of cardiac hypertrophy and hypertension, which can be ameliorated by administration of angiotensin converting enzyme inhibitors. Some, but not all, human studies have demonstrated an inverse relationship between vitamin D levels and renin levels, suggesting a role for vitamin D deficiency in the development of at least some forms of hypertension through activation of the renin angiotensin system (229,230,647). 1,25 Vitamin D suppresses ren-1c gene transcription in *in vitro* studies through interaction at a cAMP response element in the promoter region (365,715).

Pathophysiology

Vitamin D deficiency

Vitamin D deficiency's major clinical feature is the result of abnormal mineralization of osteoid in bone. In children, vitamin D deficiency presents as the clinical syndrome of rickets, characterized by decreased bone mineralization and faulty bone development as manifested by significant skeletal deformities including bowing of the legs, knock-knee deformity, flaring of the ends of the ribs (rachitic rosary), pigeon chest malformation, bossing of the skull, and kyphoscoliosis. Adults who develop vitamin D deficiency present a less dramatic clinical picture characterized predominantly by bone pain, low bone mineral density, and fractures. Frank hypocalcemia is infrequently seen, as these individuals will develop secondary hyperparathyroidism in response to the decrease in intestinal calcium absorption; however, hypophosphatemia due to the hyperparathyroidism can be seen. Lesser degrees of vitamin D deficiency, also sometimes termed vitamin D insufficiency, may be associated with no symptoms whatsoever, though decreased bone mass and secondary hyperparathyroidism of a mild degree are often seen.

Vitamin D deficiency has been implicated in a host of disorders including autoimmune diseases such as asthma and multiple sclerosis; cancers such as breast, colon, skin, and prostate cancer; hypertension; diabetes mellitus; and infections such as tuberculosis (see aforementioned *Immune system* section). These associations have been demonstrated through epidemiologic studies and have been supported experimentally to some extent. For example, breast and colon cancer cells in some individuals and in some experimental conditions express high levels of VDR (55, 157, 193, 240, 375, 392, 506, 580). Treatment with vitamin D suppresses proliferation. The mechanisms for suppression of proliferation that have been described are variable and may be tissue specific. Keratinocytes derived from animals lacking VDR show a higher expression of several oncogenes and a lower expression of

several tumor suppressor genes. Jiang and Bikle (322) have shown parallel changes in the expression of long noncoding RNAs for these genes, suggesting that vitamin D may play a critical role in regulating tumor formation through this novel genetic mechanism. Other studies have demonstrated interaction of vitamin D signaling pathways with the Wnt signaling pathway, MAPKinase signaling pathways, and hedgehog signaling (199, 200, 234, 264, 451, 483, 492, 506, 509, 627, 628, 634). Vitamin D deficiency has been associated with the development of hypertension (272, 374, 378). Vitamin D-deficient animals show higher circulating angiotensin II levels and hypertension (394, 648). Vitamin D deficiency has also been associated with endothelial dysfunction, progression of kidney disease, and hyperparathyroidism, all of which may contribute toward the development of hypertension and cardiovascular disease (25, 76, 137, 263, 620). Despite a wealth of studies using either calcitriol or other vitamin D analogs, consistent definitive studies demonstrating that vitamin D therapy can either prevent or treat any of these chronic diseases are lacking (54, 94, 95, 152, 186, 198, 288, 356, 549, 579). The role of vitamin D in extra-skeletal chronic disease pathogenesis is an area of intense interest and research.

Vitamin D deficiency may occur due to poor dietary vitamin D intake, malabsorption syndromes, or suboptimal skin conversion due to lack of sun exposure. Specific ethnic groups exhibit lower vitamin D levels, particularly those of African origin (499, 508, 575, 611). Patients with nephrotic syndrome may become vitamin D deficient due to renal wasting of DBP (50). Certain medications such as antiepileptics cause enhanced vitamin D degradation, and therefore may result in clinical vitamin D deficiency (445, 689). Relative vitamin D deficiency can be seen in syndromes of elevated FGF23 such as X-linked or autosomal dominant hypophosphatemic rickets (220, 683). Vitamin D insufficiency can be seen in up to 70% of certain populations of individuals, such as the elderly, in particular those residing in nursing home facilities (518, 603, 636). True vitamin D deficiency occurs far less frequently.

Vitamin D excess

Excessive vitamin D levels and activity are manifested predominantly as hypercalcemia and hypercalciuria, with symptoms referable to these complications such as altered mental status, polyuria due to nephrogenic diabetes insipidus, nausea and constipation, kidney stones, and kidney failure (145, 662).

Vitamin D intoxication can occur with excessive ingestion of vitamin D supplements, uncommonly with over the counter cholecalciferol but relatively commonly with prescription active vitamin D supplements such as calcitriol. Granulomatous disorders may also be accompanied by high vitamin D levels, which will present as hypercalcemia. The most common is sarcoidosis, a poorly understood autoimmune disorder with a myriad of clinical manifestations including lymphadenopathy, pulmonary nodules and fibrosis, skin lesions, arthritis, neuropathy, and interstitial kidney disease (649). The characteristic lesion of the disease is noncaseating granulomas. The source of the high vitamin D levels is the epithelioid cells of macrophage origin lining the granulomas. Treatment with glucocorticosteroids is highly effective in suppressing the vitamin D production and ameliorating the hypercalcemia. High vitamin D levels are seen considerably less frequently in other granulomatous diseases such as tuberculosis (6, 59, 297, 649, 716). Primary phosphate wasting syndromes such as hereditary hypophosphatemic rickets with hypercalciuria, caused by mutations in one of the sodium phosphate cotransporters responsible for renal phosphate reabsorption, is associated with high vitamin D levels likely due to suppressed FGF23 levels (1, 56, 67, 181, 324). Mutations in Cyp24 have also been identified in individuals with hypercalcemia and high 1,25 vitamin D (319).

Pharmacology

Vitamin D adequacy is assessed by the measurement of serum 25-hydroxyvitamin D. The optimal level remains a source of controversy. Recent Institute of Medicine recommendations, based on an extensive review of multiple studies, suggest that 20 ng/mL is adequate for healthy adults and would not constitute an indication for supplement (22). Ingestion of 600 IU/day of cholecalciferol has been suggested as the minimum daily dietary requirement for maintenance of adequate vitamin D stores for those aged 71 or less, and 800 IU for those above 71 years of age. The upper limit of ingestion is 4000 IU daily. The major sources of dietary vitamin D, either fish oils such as cod liver oil, sardines or vitamin D fortified foods generally are not predictable sources of the daily requirements, as they are not eaten by many people. Twenty minutes of sunlight exposure three times per week has also been shown to result in production of adequate vitamin D in Caucasians. However, darker skinned peoples, older individuals, and those living at high latitudes may not be able to achieve adequate conversion through sunlight exposure. To ensure adequate vitamin D homeostasis, the more recent recommendations for adults suggest 1000 to 2000 IU/day of cholecalciferol (90). Alternative regimens using high dose intermittent therapy are also commonly used, for example, ergocalciferol 50,000 IU weekly or monthly. While some investigators feel that both forms of vitamin D, cholecalciferol or ergocalciferol, are equally efficacious, others suggest that cholecalciferol may be superior (257). Additionally, as indicated previously, there is evidence that high dose, bolus therapy may be less effective due to rapid tissue uptake and sequestration. Taken as prescribed, these compounds rarely produce hypercalcemia.

For individuals with kidney failure who are unable to activate 25-hydroxy vitamin D, an active form of vitamin D can be prescribed. Calcitriol, paracalcitol, and doxercalciferol are the three currently available formulations. Calcitriol is identical to native 1,25 vitamin D. Paracalcitol and doxercalciferol

are modified analogs of ergocalciferol(430). Calcitriol and paracalcitol are themselves active compounds while doxercalciferol requires 25-hydroxylation in the liver to become activated (53, 439). The risk of hypercalcemia is much higher with the use of any of these compounds; therefore, patients on these medications should be monitored closely.

Conclusions

Vitamin D, while referred to in the singular, is in fact a family of secosteroid compounds. While 1,25-dihydroxycholecalciferol is recognized as the active circulating and autocrine form of the hormone, it is likely that at least some of the other metabolites may exert unrecognized effects. Vitamin D has widespread effects in a variety of organ systems where for the most part the VDR coexists with the cell machinery to manufacture and metabolize active vitamin D from inactive precursors. These intrinsic mechanisms are carefully regulated such that vitamin D itself, vitamin D precursors, and other hormones may activate synthesis of vitamin D, but simultaneously, mechanisms for limiting active hormone production are activated. In addition to its well-known function as a regulator of mineral metabolism, vitamin D also plays a critical role in skin function, immune regulation, and vascular health. Thus, abnormalities in vitamin D metabolism have been implicated in most if not all chronic disorders including diabetes, hypertension, cancer, and chronic kidney disease as well as a multitude of autoimmune disorders such as multiple sclerosis. Major gaps in our understanding of vitamin D metabolism and effects include the interacting and/or exclusive roles of circulating versus autocrine vitamin D, determinants of circulating levels of vitamin D precursors and metabolites, the genomic versus the nongenomic actions of vitamin D, the roles of the multiple vitamin D metabolites, and, of course, the role of vitamin D dysregulation in the genesis and maintenance of the wide variety of pathologies where it has been implicated.

Acknowledgements

This work was supported by the VA Merit Review Program (E. D. Lederer), the NIA (S. J. Khundmiri), and the University of Louisville (E. D. Lederer).

Dr. Lederer is an employee of the Department of Veterans Affairs. This work was performed in this capacity but represents the opinions of the authors alone, not the Department of Veterans Affairs.

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