Parathyroid Physiology and Molecular Biology

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Andrew M. Hinson and Brendan C. Stack Jr.

Contents

A.M. Hinson, M.D. (✉)
B.C. Stack Jr., M.D., F.A.C.S., F.A.C.E.
Department of Otolaryngology-Head and Neck Surgery, University of Arkansas for Medical Sciences, 4302 W. Markham St Slot, #806, Little Rock, AR 72205-7199, USA
e-mail: hinson.drew@gmail.com; bstack@uams.edu

Introduction

The parathyroid hormone (PTH) gene has been sequenced in more than ten different species. Phylogenetic analysis has identified an array of homologous domains associated with the synthesis, secretion, and degradation of PTH. These studies are advancing our understanding of the molecular signaling and feedback mechanisms involved in the hormonal control of calcium and phosphate metabolism. This chapter reviews these physiologic processes at the molecular level, which serves as a solid conceptual framework for understanding the pathology discussed in later chapters.

Regulation of Gene Expression

Gene

The PTH gene is located on the short arm of chromosome 11 (11p15.3–p15.1) and consists of two introns and three exons [1–3]. The gene and encoded mRNA are nearly twice as long as the primary translated product, owing to the presence of lengthy untranslated regions (UTRs) flanking both ends. The three exons represent the functional domains of the mRNA and encode the following: exon 1 → 5′ UTR; exon 2 → signal peptide (25 amino acids); and exon 3 → PTH and 3′ UTR [4–6].

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Transcription and Regulation by Vitamin D

The UTRs possess significantly more genetic variability across species compared to the coding sequences. In the 5′ UTR, however, a number of conserved domains, known as functional response elements, have been identified and are instrumental in regulating transcription [6]. Perhaps the most significant of these clinically is the vitamin D response element (VDRE). $1,25(OH)_2D_3$, or calcitriol, is the biologically active vitamin D metabolite that binds and activates the vitamin D receptor (VDR) located in the parathyroid gland. The ligand-activated VDR interacts with a neighboring retinoic acid receptor (RXR) to form a heterodimer complex. VDR-RXR binds to the VDRE in the PTH gene promoter and downregulates transcription (Fig. 4.1). This model of vitamin D-dependent gene regulation is far from exhaustive. PTH transcription is also attenuated by an array of other regulatory coactivators and corepressors [7]. In addition, calcitriol also modulates PTH transcription by increasing (i.e., amplifying the inhibitory effect) or decreasing (i.e., dampening the inhibitory effect) the concentration of VDRs and calcium-sensing receptors (CaSR) in the parathyroid chief cells [8].

The relationship between calcitriol and PTH gene suppression has been used to prevent and treat secondary hyperparathyroidism in patients with renal failure [9]. Unfortunately, despite increases in dosing, up to 20–30 % of hemodialysis patients treated with a nonselective vitamin D receptor activators (VDRA) show no decrease in serum PTH levels [10]. The underlying mechanism causing resistance has been investigated in animal and human models [11, 12]. In rats with renal failure, the VDRs possess only half of the DNA binding capacity compared to their control counterparts. In addition, the incubation of normal VDRs in a uremic plasma ultrafiltrate results in more than a 50 % loss of VDRE binding sites. Uremic toxins may alter or destroy the DNA-binding sites resulting in an inadequate compensatory response following calcitriol administration [12].

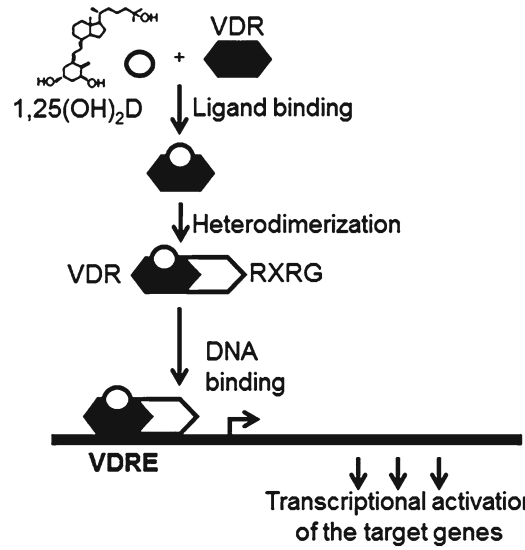

Fig. 4.1 Bioactive vitamin D activates the vitamin D receptor (VDR), which interacts with a neighboring retinoic acid receptor. This complex then binds to the vitamin D response element (VDRE) in the PTH gene promoter and downregulates PTH transcription. From: Vimaleswaran KS et al. Interaction between allelic variations in vitamin D receptor and retinoid X receptor genes on metabolic traits. BMC Genet 2014; 15:37

In humans, particular polymorphisms in the VDR gene (12q12.14) have been identified in patients with chronic kidney disease that may affect their response to intravenous calcitriol [10]. In general, a higher incidence of the *b* allele of the VDR BsmI gene has been reported in hemodialysis patients with secondary hyperparathyroidism [13]. In predialysis patients with mild-to-severe chronic renal failure, patients with the *BB* genotype have a greater reduction in PTH levels following administration of a single bolus of calcitriol, despite having corrected for calcium and phosphorous levels. The patients with *BB* genotype also show slower disease progression compared to patients with the *bb* genotype. The authors from this study concluded that patients with the *BB* genotype could remain on hemodialysis longer before requiring a parathyroidectomy [14, 15]. However, it is important to note that when the parathyroid gland specimens were removed from these patients, tissue culture analysis of PTH secretion patterns were not associated with the various VDR alleles and response

to calcitriol [15, 16]. Thus, at present, the current level of evidence does not support adapting treatment algorithms according to a patient's VDR allele status [10]. A challenge for the future will be identifying other transcription regulators and mechanisms that may serve as biomarkers or possibly even therapeutic targets to aid in the management of these patients.

Posttranscriptional Regulation by Calcium and Phosphate

The amount of PTH synthesized for translation is highly dependent on events occurring after transcription (Fig. 4.2). For example, dietary-induced hypocalcemia results in a ten-fold increase in PTH mRNA levels via posttranscriptional processes alone [17]. The amount of mRNA available for translation is highly predicated on the survival of the newly synthesized strands. In the 3′ UTR, evolutionary conserved domains are present that correspond to elements in the mRNA that are highly prone to degradation by cytosolic ribonucleases [18]. Importantly, the instability of these mRNA elements is not absolute. In the setting of hypocalcemia, cytosolic *trans (*non-DNA mediated*)* activating factors may bind to the *cis* (DNA mediated)-acting instability elements and protect the mRNA from subsequent degradation [17]. Additionally, serum phosphate, independent of changes in the serum calcium, causes decreased binding of the cytosolic proteins [17, 19]. This results in deadenylation, de-capping, and subsequent degradation of the mRNA [18] (Fig. 4.3).

Translation and Protein Processing

PTH mRNA encodes a pre- (or signal) sequence of 25 amino acids and a basic pro-peptide of 6 amino acids [21]. PreProPTH (115 amino acids) is first synthesized on ribosomes that are bound to the membrane of the endoplasmic reticulum [6, 22]. As translation proceeds, the polypeptide, rich in hydrophobic residues, is transported into the endoplasmic reticulum where two amino (N)-terminal methionines (MET) are cleaved by methionyl amino peptidase ([23]). As the polypeptide chain is translocated across the ER, further proteolytic cleavage of the remaining signal sequence occurs at the glycyl-lysyl bond, resulting in 23 more amino acids being removed from the PTH precursor [6, 23]. The formation of ProPTH from preProPTH is estimated to occur in less than a minute [24].

ProPTH is exported in vesicles that bud from the transitional ER and carry their cargo through the ER-Golgi intermediate compartment and then to the Golgi network. Following entry into the *trans*-Golgi apparatus, the basic pro-peptide directs cleavage of the pro-sequence (6 amino acids) from the N-terminal to produce mature PTH (84 amino acids) ([25]). PTH is then packaged into either cytoplasmic (for storage) or secretory granules. The entire parathyroid biosynthetic process is estimated to occur in less than 1 h [26].

Regulated Secretion and Degradation of PTH and Its Derivatives

PTH secretion is regulated predominantly by calcium sensing receptors (CaSRs) located on the surface of chief cells [18] (Fig. 4.4). The CaSR is a seven-transmembrane G-protein-coupled receptor that is highly sensitive to changes in serum calcium [18]. For instance, a decrease of less than 1 mg/dL in serum calcium can cause PTH secretion to double [27] (Fig. 4.5). Sudden and sustained hypocalcemia results in elevations in PTH within 1 min, peaks at 4–10 mins, and then steadily declines to approximately 60 % of its maximum concentration, despite sustained hypocalcemia [18]. In contrast, the rate of PTH secretion is greatly suppressed when the serum calcium exceeds 9–10 mg/dL [27] (Fig. 4.5).

Following exocytosis from the chief cell, the liver and kidney metabolize PTH into amino (N)- and carboxy (C)-terminal fragments, which are ultimately cleared by glomerular filtration. Chief cells also partially degrade PTH (1–84) and secrete both N- and C-fragments directly into the circulation [6]. Traditionally, the N-terminal portion of PTH has been thought to constitute the

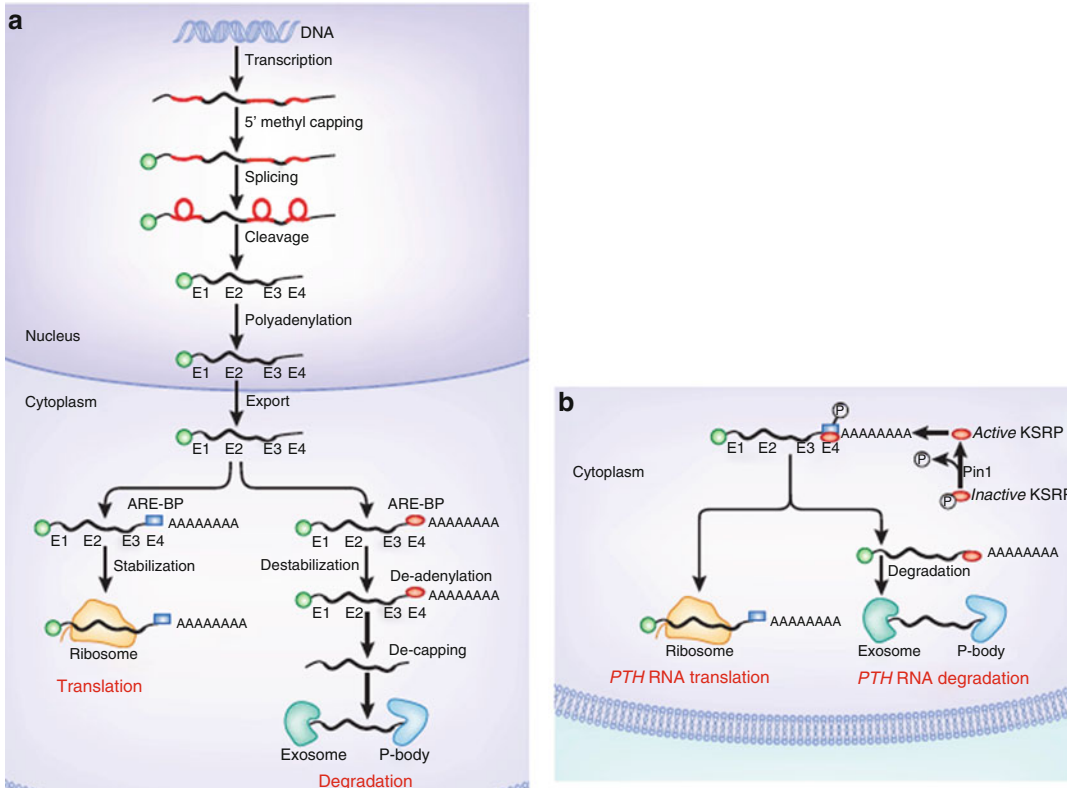

Fig. 4.2 (**a**) Cellular processing of mRNA. Nascent mRNA comprised of exons (E1 through E4) and intervening sequences (IVS) is processed in the nucleus by 5′-methyl capping, splicing, cleavage, and polyadenylation. In the cytoplasm, AU-rich element-binding proteins (ARE-BPs, blue box and red oval) bind to AREs within the 3′-region of RNA and stabilize or destabilize mRNA. Stabilized mRNA undergoes translation in ribosomes, whereas destabilized mRNA undergoes deadenylation, decapping, and degradation in exosomes or P-bodies. (Adapted from reference 130 with permission from the American Society for Clinical Investigation.) (**b**) Processing of mRNA-encoding *PTH*. Murine mRNA-encoding *PTH* is bound by ARE-PPs, which either stabilize or destabilize the mRNA. The ratio of activities of stabilizing/destabilizing ARE-binding proteins bound to mRNA-encoding *PTH* determines the half-life of the mRNA. KSRP is a mRNA-destabilizing ARE-BP for mRNA-encoding *PTH* that is active in its dephosphorylated state. The peptidyl-prolyl isomerase Pin 1 is responsible for the dephosphorylation of KSRP. In CKD, Pin 1 activity is reduced, and as a result less dephosphorylated (active) KSRP is available. Consequently, a stabilizing ARE-BP, AUF1, is active and mRNA-encoding *PTH* is degraded to a lesser extent, resulting in higher intracellular mRNA levels, more PTH synthesis, and secondary hyperparathyroidism. Abbreviation: P, phosphate. (Adapted from reference 130 with permission from the American Society for Clinical Investigation.) From: Kumar R, Thompson JR. The regulation of parathyroid hormone secretion and synthesis. J Am Soc Nephrol 2011; 22: 216–224

biologically active region [6]. Substitution or deletion of even one amino acid in the first N-terminal 34 amino acids significantly reduces the polypeptide's functional activity and potential to interact with the type 1 PTH receptor (PTH1-R) [6]. PTH fragments with conserved sequences in the first 34 amino acids [i.e., naturally occurring PTH (1–37), synthetic analogue PTH (1–34], PTHrP) are capable of mediating any number of activities that are classically associated with PTH [28].

The C-terminal of PTH (the last 50 amino acids) was previously thought to be biologically inert after translation [29]. Evidence now sug-

gests that C-PTH fragments interact with non-classical PTH receptors and exert biological effects that are independent and opposite to those of PTH (1–84) [30]. For instance, C-PTH fragments may bind to C-PTH receptors on osteoclasts and exert a direct antiresoptive effect on bone [31, 32]. A particular subset of C-PTH fragments, representing approximately 10 % of all C-PTH fragments, contains a partially preserved N-structure [33]. Compared to other C-PTH fragments, the N-truncated fragments, represented by the prototype PTH (7–84), may become increasingly important clinically because they have about a ten-fold greater affinity for the C-PTH receptor and inducing its antiresorptive effects [33]. Moreover, synthetic hPTH (7–84) has been shown to antagonize the calcemic effect of hPTH (1–84) and hPTH (1–34) in parathyroidectomized animal models, suggesting that the fragments may at least contribute to the PTH resistance commonly observed in the setting of renal failure [34, 35].

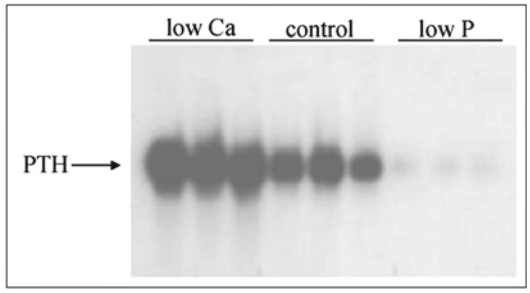

Fig. 4.3 Low dietary intake of calcium and phosphate decrease PTH mRNA levels. Weanling rats were fed control (0.6 % calcium, 03 % phosphate), low calcium (0.02 % calcium, 0.6 % phosphate) or low phosphate (0.6 % calcium, 0.02 % phosphate) diets for 14 days. Total RNA from thyro-parathyroid tissue from each rat was extracted and PTH mRNA levels determined by Northern blots. Each lane represents PTH mRNA from a single rat. From: Kilav R, Silver J, Naveh-Many T. Parathyroid hormone gene expression in hypophosphatemic rats. J Clin Invest 1995; 327–333 [20]

The relative concentrations of PTH (1–84) and C-PTH fragments are predominantly a reflection of the serum calcium and renal status of the patient. In the setting of normocalcemia and renal sufficiency, PTH (1–84) has a half-life

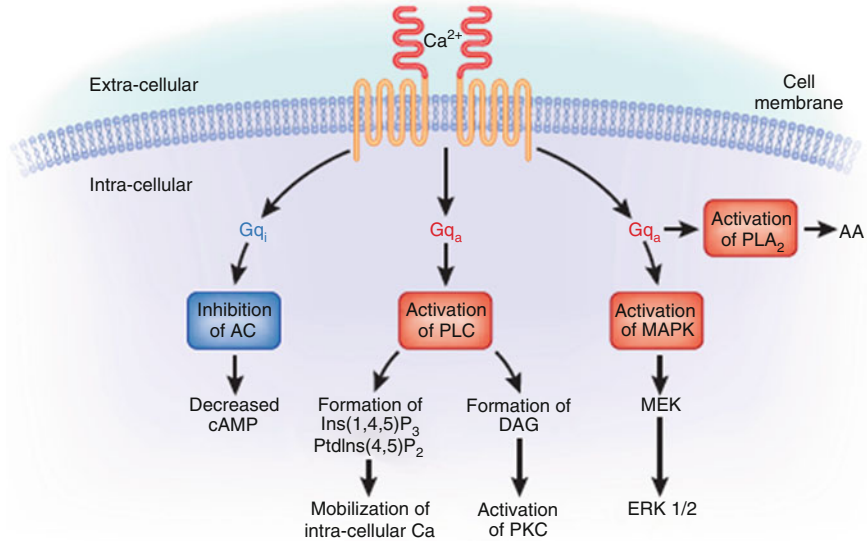

Fig. 4.4 Signaling pathway by which extracellular calcium (Ca2+) binds to the calcium sensing receptor (CaSR). Through the association of the CaSR with the i-type heterotrimeric G protein, $G_{i\alpha}$, adenylate cyclase (AC) activity is inhibited and cyclic AMP (cAMP) concentrations decrease. Association of the CaSR with the $G_{q\alpha}$ subunit of q-type heterotrimeric G protein results in the activation of PLC that increases inositol $(1,4,5)P_3$ and diacylglycerol (DAG) with attendant downstream effects, such as an increase in intracellular calcium that is mobilized from intracellular stores, and the activation of PKC. MAPK and PLA_2 are activated by $G_{q\alpha}$-dependent pathways with increases in MEK and ERK and an increase in arachidonic acid formation. From: Kumar R, Thompson JR. The regulation of parathyroid hormone secretion and synthesis. J Am Soc Nephrol 2011; 22: 216–224

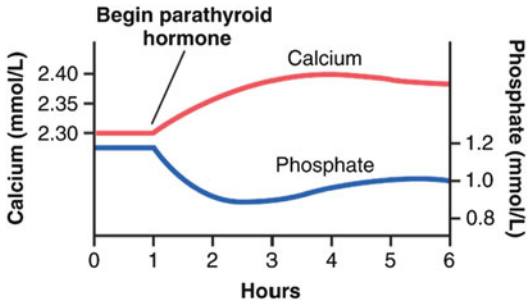

Fig. 4.5 Approximate effect of plasma calcium concentration on the plasma concentrations of parathyroid hormone and calcitonin. Note that chronic changes in calcium levels of only a few percentage points can cause as much as a 100 % change in parathyroid hormone concentration. From: Hall J. Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone and teeth, in Guyton and Hall textbook of medical physiology. Chapter 79. 11ed. Philadelphia: Saunders-Elsevier: 2011. Philadelphia 955–972

of 2–4 mins and accounts for approximately 20 % of total circulating PTH [36]. In patients with impaired renal clearance, the half-lives of PTH (1–84) and other PTH fragments with conserved sequences in the first 34 amino acids are mildly elevated and range from 4 to 6 mins [37]. In the setting of hypocalcemia and hypercalcemia, the relative concentration of PTH (1–84) compared with total circulating PTH ranges as high as 33 % or as low as 4 %, respectively [36, 26]).

In contrast to PTH (1–84), C-PTH fragments have an inherently longer half-life that ranges from 10 to 20 mins depending on the renal status of the patient [36]. C-PTH fragments account for approximately 80 % of circulating PTH in normal individuals and upwards of 95 % as glomerular filtration rate decreases [36, 26]). Similarly, the C-PTH fragments with partially preserved N-structure, such as PTH (7–84), act like other C-PTH fragments, and their concentration relative to PTH (1–84) increases in hypercalcemia and decreases in hypocalcemia [35]. In the setting of poor renal clearance, the N-truncated C-fragments accumulate and may account for up to 50 % (compared to only 15–20 % normally) of intact PTH (iPTH) immunoreactivity [34].

This at least partly explains why iPTH monitoring demonstrates a relatively slower decline following subtotal or total parathyroidectomy in the setting of chronic renal failure. Commercially available iPTH assays (first and second generations) for intraoperative iPTH monitoring lack specificity and overestimate the actual PTH (1–84) values because of cross-reactivity with PTH containing amino acids 7–84 (PTH 7–84) [37]. The artificially elevated iPTH levels may potentially hamper intraoperative evaluation of resection sufficiency leading to further surgical exploration that is otherwise unwarranted [37]. This problem of cross-reactivity with PTH (7–84) has prompted the development of a third generation of assays, which use antibodies targeted against an epitope containing the proximal 4–6 amino acids at the N-terminal [37]. While some authors propose that third-generation assays provide superior intraoperative data, it is not clear whether the implementation of these assays will translate into a reduction in failed parathyroid surgeries, decreased hypoparathyroidism, or decreased operating times [37]. It is unknown whether the clinical utility will ultimately exceed the longer incubation times and elevated costs associated with the newer assays.

Classical Actions of PTH

In general, continuous infusion of PTH causes calcium levels to rise until eventually reaching a plateau after about 4 h [27] (Figs. 4.6 and 4.7). In juxtaposition, the phosphate concentration declines relatively rapidly and reaches a plateau within 2 h [27]. This occurs because PTH increases the calcium and phosphate absorption from the bone and decreases the excretion of calcium by the kidneys. The PTH-induced decline in phosphate, then, is a consequence of the rapid excretion of phosphate, relative to the rate of phosphate reabsorption in bone [27].

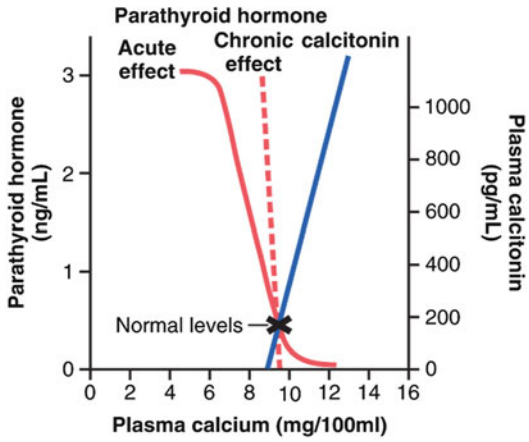

Fig. 4.6 Approximate changes in calcium concentrations during the first 5 h of parathyroid hormone infusion at a moderate rate. From: Hall J. Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone and teeth, in Guyton and Hall textbook of medical physiology. Chapter 79. 11ed. Philadelphia: Saunders-Elsevier: 2011. Philadelphia 955–972

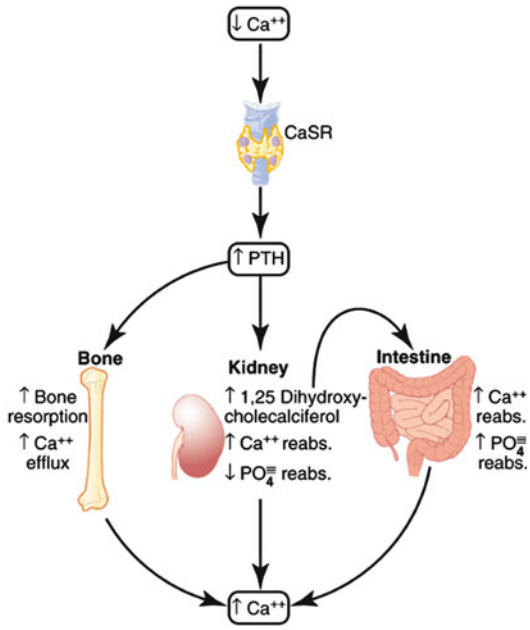

Fig. 4.7 Summary of parathyroid hormone (PTH) actions on bone, kidneys, and intestine in response to decreased extracellular calcium concentrations. *CaSR*, calcium-sensing receptor. From: Hall J. Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone and teeth, in Guyton and Hall textbook of medical physiology. Chapter 79. 11ed. Philadelphia: Saunders-Elsevier: 2011. Philadelphia 955–972

Bone

PTH acts on bone, containing upwards of 99 % of total body calcium stores, to release calcium in two stages [38]. The first phase, which occurs within minutes and rises steadily over hours, involves the release of calcium and phosphate stores from pre-existing bone cells. The bone is separated from the extracellular fluid by a membrane of interconnected osteoblasts and osteocytes referred to as the osteocytic membrane [27]. The osteocytic membrane contains a small amount of interim fluid, called bony fluid, whose calcium concentration is dictated by osteocytic pumps [26]. PTH binds to osteocyte receptors and increases the permeability of the bone fluid side of the osteocytic membrane, which causes the calcium concentration to increase in the bony fluid. The calcium ions that diffuse into the membrane cells from the bone fluid activate the calcium pump, which results in the rapid removal of calcium phosphate salts from the amorphous bone crystals that lie near the cells [27].

In the second phase, which occurs after several days or even weeks, PTH binds to osteocytes and indirectly induces the formation and proliferation of new osteoclasts [27]. The increased concentration of osteoclasts results in increased resorption of calcium phosphate salts from bone. The traditional view has been that osteoblasts, rather than osteoclasts, possess PTH receptors and activate second messenger signals through effects on RANKL and osteoprotegerin (OPG) [39]. As discussed previously, however, emerging evidence suggests that intact PTH (1–84), but not PTH (1–34), may bind directly to osteoclasts via C-terminal PTHRs [25].

Paradoxically, intermittent or pulsatile PTH administration stimulates bone formation relative to bone resorption. There is now level I evidence that daily or once-weekly subcutaneous injections of PTH (1–34) significantly increase bone mineral density at all skeletal sites except the radius and significantly reduces the risk of new fractures in postmenopausal women with prior fractures [40, 41]. It appears that PTH (1–34) improves bone collagen cross-link formation, microarchitecture, and bone mass, resulting in an overall

increase in bone strength [42]. The precise molecular mechanism by which this anabolic action occurs is not fully understood but likely occurs via the induction of particular target genes [43]. For example, when PTH binds to its associated receptor, the hormone induces a wave of RANKL expression that may induce either catabolic or anabolic processes depending on whether the PTH is given continuously or intermittently, respectively [44]. It is thought that the variable expression of RANKL in the osteoblasts may be related to varying levels of osteoclastogenesis [43]. Notably, both PTH (1–34) and PTH (1–84) have been shown to have equal potential in mediating anabolic bone formation, suggesting that the N-terminal interaction with the PTH1-R is relevant [45].

Kidney

In the kidney, PTH regulates the threshold for the excretion of calcium and phosphate. PTH1-Rs are predominantly located in the cortical thick ascending limb loop of Henle and the distal convoluted tubules of the nephron [27]. In the setting of hypocalcemia, PTH binds to PTH1-Rs on the tubule segments and stimulates active transport of Ca^{2+} preventing excessive urinary excretion. In the setting of hypercalcemia, calcium binds to CaSRs with a subsequent increase in calciuresis. PTH is also the predominant regulator of phosphate reabsorption and excretion in the nephron. The majority of renal phosphate reabsorption occurs in the proximal tubules via type IIa Na-P_i cotransporter [46]. In the setting of elevated serum phosphate, PTH internalizes and degrades the apical Na-P_i and rapidly increases the phosphate excretion [46]. Calcitriol likely plays an important role in the regulation of these cotransporters [46].

Ingested ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), which may also be synthesized from sunlight, are converted to 25-hydroxyergocalciferol (25-hydroxyvitamin D_2) and calcidiol (25-hydroxyvitamin D_3) in the liver. Following their release into the circulation, these two hepatic metabolites may be measured from the serum to determine a patient's vitamin D status. In the proximal tubules, a portion of circulating calcidiol is converted to calcitriol. Calcitriol increases both calcium and phosphate absorption from the gastrointestinal tract. Circulating PTH acts at the proximal tubules and governs the amount of calcidiol that is converted to calcitriol and indirectly regulates the rate of calcium and phosphate absorption from the intestine [38] (Fig. 4.8). When serum calcium is below approximately 9 mg/dL, PTH enhances the enzymatic activity of alpha-1-hydroxylase in the proximal tubules resulting in the synthesis of calcitriol [47]. At elevated calcium levels, PTH secretion is suppressed and calcidiol is instead converted to $24,25(OH)_2D_3$, which has less than 1/1,000 of an effect on increasing intestinal calcium and phosphate absorption [27]. The PTH-induced conversion to active vitamin D metabolite explains why approximately 50 % of patients with primary hyperparathyroidism may present with normal or elevated levels of calcitriol in spite of a 40 % prevalence of vitamin D deficiency.

As kidney function declines, parathyroid function is stimulated by (1) insufficient production of calcitriol by the kidney, (2) calcium deficiency, and (3) elevated phosphate levels [48]. In the early stages of chronic kidney disease (CKD) (GFR > 60 ml/min/1.73 m^2), dietary phosphorous intake initially suppresses calcitriol production, which subsequently induces PTH secretion and prevents the development of hyperphosphatemia [49]. As CKD progresses (GFR < 30 ml/min/1.73 m^2 of body surface), however, phosphorous levels escalate and induce hypocalcemia [49]. As discussed previously, elevated serum phosphate and low serum calcium both increase PTH secretion. Prolonged and excessive levels of PTH cause high turnover bone disease and may cause other effects that are not classically associated with the hormone: glucose intolerance, polyneuropathy, dyslipidemia, cardiac hypertrophy and dysfunction, and uremic inflammation [49]. Several studies have investigated the role of elevated PTH as a nonspecific uremic toxin. It is important to remember, however, that a complex relationship exists between elevated PTH and other potential factors involved in mineral metabolism in CKD, and thus the role of PTH as an

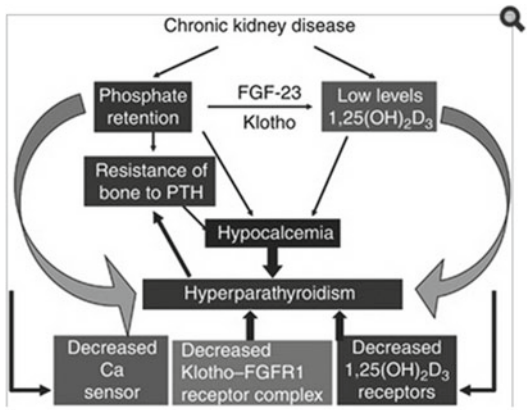

Fig. 4.8 Summary of the factors involved in the pathogenesis of secondary hyperparathyroidism. A decrease in ionizing calcium is crucial in the development of secondary hyperparathyroidism. Changes in ionized calcium are secondary to phosphate retention and low levels of $1,25(OH)_2D_3$. Phosphate retention increases fibroblast growth factor (FGF)-23, which, in conjunction with its cofactor, the Klotho protein decreases the activity of the 1 α-hydroxylase and increases the 24α-hydroxylase, thus decreasing the levels of circulating $1,25(OH)_2D_3$. In addition, phosphate retention, independent of changes in ionized calcium, increases the synthesis of parathyroid hormone (PTH). $1,25(OH)_2D_3$, independent of calcium, suppress the transcription of the *PTH* gene. Decreases in the vitamin D receptor, calcium sensor receptor, and Klotho-FGFRI receptor complex in the parathyroid gland also aggravate the development of secondary hyperparathyroidism. From: Slatopolsky E. The intact nephron hypothesis: the concept and its implications for phosphate management in CKD-related mineral and bone disorder. Kidney Int Suppl 2011; 79(S121): S3–S8

independent risk factor for uremia-related complications is not entirely clear [49].

In any case, uremic hyperparathyroidism (UHPT) is a relatively common complication occurring in patients on hemodialysis and likely contributes to the development and progression of chronic kidney disease-mineral bone disorder (CKD-MBD) [50] (Fig. 4.8). Patients with UHPT have an increased risk of all-cause and cardiovascular mortality, which has been linked to an accelerated rate of atherosclerosis and arterial calcification [50]. Thus, the prevention and control of UHPT are critical in dialysis patients as the excessive PTH and/or other uremic factors exert toxic systemic effects. At present, the major principle guiding treatment of UHPT is tight calcium and phosphorous control. While higher doses of vitamin D therapy, acting through the activation of VDR, have demonstrated efficacy in reducing hyperparathyroidism and increasing survival, the use of high-dose vitamin D has been associated with exacerbating hyperphosphatemia and causing hypercalcemia, potentially increasing the risk of atherosclerosis and arterial calcification [51, 52]. Cinacalcet has been shown to effectively lower serum iPTH, calcium, and phosphorous levels and may even provide cardiovascular protection in patients on hemodialysis [53, 54]. Cinacalcet allosterically enhances sensitivity to CaSR and also increases the expression of VDR in the parathyroid gland [50]. Moreover, the concurrent use of cinacalcet and low-dose vitamin D may increase the efficacy in treating UHPT without the elevated cardiovascular risk associated with high-dose vitamin D therapy [50]. In any case, these concepts illustrate how our evolving knowledge regarding PTH, calcium, phosphate, and vitamin D feedback mechanisms is key in the management of parathyroid-related disorders.

Summary

The biological pathway of PTH has been described from gene expression to PTH intracellular signaling. Physiologic fluctuations in plasma calcium are dependent on the proper manufacturing, secretion, and degradation of PTH. The classical actions of PTH are well known. In bone, PTH may act as a catabolic or anabolic agent depending on whether the administered PTH is continuous or pulsatile, respectively. In the distal tubular cells of the kidney, PTH directly regulates the amount of calcium excreted in the urine. In the proximal tubular cells, PTH regulates the conversion of vitamin D to its active metabolite calcitriol, which increases the amount of calcium and phosphate that is absorbed from the intestine. Finally, different circulating PTH fragments have been identified that are independent and antagonistic to the classical downstream actions of PTH (1–84). Future research is required to determine both the physi-

ological and pathological implications associated with non-classical PTH molecular signaling.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

A fundamental understanding of parathyroid physiology is crucial for both the treating physician and surgeon to master. For the physician, this understanding will be employed in diagnosis of hyperparathyroidism and the postoperative management of its sequelae. For the surgeon, this understanding is essential for confirming a diagnosis requiring surgery and assessing the response of the disease to surgical intervention.

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