The Regulation of Parathyroid Hormone Secretion and Synthesis

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The central role of the parathyroid glands in regulating Ca\(^{2+}\)/P homeostasis by modulating bone metabolism, the synthesis of 1\(\alpha\),25-dihydroxyvitamin D (1\(\alpha\),25(OH)\(_2\)D) in proximal tubules, and the reabsorption of Ca\(^{2+}\) in the distal nephron is widely appreciated by the readers of this journal.1–5 Secondary hyperparathyroidism (2°HPT) frequently occurs in the setting of chronic kidney disease (CKD), of end-stage renal disease (ESRD), or after renal transplantation,6–12 and uncontrolled 2°HPT in CKD and ESRD associates with an increased incidence of fractures and mortality.13–16

The pathogenesis of 2°HPT in CKD is complex. Phosphate retention, hyperphosphatemia, low serum Ca\(^{2+}\) (sCa\(^{2+}\)), elevated levels of parathyroid hormone (PTH), 1\(\alpha\),25(OH)\(_2\)D deficiency, intestinal Ca\(^{2+}\) malabsorption, the reduction of vitamin D receptors (VDR) and calcium-sensing receptors (CaSR) in the parathyroid glands, and altered mRNA-binding protein activities modulating PTH transcripts play a role in the development of 2°HPT.17–30 Parathyroid hyperplasia is often present as well.31,32 On the basis of these observations regarding pathogenesis, therapy for 2°HPT in the context of CKD and ESRD includes the control of serum phosphate concentrations, the administration of Ca\(^{2+}\) and vitamin D analogs, and the administration of calcimimetics.33,34,16,35,36

Nevertheless, 2°HPT remains a significant clinical problem and additional methods for the treatment of this condition would be helpful, especially in refractory situations, where other measures have failed or are only partially effective. Knowledge about the mechanisms by which parathyroid hormone secretion and synthesis occur is therefore of value in designing new approaches to the treatment of this condition. Here we briefly review the mechanisms that modulate PTH release and secretion and identify abnormalities that are present in progressive renal disease.
secretory granules within the parathyroid gland and by the synthesis of new PTH. sCa^{2+}, phosphorus, and vitamin D metabolites play a role in regulating PTH release and synthesis. Rapid PTH release from secretory granules in hypocalcemic states is modulated by the binding of Ca^{2+} to CaSRs on chief cells, whereas long-term replenishment of PTH stores is dependent on new PTH synthesis that is controlled by the availability of mRNA-encoding PTH for ribosomal translation into prepro-PTH.2,42,43,27,44–49 Hypocalcemia also retards the rate of degradation of PTH within the parathyroid gland, thus making more PTH available for release,50,51 and increases cell division in the parathyroid gland possibly through the action of the CaSR.1,42,45,52 Phosphorus additionally alters PTH synthesis, although the precise mechanisms by which changes in phosphate concentrations are detected or sensed by the parathyroid gland are unknown.28 1α,25-Dihydroxyvitamin D (1α,25(OH)_{2}D) alters the transcription of PTH and may have an indirect effect on PTH release by increasing the expression of CaSR.38–41,45,53–56

ROLE OF THE CASR IN MEDIATING PTH RELEASE

Changes in concentrations of sCa^{2+} are sensed by chief cells through a cell-surface, seven-transmembrane, G protein–coupled receptor, the CaSR, and receptor activity results in rapid alterations in PTH secretion. After the induction of abrupt and sustained hypocalcemia, plasma concentrations of PTH increase within 1 minute, peak at 4 to 10 minutes, and thereafter decline gradually to approximately 60% of the maximum at 60 minutes, despite ongoing and constant hypocalcemia. Abrupt restoration of normocalcemia from the hypocalcemic state causes levels of PTH to decrease with an apparent half-life of approximately 3 minutes. In addition to its role in the parathyroid gland, the CaSR plays an important role in regulating Ca^{2+} reabsorption in the thick ascending limb of the loop of Henle. The vital role of the CaSR in Ca^{2+} homeostasis is demonstrated by the biologic consequences of inactivating or activating mutations of the receptor. Inactivating mutations of the CaSR result in familial benign hypercalcemia or neurotensin–severe hyperparathyroidism, whereas activating mutations result in autosomal dominant hypocalcemia. The CaSR has a large extracellular domain of approximately 600 amino acids, a seven-pass transmembrane domain, and an intracellular carboxyl-terminal domain that has several phosphorylation sites. The receptor binds Ca^{2+} in its extracellular domain, most likely as a dimer in the so-called “Venus flytrap” configuration (Figure 1, A through C). Our model of the human CaSR shown in Figure 1 was obtained using multiple sequence alignments and initial coordinate models and two separate algorithms. The best model resulted from using the extracellular domain of the glutamate receptor (Protein Data Bank code 1ewk) as the template for main chain atoms. The atomic coordinates within the model were inspected and manually corrected for steric clashes, for alternative residue rotamer choices that improve hydrogen bonding, and for Ramachandran and other conformational outliers. The CaSR dimer from D23 to I528 displays perfect twofold symmetry similar to that of the glutamate receptor bound with both glutamate and gadolinium ions. The putative Ca^{2+}-binding sites were included in our CaSR model based on the presence of Gd^{3+} atomic coordinates within other glutamate receptor structures (PDBs 1ewk and 1isr). In the glutamate receptor, the Gd^{3+} location occurs at an acidic patch, including the ligating residues E238, D215, and R220. The acidic residues of equivalent positions in CaSR are conserved, although an arginine residue is not conserved. Therefore, it is likely that the Ca^{2+}-binding po-

Figure 1. A hypothetical dimeric model of residues D23 (blue) to I528 (red) of the human calcium sensing receptor extracellular domain (CaSR ECD). (A) Both monomers containing just the Venus flytrap region of the CaSR ECD are shown in a closed and presumably active configuration as was reported for the extracellular domain of the glutamate receptor with glutamate bound. The two yellow spheres (yellow arrows) indicate putative Ca^{2+}-binding sites, found at the nexus of where both lobes of a monomer meet. Most residues forming this cation-binding site are not conserved in glutamate receptor. The additional cyan spheres within the topmost lobes of the dimer designate possible Mg^{2+}-binding sites (green spheres indicated by green arrows) brought over from glutamate receptor coordinates. These Mg^{2+} sites are completely conserved in CaSR. The dimer interface of the portion of CaSR shown is completely formed from interactions between these two upper lobes. There are no intermolecular disulfide bridges linking the dimer together within this portion of the ECD of CaSR, although two intramolecular disulfides exist. (B) A model of the apo-CaSR dimer is portrayed. Again, the color ramps from blue to red from D23 to I528. The Mg^{2+} sites are present, although there is no experimental basis for this premise. Of note is the significant opening and expansion of the cavities between the upper and lower lobes of each monomer, the areas indicated by the two yellow ovals. (C) The upper lobes of the CaSR atomic coordinates shown above in (A) (with Ca^{2+} bound, now made gray in color) are superimposed on the apo-form model for the CaSR dimer drawn in rainbow as in (B). The red arrows point to a large displacement in the orientation and position of the carboxyl-terminal end of the structure near where the CaSR cysteine-rich domains (not shown) might be found. Significant conformational changes within parts of the CaSR ECD connecting with the transmembrane domains probably occur on Ca binding.
sition in the glutamate receptor and the CaSR are similar.

When Ca^{2+} binds to the CaSR, it elicits a conformational change within the extracellular domain of the receptor (compare Figure 1B with Figure 1C). These changes are possibly transmitted through the seven-pass transmembrane domain to allow interactions of the intracellular domains of the receptor with heterotrimeric G protein subunits, G_{qa} and G_{ia}. In addition to Ca^{2+}, the CaSR binds several metals, amino acids, antibiotics, and organic compounds that modulate its activity (Figure 2). For modeling of phenylalanine and neomycin, coordinates were docked into our model of CaSR manually, maximizing the number of hydrogen bonds while minimizing the number of steric clashes.

Agents such as \( L-\text{amino acids with aromatic side chains} \) exert allosteric effects on the CaSR and sensitize it to the effects of agonists such as \( \text{Ca}^{2+} \). These substances ("calcimimetic" agents) potentiate the CaSR to subthreshold concentrations of \( \text{Ca}^{2+} \). Several synthetic CaSR modulators have been developed for the treatment of hyperparathyroidism. NPS-R-467 and NPS-R-568 (phenylalkylamines) are examples of allosteric activators of the CaSR. Cinacalcet (Sensipar) is an example of a calcimimetic phenylalkylamine used to reduce PTH secretion that is now increasingly used in the treatment of 2°HPT in renal disease and in primary hyperparathyroidism. Other compounds, known as "calcytic" agents, block the CaSR and allow the release of increased amounts of PTH from the parathyroid gland for any given \( \text{Ca}^{2+} \) concentration.83,93–95 These agents, when administered intermittently, could be useful for the treatment of osteoporosis.83,93–95

When extracellular \( \text{Ca}^{2+} \) binds to the CaSR, it elicits conformational changes within the receptor. The heterotrimeric G protein subunits, G_{qa} and G_{ia}, are recruited to the receptor and alter the amounts or activity of several intracellular mediators including \( \text{Ca}^{2+} \), cAMP, and phospholipases within the chief cell (Figure 3). Intracellular \( \text{Ca}^{2+} \) is altered as a result of activation of phospholipase C (PLC) by the G_{qa} subunit of the heterotrimeric G proteins. This results in the PLC-mediated hydrolysis of phosphatidylinositol-4,5-bisphosphate and the resultant formation of inositol 1,4,5-trisphosphate and diacylglycerol. 1,4,5-Trisphosphate mobilizes intracellular \( \text{Ca}^{2+} \) stores by binding to its cognate receptor. The CaSR also interacts with \( \text{G} \alpha_{i} \) to inhibit adenylate cyclase activity that reduces intracellular cyclic AMP. In addition, activation of PLA_{2} results in the production of arachidonic acid and activation of phosphatidylinositol 4-kinase which replenishes phosphatidylinositol-4,5-bisphosphate. These changes within chief cells rapidly enhance the release of preformed PTH from the parathyroid gland.

In addition to controlling PTH release and modulating \( \text{Ca}^{2+} \) flux in the kidney, the CaSR also plays a role in the control of cellular differentiation, cellular growth, and apoptosis.96 CaSRs activate signaling pathways that regulate cellular growth through MAPKs, ERKs, and JNK kinases.96–100 The binding of CaSRs to intracellular scaffolding proteins such as filamin A is important in mediating this effect.97,101–108

The CaSR interacts with filamin A to create a scaffold necessary for the organization of G_{qa}, Rho guanine nucleotide exchange factor, and Rho signaling pathways.53 The affinity of the CaSR for filamin A is greater in the presence of \( \text{Ca}^{2+} \).104 Filamin A protects the CaSR from degradation,104 and silencing filamin A expression with siRNAs inhibits CaSR signaling.101 CaSR activation increases the activity of a serum-response element by increasing the membrane localization of the Rho protein.55

Transcription of the CaSR is not influenced by \( \text{Ca}^{2+} \) concentrations but is altered in vivo by \( 1\alpha,25(\text{OH})_{2}\text{D} \) in the parathyroid gland, in the kidney, and in thyroid C cells.\(^{24,55,54,56} \) Vitamin D response elements have been identified in the two promoter regions (P1 and P2), 380 and 160 bp upstream of the transcription start sites of the CaSR gene, respectively.55 These vitamin D response elements are atypical hexameric repeats that are separated by three nucleotides. In CKD, CaSR amounts are reduced in the parathyroid gland, most likely as a result of hyperplasia and perhaps as a result of reduced serum \( 1\alpha,25(\text{OH})_{2}\text{D} \) concentrations.\(^{109–112} \) The reductions in CaSR concentrations in the parathyroid gland attenuate the responsiveness of the gland to \( \text{Ca}^{2+} \) and contribute to 2°HPT.

THE REGULATION OF PTH SYNTHESIS

As noted earlier, replenishment of PTH stores after the release of preformed PTH is dependent on the synthesis of new prepro-PTH by ribosomes.\(^{1,2,43} \) This is dependent, in turn, upon the availability of mRNA-encoding PTH. As we discuss in the sections that follow, changes in mRNA concentrations are the result of changes in PTH gene transcription or mRNA stability.

Figure 2. Models of bound phenylalanine and neomycin molecules within the cavities of the CaSR dimer. (A) Above the predicted Ca^{2+}-binding sites shown by yellow spheres are phenylalanine molecule shown in a conformation that stacks its side-chain ring against a tryptophan residue that is unique to CaSR, whereas remaining atoms occupy the same locations as found for the glutamate molecules bound to glutamate receptor. (B) Two neomycin molecules may also be docked within a third burial location as shown in the bottom-most image.
are less well-defined and generally do not contain an AUUUA sequence.\textsuperscript{125,114,122}

As shown in Figure 4A, RNAs targeted for degradation undergo deadenylation, decapping, and degradation in a large multiprotein complex, the exosome, or in cytoplasmic compartments known as GW bodies or processing bodies (P-bodies).\textsuperscript{126–128} A 63-nucleotide ARE in the 3′-UTR of murine mRNA-encoding PTH, comprised of a core 26-nucleotide minimal binding sequence and adjacent flanking regions, regulates mRNA stability in response to changes in Ca\textsuperscript{2+} and phosphate concentrations.\textsuperscript{28,44,129} The ARE in the 3′-UTR of mRNA-encoding PTH binds two proteins, AU-rich element–binding protein 1 (AUF1) and K-homology splicing regulatory protein (KSRP).\textsuperscript{27,29} AUF1 increases mRNA half-life, whereas KSRP has the opposite effect.\textsuperscript{27,29} Both proteins are regulated by changes in sCa\textsuperscript{2+} and phosphate and are altered in CKD.\textsuperscript{27,30,130}

The Bioactivity of KSRP Is Altered by Other Intracellular Enzymes

Peptidyl-prolyl cis-trans isomerase, NIMA-interacting-1 (Pin1), a peptidyl-prolyl isomerase, alters KSRP phosphorylation and the binding of KSRP to the AREs in mRNA-encoding PTH. Pin1 binds to KSRP and prevents the phosphorylation of KSRP at serine residue 181. Nonphosphorylated KSRP is active and enhances degradation of mRNA-encoding PTH (Figure 4B). Pin1 specifically binds serine/threonine–protein motifs and catalyzes the cis-trans isomerization of peptide bonds, thereby changing the activity of proteins. Pin1 interacts with AUF1 and stabilizes mRNA-encoding GMCSF and TGFB.\textsuperscript{131,132} Interestingly, Pin1 epitopes and Pin1 enzymatic activity are detectable in rat parathyroid glands and parathyroid extracts.\textsuperscript{30} In heterologous cell systems, inhibition of Pin1 activity, or knockdown of Pin1 expression, increases mRNA-encoding PTH by inhibiting degradation, whereas overexpression of Pin1 reduces mRNA-encoding PTH by accelerating its decay. Pin1 null mice have increased levels of PTH in the parathyroid gland and circulating serum PTH concentrations without changes in sCa\textsuperscript{2+} and phosphate levels.

Induction of 25HPT by feeding rats

Figure 3. Pathways by which the CaSR homodimer signals in cells after binding of Ca\textsuperscript{2+} to the extracellular domains (red line) of the CaSR molecules in the homodimeric pair. Through the association of the CaSR with the i-type heterotrimeric G protein, Gi, adenylate cyclase (AC) activity is inhibited and cyclic AMP (cAMP) concentrations decrease. Association of the CaSR with the G\textsubscript{q} subunit of q-type heterotrimeric G protein results in the activation of PLC that increases inositol (1,4,5)P\textsubscript{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\textsubscript{2} are activated by G\textsubscript{q}–dependent pathways with increases in MEK and ERK and an increase in arachidonic acid formation.

Transcriptional Regulation of mRNA-Encoding PTH

The rate of transcription of the PTH gene is repressed by 1α,25(OH)\textsubscript{2}D.\textsuperscript{38,39,41,45} 1α,25(OH)\textsubscript{2}D binds to the VDR receptor and the liganded VDR, in association with the retinoic acid X receptor (RXR), binds to a vitamin D response element within the promoter region of the PTH gene.\textsuperscript{113} Structurally, this response element resembles those found in other genes that are upregulated by 1α,25(OH)\textsubscript{2}D. Reduced 1α,25(OH)\textsubscript{2}D concentrations in CKD or ESRD, as well as reduced VDR concentrations within the parathyroid gland, contribute to 25HPT.\textsuperscript{21}

Role of RNA-Binding Proteins in the Regulation of mRNA-Encoding PTH by Changing mRNA Stability

When sCa\textsuperscript{2+} concentrations decrease, levels of mRNA-encoding PTH increase within the parathyroid gland.\textsuperscript{46,47} Surprisingly, changes in mRNA synthesis in response to decreases in sCa\textsuperscript{2+} are not due to changes in PTH gene transcription.\textsuperscript{28,27,44,48,49} Rather, levels of bovine and murine mRNA-encoding pitl are regulated by proteins that bind elements within the 3′-untranslated region that influence mRNA stability.\textsuperscript{28,27,44,48,49}

By way of background, after transcription, nascent RNA undergoes 5′-methyl capping, splicing, cleavage, and polyadenylation in the nucleus (Figure 4A).\textsuperscript{114–117} After export from the nucleus, mRNA transcripts interact with RNA-binding proteins that influence RNA half-life and stability within the cell (Figure 4A).\textsuperscript{95,118–120} RNA-binding proteins interact with sequence-specific elements, adenine- and uridine-rich elements (AREs), that are usually present within the 3′-untranslated regions (3′-UTRs) of RNA and regulate the rate at which mRNAs are translated or degraded in cells.\textsuperscript{121,114,122–124} The fate of an mRNA species containing an ARE bound to ARE-binding proteins is partly dependent upon the relative amounts of different bound stabilizing or destabilizing ARE-binding proteins. AREs have a variable structure; Class I AREs contain several copies of the AUUUA motif dispersed within U-rich regions; Class II AREs possess at least two overlapping UUAUUUA(U/A) nonamers; Class III AREs
a low Ca\(^{2+}\) diet or by inducing CKD with adenine reduces Pin1 activity in the parathyroid gland. Reduced Pin1 activity correlates with increased levels of mRNA-encoding PTH in the PT glands of rats fed a low Ca diet or rats with renal failure. As a result of low Pin1 activity, less nonphosphorylated KSRP is available to bind to the ARE in the 3′-UTR of mRNA-encoding PTH. The reduction in Pin1 activity reduces the ratio of the ARE-BPs, KSRP, and AUF1. AUF1 activity predominates, and the half-life and stability of mRNA-encoding PTH is increased because of unopposed AUF1 activity. Increased amounts of mRNA allow more PTH to be synthesized in ribosomes and hyperparathyroidism results. It is not known what triggers the reduction in Pin1 activity in the

**Figure 4.** (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-BPs, 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 Pin1 is responsible for the dephosphorylation of KSRP. In CKD, Pin1 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.)
parathyroids in CKD and Ca$^{2+}$ deficiency.

**CONCLUSIONS**

Thus, in CKD and ESRD, multiple abnormalities contribute to the development of 2°HPT by enhancing the rate of PTH release and synthesis (Figure 5). These factors include a reduction in number of CaSRs in the parathyroid gland, and a reduction in the number of VDRs, which influence the transcription of CaSR and PTH. In addition, there are changes in the amounts of mRNA-encoding PTH binding proteins, specifically those that increase mRNA degradation and that favor an increase in levels of mRNA-encoding PTH within the chief cell. Modulators of CaSR and VDR already are available and are in widespread use for the treatment of 2°HPT in CKD and ESRD. The development of parathyroid gland specific modulators of ARE-binding proteins might result in drugs that are effective for the control of secondary hyperparathyroidism and parathyroid hyperplasia. Such drugs might be used in conjunction with vitamin D analogs and calcimimetic agents for the treatment of 2°HPT.

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**DISCLOSURES**

None.

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