The Regulation of Parathyroid Hormone Secretion and Synthesis

Rajiv Kumar* and James R. Thompson†

*Division of Nephrology and Hypertension, Department of Internal Medicine, Biochemistry and Molecular Biology, and †Department of Physiology, Biophysics and Bioengineering, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minnesota

ABSTRACT

Secondary hyperparathyroidism classically appears during the course of chronic renal failure and sometimes after renal transplantation. Understanding the mechanisms by which parathyroid hormone (PTH) synthesis and secretion are normally regulated is important in devising methods to regulate overactivity and hyperplasia of the parathyroid gland after the onset of renal insufficiency. Rapid regulation of PTH secretion in response to variations in serum calcium is mediated by G-protein coupled, calcium-sensing receptors on parathyroid cells, whereas alterations in the stability of mRNA-encoding PTH by mRNA-binding proteins occur in response to prolonged changes in serum calcium. Independent of changes in intestinal calcium absorption and serum calcium, 1α,25-dihydroxyvitamin D also represses the transcription of PTH by associating with the vitamin D receptor, which heterodimerizes with retinoic acid X receptors to bind vitamin D-response elements within the PTH gene. 1α,25-Dihydroxyvitamin D additionally regulates the expression of calcium-sensing receptors to indirectly alter PTH secretion. In 2°HPT seen in renal failure, reduced concentrations of calcium-sensing and vitamin D receptors, and altered mRNA-binding protein activities within the parathyroid cell, increase PTH secretion in addition to the more widely recognized changes in serum calcium, phosphorus, and 1α,25-dihydroxyvitamin D. The treatment of secondary hyperparathyroidism by correction of serum calcium and phosphorus concentrations and the administration of vitamin D analogs and calcimimetic agents may be augmented in the future by agents that alter the stability of mRNA-encoding PTH.


The central role of the parathyroid glands in regulating Ca2+ homeostasis by modulating bone metabolism, the synthesis of 1α,25-dihydroxyvitamin D (1α,25(OH)₂D) in proximal tubules, and the reabsorption of Ca²⁺ 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 Ca²⁺ (sCa²⁺), elevated levels of parathyroid hormone (PTH), 1α,25(OH)₂D deficiency, intestinal Ca²⁺ 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 Ca²⁺ 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.

**PTH RELEASE AND SYNTHESIS DETERMINE SERUM PTH CONCENTRATIONS**

Serum PTH concentrations are dependent upon the release of PTH stored in
secretory granules within the parathyroid gland and by the synthesis of new PTH.\(^{1,37}\) sCa\(^{2+}\), phosphorus, and vitamin D metabolites play a role in regulating PTH release and synthesis.\(^{1,3,28,38–41}\)

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 pro-pro-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 translocation 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,\(^{42,57–59}\) and receptor activity results in rapid alterations in PTH secretion.\(^{57}\) 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.\(^{60–62}\)

The vital role of the CaSR in Ca\(^{2+}\) homeostasis is demonstrated by the biological consequences of inactivating or activating mutations of the receptor. Inactivating mutations of the CaSR result in familial benign hypercalcemia or neonatal severe hyperparathyroidism, whereas activating mutations result in autosomal dominant hypocalcemia.\(^{62,63,33,64–68}\)

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.\(^{69}\) 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).\(^{70–73}\) Our model of the human CaSR shown in Figure 1 was obtained using multiple sequence alignments and initial coordinate models and two separate algorithms.\(^{74–77}\)

The best model resulted from using the extracellular domain of the glutamate receptor (Protein Data Bank code 1ewk)\(^{78}\) 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.\(^{79}\) 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 1sir). In the glutamate receptor, the Gd\(^{3+}\) location occurs at an acidic patch, including the ligating residues E238, D215, and E224 with one standout residue R220.

In the glutamate receptor, the Gd\(^{3+}\) location occurs at an acidic patch, including the ligating residues E238, D215, and E224 with one standout residue 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-
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).

Agents such as \(\text{L-amino acids with aromatic side chains} \) exert allosteric effects on the CaSR and sensitize it to the effects of agonists such as Ca\(^{2+}\).80,81,86 – 89 These substances (“calcimimetic” agents) potentiate the CaSR to subthreshold concentrations of 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 “calcilytic” agents, block the CaSR and allow the release of increased amounts of PTH from the parathyroid gland for any given sCa\(^{2+}\) concentration.83,93–95 These agents, when administered intermittently, could be useful for the treatment of osteoporosis.

When extracellular 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 Ca\(^{2+}\), cAMP, and phospholipases within the chief cell (Figure 3).42,59,70 Intracellular 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-biphosphate and the resultant formation of inositol 1,4,5-trisphosphate and diacylglycerol. 1,4,5-Trisphosphate mobilizes intracellular Ca\(^{2+}\) stores by binding to its cognate receptor. The CaSR also interacts with G\(_{ia}\) to inhibit adenylate cyclase activity that reduces intracellular cyclic AMP.42 In addition, activation of PLA\(_2\) results in the production of arachidonic acid and activation of phosphatidylinositol 4-kinase which replenishes phosphatidylinositol-4,5-biphosphate.42,59,70 These changes within chief cells rapidly enhance the release of preformed PTH from the parathyroid gland.

In addition to controlling PTH release and modulating 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.55 The affinity of the CaSR for filamin A is greater in the presence of 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 Ca\(^{2+}\) concentrations but is altered in vivo by 1\(\alpha\),25(OH)\(_2\)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(OH)\(_2\)D concentrations.109–112 The reductions in CaSR concentrations in the parathyroid gland attenuate the responsiveness of the gland to sCa\(^{2+}\) 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.
Transcriptional Regulation of mRNA-Encoding PTH

The rate of transcription of the PTH gene is repressed by 1α,25(OH)₂D. 1α,25(OH)₂D 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. Structurally, this response element resembles those found in other genes that are upregulated by 1α,25(OH)₂D. Reduced 1α,25(OH)₂D concentrations in CKD or ESRD, as well as reduced VDR concentrations within the parathyroid gland, contribute to 2°HPT.

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

When sCa²⁺ concentrations decrease, levels of mRNA-encoding PTH increase within the parathyroid gland. Surprisingly, changes in mRNA synthesis in response to decreases in sCa²⁺ are not due to changes in PTH gene transcription. Rather, levels of bovine and murine mRNA-encoding PTH are regulated by proteins that bind elements within the 3'-untranslated region that influence mRNA stability.

By way of background, after transcription, nascent RNA undergoes 5'-methyl capping, splicing, cleavage, and polyadenylation in the nucleus (Figure 4A). After export from the nucleus, mRNA transcripts interact with RNA-binding proteins that influence RNA half-life and stability within the cell (Figure 4A). 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. 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 AUUUAUA(U/A) nonamers; Class III AREs are less well-defined and generally do not contain an AUUUA sequence.

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). 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 Ca²⁺ and phosphate concentrations. 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). AUF1 increases mRNA half-life, whereas KSRP has the opposite effect. Both proteins are regulated by changes in sCa²⁺ and phosphate and are altered in CKD.

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 TGFβ. Interestingly, Pin1 epitopes and Pin1 enzymatic activity are detectable in rat parathyroid glands and parathyroid extracts. 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 sCa²⁺ and phosphate levels.

Induction of 2°HPT by feeding rats
a low Ca\textsuperscript{2+} diet or by inducing CKD with adenine reduces Pin1 activity in the parathyroid gland.\textsuperscript{30} Reduced Pin1 activity correlates with increased levels of mRNA-encoding \textit{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 \textit{PTH}.\textsuperscript{30} 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 \textit{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 \textit{PTH}. Murine mRNA-encoding \textit{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 \textit{PTH} determines the half-life of the mRNA. KSRP is a mRNA-destabilizing ARE-BP for mRNA-encoding \textit{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 \textit{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.)
Increased expression levels of mRNA-encoding radation and that favor an increase in efficiency.

J Am Soc Nephrol

of VDRs, which influence the transcription gland, and a reduction in the number of CaSRs in the parathyroid These factors include a reduction in of PTH release and synthesis (Figure 5).

CONCLUSIONS

Thus, in CKD and ESRD, multiple abnormalities contribute to the development of 2°HPT by enhancing the rate of 2°HPT by enhancing the rate of normalities contribute to the development of parathyroid gland specific alterations within the parathyroid gland that favor the development of 2°HPT in CKD and ESRD. The development of parathyroid gland specific abnormalities contribute to the development 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.

Disclosures

Dr. Kumar’s laboratory is supported by NIH grants DK76829 and DK77669, and grants from Genzyme (GRIP) and Abbott.

DISCLOSURES

None.

REFERENCES

18. Slatopolsky E, Caglar S, Gradowska L, Can-

Figure 5. Alterations within the parathyroid gland that favor the development of 2°HPT in the context of CRF and ESRD.
terbury J, Reiss E, Bricker NS. On the preve-

vention of secondary hyperparathyroidism in experimental chronic renal disease using “proportional reduction” of dietary phos-


19. Slatopolsky E, Caglar S, Pennell JP, Tag-

gart DD, Canterbury JM, Reiss E, Bricker NS. On the pathogenesis of hyperparathy-

roidism in chronic experimental renal insuf-

ficiency in the dog. *J Clin Invest* 50: 492–

499, 1971

20. Slatopolsky E, Gradowska L, Khammash-

C, Keltner R, Manley C, Bricker NS. The control of phosphate excretions in uremia. 

*J Clin Invest* 45: 672–677, 1966

21. McCarthy JT, Kumar R: Behavior of the vi-

tamin D endocrine system in the develop-


22. McCarthy JT, Kumar R: Renal osteodystro-

phy. *Endocrinol Metab Clin North Am* 19:

65–93, 1990


Finch J, Groops P, Slatopolsky E: 1,25-

(OH)2D receptors are decreased in para-


stores parathyroid calcium-sensing receptor expression and function. *J Bone Miner Res* 17: 2206–2213, 2002


29. Nechama M, Ben-Dov IZ, Biata P, Gherzi R, Naveh-Many T: The mRNA decay promoting factor K-homology splicing regula-

tor protein post-transcriptionally deter-


31. Dusso AS, Arcidiacono MV, Sato T, Al-

varez-Hernandez D, Yang J, Gonzalez-Su-

arez I, Tominaga Y, Slatopolsky E: Molecu-


32. Dusso AS, Sato T, Arcidiacono MV, Alvarez-

Hernandez D, Yang J, Gonzalez-Suarez I, To-

minaga Y, Slatopolsky E: Pathogenic mecha-


33. Locatelli F, Cannata-Andia JB, Druke TB, 


34. Moe SM, Druke TB: Management of sec-

ondary hyperparathyroidism: The impor-

tance and the challenge of controlling parathyroid hormone levels without elevat-

ing calcium, phosphorus, and calcium-

phosphorus product. *Am J Nephrol* 23:

369–379, 2003

35. Block GA, Martin KJ, de Francisco AL, 

Coyne DW, Locatelli F, Cohen RM, Even-

poel P, Moe SM, Fournier A, Braun J, McC-

cary LC, Zani VJ, Olson KA, Druke TB, Good-


1525, 2004

36. Shoben AB, Rudser KD, de Boer HI, Young B, Kestenbaum B: Association of oral calci-

bital with improved survival in nondia-

lyzed CKD. *J Am Soc Nephrol* 19: 1613– 

1619, 2008

37. Fox J, Heath H 3rd: The “calcium clamp”: Effect of constant hypocalcemia on para-

thyroid hormone secretion. *Am J Physiol*


38. Cantley LK, Russell J, Lettieri D, Sherwood LM: 1,25-Dihydroxyvitamin D3 suppresses parathyroid hormone secretion from bo-

vine parathyroid cells in tissue culture. *En-

docrinology* 117: 2114–2119, 1985

39. Russell J, Lettieri D, Sherwood LM: Sup-

pression by 1,25(OH)2D3 of transcription of the pre-parathyroid hormone gene. *Endocrinology* 119: 2864–2866, 1986

40. Silver J, Naveh-Many T, Mayer H, Schmel-

zer HJ, Popovtzer MM: Regulation by vita-


41. Silver J, Russell J, Sherwood LM: Regula-

tion by vitamin D metabolites of messen-

ger ribonucleic acid for preproparathyroid hormone in isolated bovine parathyroid cells. *Proc Natl Acad Sci USA* 82: 4270– 

4273, 1985


43. Potts JT, Gardella TJ: Progress, paradox, and potential: Parathyroid hormone re-


44. Moallem E, Kilav R, Silver J, Naveh-Many T: RNA-Protein binding and post-transcrip-

tional regulation of parathyroid hormone gene expression by calcium and phos-


45. Russell J, Bar A, Sherwood LM, Hurwitz W: Interaction between calcium and 1,25-di-

hydroxyvitamin D3 in the regulation of preproparathyroid hormone and vitamin D receptor messenger ribonucleic acid in 

avian parathyroids. *Endocrinology* 132: 

2639–2644, 1993


47. Hawa NS, O’Riordan JL, Farrow SM: Post-

transcriptional regulation of bovine para-

thyroid hormone synthesis. *J Mol Endocri-

nol* 10: 43–49, 1993

48. Vadhier S, Hawa NS, O’Riordan JL, Farrow SM: Translational regulation of parathyroid hormone gene expression and RNA: Pro-

tein interactions. *J Bone Miner Res* 11: 

746–753, 1996

49. Habener JF, Kemper B, Potts JT Jr.: Calci-

um-dependent intracellular degradation of parathyroid hormone: A possible mecha-

nism for the regulation of hormone stores. *Endocrinology* 97: 431–441, 1975

50. Morrissey JJ, Cohn DV: Secretion and de-

gradation of parathormone as a function of in vivo maturation of hormone pools. 

Modulation by calcium and dibutylryc cyclic 

AMP. *J Cell Biol* 83: 521–528, 1979

51. Roth SJ, Raiz L: Effect of calcium concen-

tration on the ultrastructure of rat parathy-

roid in organ culture. *Lab Invest* 13: 331– 

345, 1964

52. Bai M, Quinn S, Trivedi S, Kifor O, Pearce SH, Pollak MR, Krapcho K, Hebert SC, 


53. Rogers KV, Dunn CK, Conklin RL, Hadfield S, Petty BA, Brown EM, Hebert SC, Nem-

eth EF, Fox J: Calcium receptor messenger 

ribonucleic acid levels in the parathyroid glands and kidney of vitamin D-deficient rats are not regulated by plasma calcium or 


54. Canaff L, Hendy GN: Human calcium-

sensing receptor gene. Vitamin D re-

sponse elements in promoters P1 and P2

www.jasn.org

BRIEF REVIEW
94. Rubin MR, Bilezikian JP: New anabolic ther-
96. Tfelt-Hansen J, Chattopadhyay N, Young SH, Yuan J, Slice L, Rozen-

Loretz CA, Pollina C, Hyodo S, Takei Y, Chang W, Shoback D: cDNA cloning and functional expression of a Ca2+-sensing receptor with truncated C-terminal tail from the Mozambique tilapia (Oreochroma-