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.


BRIEF REVIEW

The central role of the parathyroid glands in regulating Ca\(^{2+}\) homeostasis by modulating bone metabolism, the synthesis of 1α,25-dihydroxyvitamin D (1α,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, 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), 1α,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,1,37 sCa\textsuperscript{2+}, phosphorous, 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\textsuperscript{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)\textsubscript{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\textsuperscript{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.37 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\textsuperscript{2+} reabsorption in the thick ascending limb of the loop of Henle.50–62 The vital role of the CaSR in Ca\textsuperscript{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.62,63,65–68

The CaSR has a large extracellular domain of approximately 600 amino acids, a seven-pass transmembrane domain, and an intracellular carboxy-terminal domain that has several phosphorylation sites.69 The receptor binds Ca\textsuperscript{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 gadoxilium ions.79 The putative Ca\textsuperscript{2+}-binding sites were included in our CaSR model based on the presence of Gd\textsuperscript{3+} atomic coordinates within other glutamate receptor structures (PDBs 1ewk and 1isr). In the glutamate receptor, the Gd\textsuperscript{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\textsuperscript{2+}-binding po-

![Figure 1](image-url)
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, $G_{q\alpha}$ and $G_{i\alpha}$. In addition to Ca$^{2+}$, the CaSR binds several metals, amino acids, antibiotics, and organic compounds that modulate its activity (Figure 2).$^{80-85}$ 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-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 (SensiCalc) 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.$^{90-92}$ 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.$^{83,93-95}$

When extracellular Ca$^{2+}$ binds to the CaSR, it elicits conformational changes within the receptor. The heterotrimeric G protein subunits, $G_{q\alpha}$ and $G_{i\alpha}$, 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 $G_{q\alpha}$ 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 Ca$^{2+}$ stores by binding to its cognate receptor. The CaSR also interacts with $G_{i\alpha}$ to inhibit adenylyl 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-bisphosphate.$^{42,59,70}$ 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 $G_{q\alpha}$, Rho guanine nucleotide exchange factor, and Rho signaling pathways.$^{95}$ 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 1α,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 1α,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.

**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 molecules 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 buried location as shown in the bottom-most image.
Transcriptional Regulation of mRNA-Encoding PTH

The rate of transcription of the PTH gene is repressed by 1α,25(OH)₂D₃. After transcription, nascent RNA undergoes 5'-methyl capping, splicing, cleavage, and polyadenylation in the nucleus. After export from the nucleus, mRNA transcripts interact with RNA-binding proteins that influence RNA half-life and stability within the cell. RNA-binding proteins interact with sequence-specific elements, adenosine- 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 is partly dependent upon the relative amounts of different binding stabilizing or destabilizing ARE-binding proteins. AREs have a variable structure: Class I AREs contain several copies of the AAUAAA motif dispersed within U-rich regions; Class II AREs possess at least two overlapping AAUAAA(U/A) nonamers; Class III AREs are less well-defined and generally do not contain an AAUAAA 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).

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 GMSCF and TGFβ.

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 changes 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, RNA-binding proteins that influence RNA half-life and stability within the cell interact with sequence-specific elements, adenosine- 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 is partly dependent upon the relative amounts of different binding stabilizing or destabilizing ARE-binding proteins. AREs have a variable structure: Class I AREs contain several copies of the AAUAAA motif dispersed within U-rich regions; Class II AREs possess at least two overlapping AAUAAA(U/A) nonamers; Class III AREs are less well-defined and generally do not contain an AAUAAA sequence.
a low Ca\(^{2+}\) diet or by inducing CKD with adenine reduces Pin1 activity in the parathyroid gland.\(^{30}\) Reduced Pin1 activity correlates with increased levels of mRNA-encoding \(\text{PTH}\) 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 within the 3\(^{\prime}\)-region of mRNA 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 \(\text{PTH}\). Murine mRNA-encoding \(\text{PTH}\) 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 \(\text{PTH}\) determines the half-life of the mRNA. KSRP is a mRNA-destabilizing ARE-BP for mRNA-encoding \(\text{PTH}\) 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 \(\text{PTH}\) is degraded to a lesser extent, resulting in higher intracellular mRNA levels, more \(\text{PTH}\) 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\textsuperscript{2+} deficiency.

**CONCLUSIONS**

Thus, in CKD and ESRD, multiple abnormalities contribute to the development of 2\textsuperscript{nd} 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\textsuperscript{nd} 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\textsuperscript{nd} HPT.

**Disclosures**

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

**REFERENCES**

18. Slatopolsky E, Caglar S, Gradowska L, Can...
terbury J, Reiss E, Bricker NS: On the pre-
vention of secondary hyperparathyroidism in experi-
mental chronic renal disease using “proportional re-
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
21. McCarthy JT, Kumar R: Behavior of the vi-
tamin D endocrine system in the develop-
22. McCarthy JT, Kumar R: Renal osteodyst-
Finch J, Groops P, Slatopolsky E: 1,25-
(OH)2D receptors are decreased in para-
27. Naveh-Many T, Bell O, Silver J, Kilav R: Cis-
28. Dusso AS, Arcidiacono MV, Sato T, Al-
varez-Hernandez D, Yang J, Gonzalez-Su-
arez I, Tominaga Y, Slatopolsky E: Molecu-
29. Dusso AS, Sato T, Arcidiacono MV, Alvarez-
Hernandez D, Yang J, Gonzalez-Suarez I, To-
inaga Y, Slatopolsky E: Pathogenic mecha-
30. Nechama M, Uchida T, Mor Yosef-Levi I, Silver J, Naveh-Many T, Mayer H, Silver J: Calcium regulates parathyroid hormone messenger ribonucleic acid (mRNA), but not calcitonin mRNA in vivo in the rat. Dominant role of 1,25-dihydroxyvi-
tamin D. Endocrinology 125: 275–280, 1989
31. Dusso AS, Sato T, Arcidiacono MV, Alvarez-
Hernandez D, Yang J, Gonzalez-Suarez I, To-
inaga Y, Slatopolsky E: Pathogenic mecha-
32. Dusso AS, Sato T, Arcidiacono MV, Alvarez-
Hernandez D, Yang J, Gonzalez-Suarez I, To-
inaga Y, Slatopolsky E: Pathogenic mecha-
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-
36. Shoben AB, Rudser KD, de Boer IH, Young B, Kestenbaum B: Association of oral cal-
citriol with improved survival in nondia-
lysed CKD. J Am Soc Nephrol 19: 1613–
1619, 2008
37. Fox J, Heath H 3rd: The “calcium clamp”: Effect of constant hypercalcemia on para-
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 pro-parathyroid hormone gene. En-
docrinology 119: 2864–2866, 1986
40. Silver J, Naveh-Many T, Mayer H, Schmel-
zier 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-tran-
scriptional 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
46. Naveh-Many T, Friedlaender MM, Mayer H, Silver J: Calcium regulates parathyroid hormone messenger ribonucleic acid (mRNA), but not calcitonin mRNA in vivo in the rat. Dominant role of 1,25-dihydroxyvi-
tamin D. Endocrinology 125: 275–280, 1989
47. Naveh-Many T, Silver J: Regulation of para-
thyroid hormone gene expression by hy-
48. Hawa NS, O’Riordan JL, Farrow SM: Post-
transcriptional regulation of bovine para-
thyroid hormone synthesis. J Mol Endocri-
no10: 43–49, 1993
50. 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
51. Morrissey JJ, Cohn DV: Secretion and deg-
52. Roth SI, Raiz LG: Effect of calcium concen-
tration on the ultrastructure of rat parathy-
roid in organ culture. Lab Invest 13: 331–
345, 1964

8 Journal of the American Society of Nephrology
96. Tfelt-Hansen J, Chattopadhyay N, Yano S, Hjalm G, MacLeod RJ, Kifor O, Chatto-
dhryay N: Regulation of a Ca2+-acti-
vated K+ channel by calcium-sensing
receptor involves p38 MAP kinase.
97. Arthur JM, Lawrence MS, Payne CR, Rane
M, McLeish KR: The calcium-sensing re-
ceptor stimulates JNK in MDCK cells. Bio-
chem Biophys Res Commun 275: 538–541,
2000
98. Hobson SA, Wright J, Lee F, McNeil SE, Bilderc-
back T, Rodland KD: Activation of the
MAP kinase cascade by exogenous cal-
cium-sensing receptor. Mol Cell Endocri-
99. Ye CP, Yano S, Tfelt-Hansen J, MacLeod
RJ, Ren X, Terwilliger E, Brown EM, Chat-
topadhyay N: Regulation of a Ca2+-acti-
vated K+ channel by calcium-sensing
receptor involves p38 MAP kinase. J Neur-
osci Res 75: 491–498, 2004
100. Huang C, Wu Z, Hujer KM, Miller RT: Si-
lencing of filamin A gene expression inhib-
101. Hoeben SA, Wright J, Lee F, McNeil SE, Bilderc-
back T, Rodland KD: Activation of the
MAP kinase cascade by exogenous cal-
cium-sensing receptor. Mol Cell Endocri-
102. Davies SL, Gibbons CE, Vizard T, Ward DT:
Ca2+-sensing receptor induces Rho ki-

103. Reed O, Young SH, Yuan J, Slice L, Rozen-
gurt E: Amino acid-stimulated Ca2+ oscilla-
tions produced by the Ca2+-sensing re-
sceptor are mediated by a phospholipase
C/inositol 1,4,5-trisphosphate-independent
pathway that requires G12, Rho, filamin-A,
104. Zhang M, Breitwieser GE: High affinity in-
teraction with filamin A protects against cal-
cium-sensing receptor degradation. J Biol
Chem 280: 11140–11146, 2005
105. 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 (Oreochro-
106. Ward DT: Calcium receptor-mediated in-
tracellular signalling. Cell Calcium 35: 217–228, 2004
107. Zaddan-Diaz P, Penalva LO: Post-tran-
scription meets post-genomic: The saga of
RNA binding proteins in a new era. RNA
GH, Eisenberg RJ, Wiley DC: Crystalliza-
tion and preliminary diffraction studies of
the ectodomain of the envelope glycopro-
tein D from herpes simplex virus 1 alone and in complex with the ecto-
domain of the human receptor HveA. Acta
Crystallogr D Biol Crystallogr 58: 836–838,
2002
S, Kitazawa R: Association of decreased
calcium-sensing receptor with truncated C-terminal tail
from the Mozambique tilapia (Oreochro-
107. Zaddan-Diaz P, Penalva LO: Post-tran-
scription meets post-genomic: The saga of
RNA binding proteins in a new era. RNA
GH, Eisenberg RJ, Wiley DC: Crystalliza-
tion and preliminary diffraction studies of
the ectodomain of the envelope glycopro-
tein D from herpes simplex virus 1 alone and in complex with the ecto-
domain of the human receptor HveA. Acta
Crystallogr D Biol Crystallogr 58: 836–838,
2002
S, Kitazawa R: Association of decreased
calcium-sensing receptor with truncated C-terminal tail
from the Mozambique tilapia (Oreochro-
107. Zaddan-Diaz P, Penalva LO: Post-tran-
scription meets post-genomic: The saga of
RNA binding proteins in a new era. RNA
GH, Eisenberg RJ, Wiley DC: Crystalliza-
tion and preliminary diffraction studies of
the ectodomain of the envelope glycopro-
tein D from herpes simplex virus 1 alone and in complex with the ecto-
domain of the human receptor HveA. Acta
Crystallogr D Biol Crystallogr 58: 836–838,
2002
S, Kitazawa R: Association of decreased
calcium-sensing receptor with truncated C-terminal tail
from the Mozambique tilapia (Oreochro-
107. Zaddan-Diaz P, Penalva LO: Post-tran-
scription meets post-genomic: The saga of
RNA binding proteins in a new era. RNA
GH, Eisenberg RJ, Wiley DC: Crystalliza-
tion and preliminary diffraction studies of
the ectodomain of the envelope glycopro-
tein D from herpes simplex virus 1 alone and in complex with the ecto-
domain of the human receptor HveA. Acta
Crystallogr D Biol Crystallogr 58: 836–838,
2002
S, Kitazawa R: Association of decreased
calcium-sensing receptor with truncated C-terminal tail
from the Mozambique tilapia (Oreochro-
107. Zaddan-Diaz P, Penalva LO: Post-tran-
scription meets post-genomic: The saga of
RNA binding proteins in a new era. RNA
GH, Eisenberg RJ, Wiley DC: Crystalliza-
tion and preliminary diffraction studies of
the ectodomain of the envelope glycopro-
tein D from herpes simplex virus 1 alone and in complex with the ecto-
domain of the human receptor HveA. Acta
Crystallogr D Biol Crystallogr 58: 836–838,
2002
S, Kitazawa R: Association of decreased
calcium-sensing receptor with truncated C-terminal tail
from the Mozambique tilapia (Oreochro-
107. Zaddan-Diaz P, Penalva LO: Post-tran-
scription meets post-genomic: The saga of
RNA binding proteins in a new era. RNA
GH, Eisenberg RJ, Wiley DC: Crystalliza-
tion and preliminary diffraction studies of
the ectodomain of the envelope glycopro-
tein D from herpes simplex virus 1 alone and in complex with the ecto-
domain of the human receptor HveA. Acta
Crystallogr D Biol Crystallogr 58: 836–838,