Molecular biology of the parathyroid hormone: biological actions

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Summary

Parathyroid hormone (PTH); the principal parathyroid hormone receptor (PTH1R); a G protein-linked heptahelical membrane receptor; and a second heptahelical receptor, the calcium-sensing receptor (CaR) through a tightly regulated endocrine feedback system together constitute the principal regulators of calcium homeostasis. The effectors of the calcium regulation are coordinated responses in target tissues. These responses as well as hormone biosynthesis, secretion and signaling are all under precise genetic control. Inactivating mutations in these genes controlling the multi-step process of calcium homeostasis lead to hypocalcemic disorders, as outlined in accompanying articles.

KEY WORDS: parathyroid hormone, parathyroid hormone receptor, calcium-sensing receptor, calcium homeostasis.

Introduction

Secreted by the parathyroid glands, PTH is an important regulator of blood calcium concentration in all terrestrial vertebrate species from amphibians to mammals. PTH-related peptide (PTHrP), a slightly larger molecule than PTH, was discovered more recently through efforts to identify the factor that causes, when produced in excess by certain tumors, the humoral hypercalcemia of malignancy syndrome. In contrast to PTH, which is produced by discrete endocrine glands, PTHrP is produced as a paracrine/autocrine factor in many different adult and fetal tissues and has, unlike PTH, multiple functions (1, 2).
PTH and PTHrP likely evolved from a common ancestral precursor. Despite this common evolutionary origin, both peptides share only limited overall amino acid sequence identity, yet at least their N-terminal regions are sufficiently homologous to enable them to bind to and activate a common G protein-coupled receptor, the PTH/PTHrP receptor (also referred to as PTH1R) (1). This receptor mediates the most important biologic actions of both peptides: PTH-dependent regulation of calcium homeostasis and PTHrP-dependent regulation of endochondral bone formation (1, 3).

Calcium homeostasis, the regulation of Ca^{2+} concentration in blood within precise limits, depends on two principal regulators, PTH and the active form of vitamin D, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] (1). Synthesis and secretion of PTH are stimulated by any decrease in blood calcium, and conversely, secretion of the hormone is inhibited by an increase in blood calcium. This rapid negative feedback regulation of PTH production, along with the biologic actions of the hormone on different target tissues, represents the most important homeostatic mechanism for minute-to-minute control of calcium concentration in the extracellular fluid (ECF) (1-3). In contrast to the rapid actions of PTH, $1,25(OH)_2D_3$ is of critical importance for long-term, day-to-day, and week-to-week calcium balance.
At least three distinct, but coordinated actions of PTH increase the flow of calcium into the ECF and thus increase the concentration of blood calcium (1, 3). Through its rapid actions on the kidney and bone, which are all mediated through the PTH/PTHrP receptor and subsequent secondary messengers in specific and highly specialized cells, PTH (1) increases the release of calcium from bone, (2) reduces the renal clearance of calcium, and (3) stimulates the production of $1,25(OH)_2D_3$ by activating the gene encoding 25-hydroxyvitamin D-1α-hydroxylase (1α-hydroxylase) in the kidney.

Chemistry

The first biologically active extracts from bovine parathyroid glands were made in 1925 (4), and the content of biologically active PTH was assessed by the hypercalcemic properties of extracts or partially purified preparations. However, it was not until 1959, when Aurbach (5) and Rasmussen and Craig (6) developed improved extraction procedures, that it became possible to isolate and purify sufficient quantities to determine the primary structure of bovine, porcine, and human PTH (7-11). Based on these amino acid sequences, the PTH(1-34) fragments of the different species were synthesized, and their biologic activities were compared *in vitro* and *in vivo* with those of highly purified intact PTH from the same species (1, 3). Molecular cloning techniques also led to deduction of the amino acid sequences of rat, chicken and dog PTH (Fig. 1) (1, 3). Analyses of the complete genome of fugu fish and zebrafish have provided more recently several additional PTH and PTHrP structures.
Extensive sequence homology is present in the known mammalian PTH species. All of these molecules consist of a single-chain polypeptide with 84 amino acids and a molecular weight of approximately 9400 Da. That of human PTH(1-84) is 9425 Da; fish PTH molecules are shorter. After the original work establishing that the first 34 amino acids of PTH were sufficient to produce a fully active synthetic peptide (12), much work has centered on defining the minimum pharmacophore essential for biological activity. Assays performed with products of various combinations of shortened and modified PTH ligands and mutagenized receptors, as well as generation of a fusion protein consisting of ligand substituted for a portion of the receptor extracellular domain (tethered receptor) have defined a much smaller minimum chain length of PTH peptide needed for biological activity (Fig. 2).

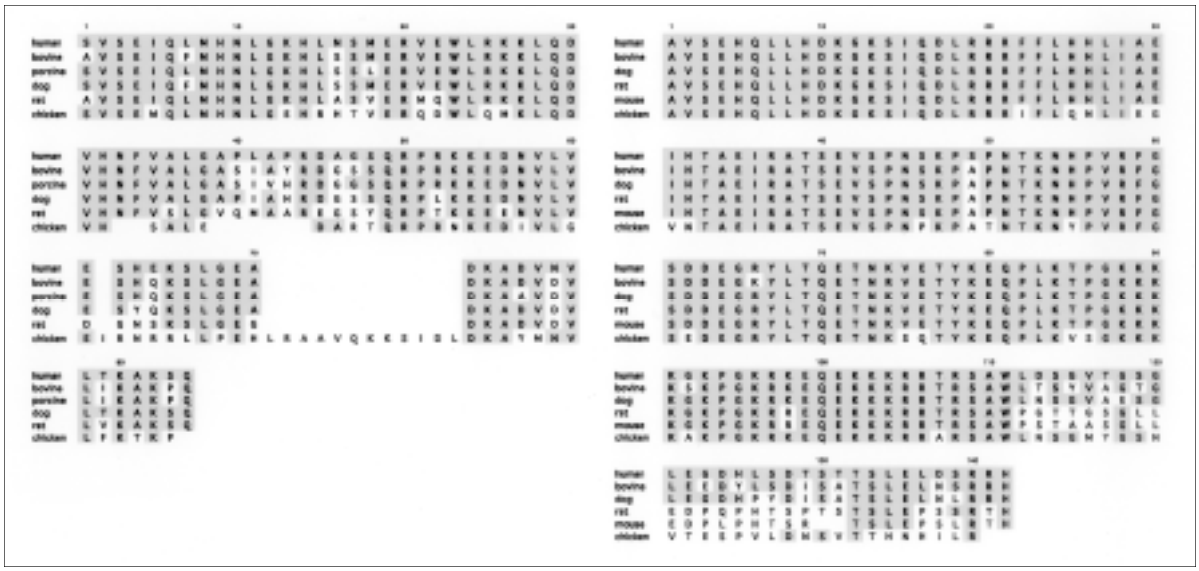

Figure 1 - Alignment of amino acid sequences of typical mammalian and chicken PTH (*left*) and PTHrP species (*right*). Conserved residues are shaded; numbers indicate positions of amino acids in the mammalian peptide sequences. (Reproduced with permission from Jüppner H, Potts JT Jr: The roles of parathyroid hormone and parathyroid hormone-related peptide in calcium metabolism and bone biology: their biological actions and receptors. In, Fray J (editor): Handbook of Physiology - Endocrine Regulation of Water and Electrolyte Balance. UK: Oxford University Press, 1997)

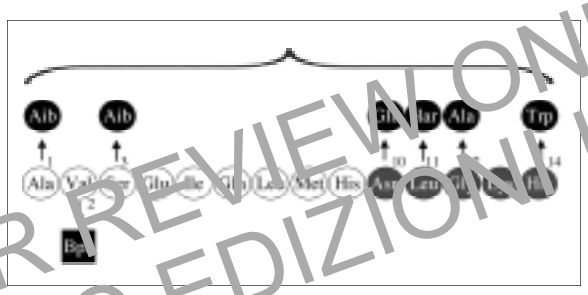

Figure 2 - The PTH(1-14) pharmacophore. Shown is the native (rat) PTH(1-14) sequence and some of the activity-modifying substitutions identified in structure-activity relationship studies performed on the PTH(1-14) peptide. The six substitutions depicted above the sequence enhance activity by as much as 100,000-fold when combined and as assessed in *in vitro* cell-based assays of camp formation. The Bpa[2] substitution shown below confers antagonist properties to the peptide. Within the PTH(1-14) scaffold, the (10-14) region has been found to be tolerant of many amino acid substitutions, whereas the (1-9) region is relatively intolerant and is thus thought to contain the minimum agonist pharmacophore of the ligand. The (1-9) region is the current minimum chain length pharmacophore. Non-encoded amino acids include amino-isobutyric acid (Aib), homoarginine (Har) and *para*-benzoyl-L-phenylalanine (Bpa).

The activity of native PTH(1-14), which is quite weak, is improved 100,000-fold by the modification indicated in Figure 2. These shorter peptides have been shown to be active in vivo as well, causing hypercalcemia and being anabolic on bone, although their potency is much less than that of PTH(1-34). Using the various approaches, it has been established that peptides as short as PTH(1-9) (tethered constructs) or highly-modified peptides as short as PTH(1-10), tested as free peptides, are active *in vitro*.

PTH biosynthesis and intracellular processing

During synthesis of the hormone precursor, the prepro-PTH molecule, the signal sequence from the PTH gene located on chromosome 11, which comprises the 25 amino acids contained in the “pre” sequence, is cleaved off after entry of the nascent peptide chain into the intracisternal space bounded by the endoplasmic reticulum. A heterozygous mutation in this leader sequence changes a cysteine to an arginine at position -8 and thus impairs processing of prepro-PTH to pro-PTH. This mutation has been identified as the most plausible molecular cause of an autosomal dominant familial form of hypoparathyroidism (13). Although it remains uncertain how this missense mutation in one allele can cause a dominant disorder, it illustrates the importance of the signal peptide in normal processing of the hormonal precursor.

Regulation of PTH secretion

A large number of factors modulate PTH secretion *in vitro* (14), but most of these factors are not thought to control hormonal secretion *in vivo* in a biologically relevant manner. Factors that are physiologically meaningful regulators of PTH secretion include the extracellular ionized calcium concentration itself (Ca^{2+}), $1,25(OH)_2D_3$, and the level of extracellular phosphate ions. Of these three, Ca^{2+} is most important in the minute-to-minute control of PTH secretion. The actions of $1,25(OH)_2D_3$ and phosphate ions on the secretion of PTH probably result, at least in part, from their effects on hormonal biosynthesis rather than secretion (14).

The molecular mechanism underlying Ca^{2+}-regulated PTH secretion involves activation of a G protein-coupled cell surface Ca^{2+}-sensing receptor (abbreviated as CaR or sometimes as CaSR). The CaR mediates the inhibitory actions of Ca^{2+} on PTH secretion, parathyroid cellular proliferation and probably also on PTH gene expression (14). In the kidney, the CaR, pre-

sent in the cortical thick ascending limb of the nephron, mediates direct, high Ca^{2+}-induced inhibition of the tubular reabsorption of Ca^{2+} and Mg^{2+} (14). Therefore, raising Ca^{2+} both directly increases renal calcium excretion and reduces PTH secretion.
There are hypercalcemic (e.g., familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism) (15) and hypocalcemic (i.e., autosomal dominant hypocalcemia) (16) disorders caused by inactivating versus activating mutations of the CaR, respectively. Another cause of primary hypoparathyroidism, therefore, is the occurrence of activating mutations in the CaR, a very difficult syndrome to treat because of the excessive urinary calcium excretion which worsens with therapy using vitamin D analogues and high oral calcium.

PTH-dependent regulation of mineral ION homeostasis mediated through the PTH/PTHrP receptor (type 1 receptor)

PTH maintains blood calcium concentration within narrow limits through its actions on the kidney and bone. In bone it stimulates the release of calcium and phosphate, and in the kidney it enhances renal tubular reabsorption of calcium (via the CaR receptor), stimulates the urinary excretion of phosphate and increases $1,25(OH)_2D_3$ production--thus increasing, albeit indirectly, intestinal absorption of calcium (and phosphate). These direct and indirect endocrine actions of PTH are mediated through the PTH/PTHrP receptor (PTH1R), a G protein-coupled receptor that is abundantly expressed in cells in both major target tissues of bone and kidney (1, 3).
PTH is of major importance for maintaining normal blood calcium levels, but it is not the principal regulator of the serum phosphate concentration, which appears to depend upon specific phosphaturic factors, such as FGF23 (17). However, when PTH causes an increase in bone resorption (as might occur with prolonged dietary calcium deprivation), both calcium and phosphate increase simultaneously in the blood. Although calcium is needed, phosphate is not and would in fact minimize the benefit of increasing supplies of calcium. Phosphate, therefore, is best excreted, which is mainly accomplished by a PTH-stimulated increase in renal phosphate clearance. The potent, PTH-dependent reduction in renal phosphate reabsorption occurs in both the proximal and distal tubules (18), but the proximal effects of the hormone are quantitatively more important (19). This failure to excrete phosphate appropriately due to deficiencies in PTH responsiveness selectively in renal cortical sites, including proximal tubules, is a major contributor to the hypocalcemia seen in pseudohypoparathyroidism.
Recent evidence suggests that the scaffold protein NHERF-1 (Na^+/H^+-exchanger regulatory factor) regulates the sodium-dependent phosphate co-transporter, NPT2, that mediates the phosphaturic actions of PTH via direct interactions with the C-terminus of the transporter (20). NHERF-1 promotes apical localization of NPT2 in opossum kidney cell models (21). Furthermore, targeted disruption of NHERF-1 in mice results in a decrease in NPT2 localization to the brush-border of the proximal tubule and renal phosphate wasting (22). Through a still poorly-defined mechanism, PTH induces internalization and lysosomal degradation of NPT2 (21), thereby promoting phosphate excretion.

Actions of PTH on bone

PTH affects a wide variety of the highly specialized bone cells, including osteoblasts, osteoclasts, and stromal cells. Some of these effects reflect direct actions of PTH; others are indirect and mediated in an autocrine/paracrine manner through factors released by cells expressing PTH/PTHrP receptors that regulate the activity of yet other cells that lack these receptors (such as osteoclasts) (1, 3).
Considerable progress has been made in elucidating the mechanisms through which bone cells respond to PTH and to other autocrine/paracrine factors. The major pathway for calcium release from bone involves osteoclasts, the principal cells capable of resorbing bone; osteoclasts undergo multiple cellular changes involving the activation of cellular transporters and pumps, as well as the secretion of enzymes such as cathepsin K and collagenases.
Osteoblasts express the PTH/PTHrP receptor most abundantly and show the most vigorous response to the hormone (1, 3, 23). A remarkable number of cellular activities of osteoblasts are influenced by PTH, including cellular metabolic activity, ion transport, cell shape, gene transcriptional activity, and secretion of multiple proteases; cellular proliferation/differentiation events that result in mature osteoblasts are also affected by PTH (1, 3). Many other factors also affect osteoblast function and bone formation. Continuous PTH administration *in vivo* results in decreased bone mass, whereas intermittent administration of PTH leads to an increase (24). Further exploration of the cellular mechanisms whereby intermittent PTH administration selectively enhances bone formation is critical for understanding the hormone's therapeutic effects as a bone anabolic agent (a surprising but pharmacologically important paradox) (25).
To stimulate bone resorption, PTH signals to osteoclasts indirectly through osteoblasts which, unlike osteoclasts, clearly have abundant PTH/PTHrP receptors on the surface and respond to the hormone with a dramatic change in cellular activity.
Several cytokines are central in the paracrine signaling cascade from osteoblasts and/or osteoblast precursors to recruit/activate osteoclasts. These molecules include the receptor activator of nuclear factor κβ (RANK) ligand (RANKL) (26-29), a membrane-associated protein with homology to the family of tumor necrosis factors (TNFs) that induces – upon cell-to-cell contact and in the presence of macrophage colony-stimulating factor – the differentiation of osteoclast precursors into mature bone-resorbing osteoclasts (26-29). These effects of RANKL are mediated through RANK, a member of the TNF receptor family that is expressed on osteoclast precursors. However, RANKL also interacts with osteoprotegerin (OPG), a soluble decoy receptor with homology to the TNF receptor family (30); this molecule acts as the inhibitory arm of osteoclast regulation. Transgenic expression of osteoprotegerin in mice leads to impaired osteoclastogenesis and thus to osteopetrosis, whereas ablation of the osteoprotegerin gene through homologous recombination in mice results in osteoporosis associated with arterial calcifications.
PTH, as well as other cytokines such as interleukin-6, interleukin-11, prostaglandin E_2 and $1,25(OH)_2D_3$, has an important role in the paracrine stimulation of osteoclast formation and can stimulate directly the production of RANKL by osteoblasts and suppress OPG production (1, 3). Cellular responses involved in bone resorption include the development of vitronectin-mediated anchorage of osteoclasts to the bone surface, acidification of the circumscribed and sealed-off extracellular environment that is created between the osteoclast and bone, and in addition, the secretion of a variety of proteases and other enzymes.

Receptors for PTH and PTHrP

Because of the diverse actions of PTH, which were shown to involve multiple signal transduction mechanism, it was initially thought that several different receptors must mediate the

pleiotropic actions of this peptide hormone, but only one receptor type seems to mediate many of these actions. This PTH/PTHrP receptor is now known to interact similarly with PTH and PTHrP and to activate several distinct second messenger pathways--including adenylate cyclase/PKA, phospholipase C (PLC)/protein kinase C (PKC), and calcium transcellular fluxes.

Most of the endocrine actions of PTH and the paracrine/autocrine actions of PTHrP are mediated through this single PTH/PTHrP receptor. Subsequent studies, however, led to the isolation of two other novel, closely related G protein-coupled receptors. One of these receptors, the PTH2 receptor (PTH2R), mediates the actions of TIP39 (tubular infundibular peptide of 39 amino acids), a more recently discovered hypothalamic peptide; human PTH2R, but not the rat receptor homologue, is also efficiently activated by PTH. The second novel receptor, the PTH3 receptor (PTH3R) (which seems not to be present in the human or other mammalian genomes), has been cloned from zebrafish, and it responds to human PTHrP more efficiently than to human PTH. Furthermore, there is both functional and physicochemical evidence of additional receptors that interact with more carboxyl terminal fragments of PTH and PTHrP; however, cDNAs encoding these novel receptors have not yet been isolated.

The PTH/PTHrP receptor (PTH1R) belongs to a distinct family of G protein-coupled receptors (Family B). The first cDNAs encoding mammalian PTH/PTHrP receptor species were isolated through expression cloning techniques from opossum kidney cells and rat osteoblast-like osteosarcoma cells. Subsequently, cDNAs encoding human, mouse, rat, chicken, porcine, dog, frog, and fish PTH/PTHrP receptors were isolated (1, 3).

Scores of synthetic peptide fragments and analogs have been used to explore the structure-activity relations in the hormone. The quantification of ligand-binding affinity through radioreceptor studies showed that receptor affinity progressively decreased as PTH(1-34) was truncated either from the amino-terminus or the carboxyl-terminus. Furthermore, fragments such as PTH(7-34), which show little or no agonist activity, proved to inhibit the actions of PTH(1-34), at least when present in high molar excess. These early studies that broadly defined the structural requirements for biologically active PTH and suggested that the receptor-binding and -activation functions resided in separable domains, provided the groundwork for the subsequent intensive study of structure/activity relations (SAR) for hormone and receptor.

A general scheme of interaction between ligand and receptor, which may apply to the entire class B family of peptide hormone-binding G protein-coupled receptors, was established. A hybrid ligand, calcitonin(1-11)/PTH(15-34), was shown to activate a chimeric calcitonin-PTH/PTHrP receptor. The chimeric receptor contained the amino-terminal, extracellular domain (the N domain) of the PTH/PTHrP receptor fused to the portion of the calcitonin receptor containing the seven membrane-embedded helices, the connecting loops, and carboxy-terminal tail (the juxtamembrane or J domain).

The data confirmed that for PTH, the amino-terminus of the ligand interacts with the J domain of the receptor, while the carboxyl-terminus of the ligand interacts with the N domain. This hypothesized mode of binding inferred from functional analyses has now largely been verified and extended by the more direct method of photoaffinity cross-linking analysis. In conventional radioreceptor assays, the PTH(1-14) fragment was unable to inhibit the binding of ^{125}I-PTH(1-34) to the intact PTH/PTHrP receptor, suggesting that the interaction between the N-terminal residues of PTH and the membrane-embedded portion of the receptor, was of low-affinity. This observation further led to the conclusion that the intrinsic signaling efficacy of the native PTH(1-14) fragment must be high, such that even a brief encounter with the receptor can trigger signal transduction. These considerations had suggested that it might be possible to modify the PTH(1-14) fragment to improve affinity and to thus obtain potent agonist ligands of minimum peptide chain length. A series of structure-activity relationship studies was thus conducted on the PTH(1-14) scaffold, and this led to the identification of a number of activity-enhancing substitutions at several residue positions (i.e., 1, 3, 10, 11, 12 and 14), which, when combined, led to substantial improvements in potency (31). Among the amino acid changes tested were the paired subsitutions of the conformationally constrained amino acid, α-aminoisobutyric acid (Aib) at positions 1 and 3, that together provided a 100-fold gain in potency and, combining these with other activity-enhancing substitutions at positions 10-14, collectively referred to as the "M" substituions, resulted in analogs such as [Aib^{1,3},Gln^{10},Har^{11},Ala^{12},Trp^{14}]PTH(1-14) or [Aib^{1,3},M]PTH(1-14) that are as much as 100,000-fold more potent than PTH(1-14) and nearly as potent as PTH(1-34) for cAMP formation in cell-based assays utilizing the intact PTH receptor. These analogs constitute the minimum requisite pharmacophore, as noted in Figure 2. The enhanced analogs also exhibited high (nanomolar) potency on PPR-delNt, the J domain of the receptor The substitutions also conferred activity to even shorter peptides, previously found to be inactive, such as PTH(1-10) (31), and extending the analogs C-terminally to position 20 or 21 and including the substitution of Glu^{19}→Arg further enhanced potency on both the wild-type PPR and on PPR-delNt.

These studies demonstrate the critical role for the amino-terminal residues of PTH (and PTHrP) in activating the PTH/PTHrP receptor, and are fully consistent with the strong evolutionary conservation of this portion of PTH and PTHrP over a wide range of vertebrate species. Nevertheless, the very weak signaling potency of unmodified PTH(1-14), relative to that of intact PTH(1-34) (EC_{50s}=200 μM and 2 nM, respectively) highlights the crucial role that the carboxyl-terminal amino acid residues of PTH(1-34) play in the overall biological activity of the native hormone in providing important binding energy for PTH. It is now clear that the C-terminal portion of PTH(1-34) provides critical docking interactions for the receptor and thereby enables the otherwise poorly binding amino-terminal domain of the ligand to associate with the J domain of the receptor--i.e., the extracellular loops (ECLs) and extracellular ends of the transmembrane helical domains (TMs). As one test of such a tethering role for the carboxyl-terminal domain of PTH(1-34), PTH analogs were synthesized in which the PTH(1-9) segment, representing the essential elements of the PTH agonist pharmacophore, was linked by a five-residue glycine spacer to the PTH(15-31) domain; although the resulting peptide was less potent than PTH(1-34) (EC_{50s} ~ 100 nM and 1 nM, respectively), the Gly-linker analog achieved the same maximal cAMP response as that induced by PTH(1-34), whereas, in contrast, the individual fragment peptides, PTH(1-9) and PTH(15-31), were inactive (31). In another test of the thethering concept, the PTH(1-9) sequence was directly linked, via site directed mutagenesis methods, to the J domain of the PTH/PTHrP receptor at a site (Glu-182) just N-terminal of the extracellular end of TM1; COS-7 cells transfected with this "tethered" PTH(1-9)/PTH/PTHrP receptor construct exhibited intracellular cAMP levels that, in the absence of added agonist ligand, were approximately equivalent to those seen in cells transfected with the wild-type PTH/PTHrP receptor and maximally treated with PTH(1-34) and further supporting the schema shown in Figure 2 (31).

Further studies will lead to a more definitive model of the molecular mechanisms by which PTH binds to and activates its receptor. The overall data so far are fully consistent with the two-site binding mechanism of interaction, shown in Figure 4. The C-terminal domain of PTH(1-34) binds to the N-terminal do-

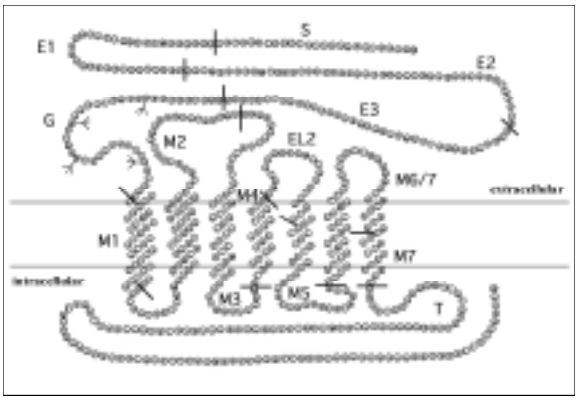

Figure 3 - Schematic representation of the human PTH/PTHrP and its gene organization. Amino acids are shown in single-letter code; amino terminus of the receptor is at top; potential site for *N*-linked glycosylation (*three-pronged branches*); *bars* indicate boundaries between each of 14 coding exons; exon S encodes the putative signal peptide. (Reproduced with permission from Jüppner H, Potts JT Jr: The roles of parathyroid hormone and parathyroid hormone-related peptide in calcium metabolism and bone biology: their biological actions and receptors. In, Fray J (editor): Handbook of Physiology - Endocrine Regulation of Water and Electrolyte Balance. UK: Oxford University Press, 1997)

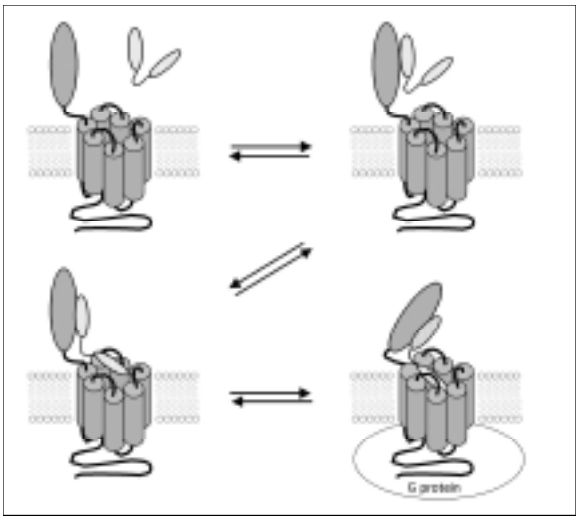

Figure 4 - Model for modulation of ligand binding to the PTH1 receptor by G protein. The C terminal portion of the ligand interacts with the *N*-domain of the receptor. Subsequently, the *N*-terminal portion of the ligand binds to the J-domain of the receptor. Receptor/G protein interaction (lower right) increases the affinity of the ligand/J interaction, which can be modified as a more closed receptor conformation. Reciprocally, interaction of the ligand with the J domain increases the affinity of receptor for G protein, stimulating G protein activation. Binding of G protein to the other states of the receptor (R and RL.N) has been omitted for clarity. In: Hoare SR, Gardella TJ, Usdin TB. Evaluating the signal transduction mechanism of the parathyroid hormone 1 receptor.Effect of receptor-G-protein interaction on the ligand binding mechanism and receptor conformation. J BiolChem.2001; 276(11):7741-7753.

main of the receptor, and this high affinity interaction enables the subsequent, low affinity interaction of the N-terminal domain of the ligand with the juxtamembrane region of the receptor which, in turn, induces or stabilizes the conformation of receptor and ligand (31). The overall interaction is likely to be a multi-step, concerted process, as discussed for other GPCRs (32), and such a process could enable the formation of different activated states of the PTHR each of which might activate a distinct set of signal transduction pathways and/or post-activation regulatory mechanisms. Indeed, recent functional studies on the signaling pathways and desensitization mechanisms used by the PTH/PTHrP receptor provide evidence to support the notion that multiple activation states are possible for the PTH/PTHrP receptor.

This brief summary of the current state of knowledge about the molecular and cellular biology of PTH actions serves as a background for understanding the etiologies of hypoparathyroidism as discussed in the subsequent articles. Several examples of such causes of hypocalcemia due to defects in PTH-mediated calcium homeostasis have been mentioned above, such as interference with intracellular biosynthesis and processing of the hormonal precursor (mutation in the “pre” sequence) or interference at the post-receptor response to PTH when responses are defective due to inactivating mutation in specific G proteins (pseudohypoparathyroidism). Mutational changes in the G protein-coupled receptor, CaR, that regulates PTH secretion and modulates renal calcium excretion (also mentioned above) constitute a third example.

The multi-step process in the calcium homeostatic system involving several key molecules (including hormone, hormone receptor, and CaR) and complex cellular responses in hormone target tissues (bone and kidney) can be impaired at any step in its complex genetic control extending from failed parathyroid gland organogenesis (hence, impaired or absent hormone production) to inadequate peripheral responses (defective receptor or G protein production). In contrast to the prevalence of hypercalcemic disorders, diseases associated with hypocalcemia are much rarer; this may be explained by negative evolutionary selection pressure and perhaps even some still unappreciated redundancies in the system. Fortunately, given the burden of symptoms associated with hypoparathyroidism, many patients can be adequately treated, as explained in the accompanying articles.

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