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Parathyroid hormone signaling in bone and kidney

Minnkyong Lee and

Department of Physiology and Biophysics, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Piscataway, New Jersey 08854

Nicola C. Partridge

Department of Physiology and Biophysics, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Piscataway, New Jersey 08854

Abstract

Purpose of review—Parathyroid hormone (PTH) maintains a physiological balance of calcium and phosphate concentrations by binding to its receptor on the plasma membrane of cells in bone and kidney. It signals through multiple pathways, including protein kinase A (PKA) and protein kinase C (PKC), although a preference for certain pathways is apparent in each organ and function. Here, we will review the recent advancements regarding PTH signaling in bone and kidney.

Recent findings—Wnt proteins have been reported as important regulators of bone metabolism in both PTH-dependent and independent pathways. Recent studies emphasize its role as a mediator of PTH signaling, since PTH treatment increased the expression of *wnt4* and *sfrp4* and decreased the expression of Wnt inhibitors such as Sost and sclerostin, leading to an increase in Wnt signaling. In kidney, sodium-hydrogen exchanger regulatory factor (NHERF) 1, originally known for its role in the retention of NaPi-IIa at the apical membrane, was shown to have multiple roles in PTH signaling, both as a mediator and regulator.

Summary

PTH activates a number of different signaling pathways by binding to a single receptor in bone and kidney. Recent studies demonstrate the involvement of novel factors, as well as additional roles for previously identified downstream-factors of PTH.

Keywords

Parathyroid hormone; PTH1R; PKA; PKC; NHERF1

Correspondence to Nicola C. Partridge, Dept. of Physiology and Biophysics, UMDNJ-Robert Wood Johnson Medical School, 683 Hoes Lane, Research Building 259, Piscataway, NJ 08854. Tel: 732-235-4552; Fax: 732-235-5038; partrinc@umdnj.edu.

Introduction

PTH plays a central role in calcium and phosphate homeostasis by targeting two main organs, bone and kidney. In kidney, it increases calcium reabsorption and inhibits phosphate reabsorption, and stimulates the conversion of 25-hydroxyvitamin D_3 to 1, 25-dihydroxyvitamin D_3, which promotes intestinal calcium and phosphate absorption. In bone, PTH stimulates bone degradation, which leads to an increase in calcium and phosphate release. Produced by the chief cells of the parathyroid glands in response to low serum calcium concentration or high phosphate levels, PTH is cleaved to its biologically active form of 84-amino acids prior to secretion. Under normal conditions, binding to its receptor, PTH/PTHrP type1 receptor (PTH1R) [1, 2], activates multiple signaling pathways that collectively result in the restoration of serum calcium and phosphate levels.

PTH signaling through PTH1R

PTH1R is a seven transmembrane, G-protein coupled receptor linked to heterotrimeric G-proteins, Gs and Gq, implicated in the activation of adenylyl cyclase (AC)-PKA and phospholipase C (PLC)-PKC signaling pathways, respectively [2]. Calcium ion channels, such as transient receptor potential vanilloid 5 (TRPV5) in kidney [3, 4*], and other pathways, including phospholipase D and extracellular signal-regulated kinases (ERK)/mitogen-activated protein kinases (MAPK) [5, 6], have been shown to be activated as well. In humans and rodents, PTH predominantly functions through PTH1R found on the surface of osteoblasts and stromal cells in bone and of kidney cells on the apical and basolateral membranes of tubules [1, 2, 7, 8], although additional receptors have been identified in other species and tissues [9, 10]. Different PTH peptide fragments that stimulate only certain pathways have been useful in dissecting the separate signaling pathways that mediate PTH signaling. The synthetic peptide PTH (1–34) has the same biological effect as the full-length endogenous PTH protein (1–84), whereas PTH (1–31) only activates PKA pathways, and PTH (3–34) only activates PKC pathways [11]. Binding of residues 1 and 2 of PTH (1–34) occurs in the third extracellular loop of PTH1R [12]. Residues 1–9 are critical for receptor activation through interaction with the transmembrane region of the receptor [13], while binding affinity is primarily determined by association of residues 15–34 and the amino-terminal extracellular domain of PTH1R [14].

Termination of PTH1R signaling is achieved through negative feedback of PTH secretion in response to restoration of calcium levels, or by a desensitization-internalization process of the receptor that requires GPCR kinase-2 (GRK2). Phosphorylation of PTH1R at its carboxy-terminal tail by GRK2 occurs promptly after PTH binding, which initiates desensitization of the receptor, ultimately leading to receptor internalization and termination of the signal [15]. Substituting PTH1R with a phosphorylation-deficient receptor has been shown to impair internalization and prolong cAMP generation [16]. PTH signaling is also regulated by PTH-regulated proteins, such as osteopontin, which suppresses PTH signaling in osteoblasts [17], and PTH1R expression is down-regulated by PTH itself as well [18, 19]. In addition, PTH1R is able to bind NHERF1, a cytoplasmic scaffolding protein, which confers added levels of regulation. Through direct interaction, NHERF1 promotes PTH1R

relocation to regions in the plasma membrane that are closer to cytoskeletal fibers [20], as well as inhibition of PTH1R down-regulation [21**].

PTH signaling in bone

Bone undergoes constant remodeling in response to endocrine and paracrine signals, and is maintained through a delicate balance between bone formation and degradation. Bone resorption leads to the release of calcium and phosphate ions as a result of the degradation of hydroxyapitite, a main mineral component of bone matrix. PTH has a dichotomous role regarding bone metabolism; continuous infusion causes a catabolic response resulting in bone loss, whereas intermittent injection leads to an anabolic response characterized by increased bone mineral density (BMD). The classic role of PTH as a catabolic agent has been well-studied; however the mechanism underlying its anabolic role remains to be understood. PTH primarily utilizes the PKA pathway in exerting both its catabolic and anabolic effects [19, 22, 23*]. PKC activation by PTH has been associated with the activation of L-type voltage-gated calcium channels [24] or ERK/MAPK pathways [5]. However, activation of PKC and intracellular calcium signaling pathways seems to play a limited role in PTH signaling in bone, especially in its anabolic responses [19], thus it is likely that the dual effects of PTH arise from the divergent pathways it activates.

Upon binding to its receptor, PTH signals a shift in gene expression patterns in osteoblasts, which normally function as bone-forming cells, to participate in the bone-resorption process by secreting various cytokines and bone-degrading proteases. Among these factors, several are involved in regulating osteoclast differentiation and activation. Two such crucial molecules are macrophage colony-stimulating factor and receptor activator of nuclear factor kappa B ligand (RANKL). The expression of RANKL is increased by PTH mainly through the PKA pathway in osteoblasts and bone marrow cultures [25] as well as *in vivo* [19]. The cytokines, monocyte chemoattractant protein-1 (MCP-1) and interleukin-18 (IL-18) [26*], are also molecules synthesized by osteoblasts upon PTH treatment that target and control osteoclasts. Both molecules are regulated via the PKA signaling pathway *in vitro* and *in vivo*. MCP-1 induces osteoclastogenesis, especially by enhancing fusion [27, 28], and IL-18 inhibits osteoclast formation [29]. Thus, through its action on osteoblasts, PTH is able to regulate the bone microenvironment both directly and indirectly. It appears that the anabolic protocol regulates the cytokines transiently, while the catabolic protocol causes their constant expression leading to prolonged activation of osteoclasts.

Many transcription factors are regulated through the PKA pathway with PTH stimulation, contributing to the change in gene expression in osteoblasts described before. Members of the ATF/CREB family of leucine zipper transcription factors which bind to cAMP response elements (CRE) are among those factors activated by PTH through PKA. In addition to the well-studied phosphorylation of CREB via PKA [30–32], PTH-stimulation of activating transcription factor 4 (ATF4) transcriptional activity is also PKA-dependent [23*]. Promoter analysis of PTH-regulated genes identified ATF4 as a transcription factor that plays a role in PTH-signal transduction in osteoblastic cells, and its own expression was also increased with PTH treatment [23*, 33]. Another member of the ATF/CREB family, CRE modulator (CREM), has been shown to be implicated in PTH signaling, where mice lacking CREM

responded with increased osteoclastogenesis in a catabolic manner to PTH intermittent injections, rather than having the typical anabolic response [34]. In the microarray analyses performed in our laboratory, CREM expression was also shown to be regulated by PTH, with a 20-fold increase after intermittent administration of PTH [19]. Thus, it is likely that CREM is stimulated by PTH as a negative regulator of osteoclast formation in inducing the anabolic response. The expression and activity of Runx2, an osteoblast-specific transcription factor essential for osteogenesis, is also augmented by PTH [35, 36]. Phosphorylation of Runx2 increases with PTH treatment in osteoblastic cells by a PKA-dependent pathway [36], and allows it to function as a transcriptional activator of certain genes upregulated by PTH, such as matrix metalloproteinase 13 and Bcl-2, an anti-apoptotic gene [37]. This increase of Bcl-2 contributes to the anabolic response to PTH, most likely by increasing osteoblast number by enhancing survival signaling, leading to increased bone formation.

Recently, Wnt proteins have become acknowledged as important regulators of bone metabolism in both PTH-dependent and independent responses [38**, 39]. Wnt proteins, classically known for their essential role in developmental processes, are secreted glycoproteins that bind to their receptors, one of ten Frizzled molecules, found in a variety of tissues. Canonical Wnt signaling involves a receptor complex composed of one Frizzled receptor and LDL receptor-related protein (LRP) 5 or 6, which leads to the activation of β-catenin and subsequent regulation of gene expression. Microarray analyses of femoral RNA from rats treated with either intermittent or continuous PTH show that the expression of genes encoding proteins implicated in Wnt signaling pathways, including *wnt4* and *sfrp4* (secreted frizzled related protein 4), an antagonist of Wnt signaling, are up-regulated by both treatment conditions [19]. However, Wnt4 seems to signal through non-canonical pathways in mature osteoblasts [40]. PTH regulation of Wnt signaling in bone was further demonstrated by a recent study which used transgenic mice expressing a constitutively active PTH receptor exclusively in osteocytes [38**]. These mice, which display increased BMD and bone remodeling, had increased Wnt signaling due to decreased expression of Wnt antagonists Sost and sclerostin. Furthermore, deletion of LRP5 in these mice led to the loss of the increased BMD phenotype, indicating a role for LRP5 in PTH-regulated Wnt signaling. In another study, LRP6 was shown to be involved in PTH signaling in osteoblasts by forming a complex with PTH1R [41]. These data suggest a role for canonical Wnt signaling in mediating PTH signaling in bone.

PTH signaling in kidney

The kidney is the primary organ that regulates ion homeostasis across the whole body by carefully coupling the excretion and reabsorption of ions. In kidney, PTH stimulates calcium reabsorption in the distal tubule by activating specific ion channels, such as TRPV5 [3, 4*], and increases phosphate excretion in the proximal tubule mainly by regulating sodium-coupled cotransporters via both PKA and PKC-dependent pathways. It also enhances intestinal calcium and phosphate uptake by stimulating the conversion of 25-hydroxyvitamin D_3 to 1, 25-dihydroxyvitamin D_3, the biologically most potent form, by transcriptional activation of 25-hydroxyvitamin D 1α hydroxylase [42].

Phosphate reabsorption across the apical membrane of renal proximal tubules mainly occurs through two sodium-dependent phosphate cotransporters, NaPi-IIa and NaPi-IIc, that are exclusively expressed in the brush border membrane (BBM) of the proximal tubules [43]. PTH binding to its receptors at either membrane, apical or basolateral, results in the down-regulation of NaPi-IIa and NaPi-IIc in which the transporter is removed from the BBM via clathrin-coated pits [44, 45]. The two signals are initiated through different pathways; activation of apical receptors leads to PLC-PKC stimulation, whereas basolateral receptors utilize the PKA pathway [46]. While it was previously proposed that the two pathways eventually converge downstream to activate ERK/MAPK [47], a recent study by the same team suggests otherwise that in fact, ERK/MAPK most likely plays an insignificant role in PTH-induced inhibition of phosphate reabsorption [48]. Following endocytosis, NaPi-IIa is eventually transported to the lysosome for degradation [44]. Both PTH1R and NaPi-IIa have a postsynaptic density 95/disc-large/zona occludens (PDZ)-binding motif, which allows them to interact directly with PDZ-containing proteins, including NHERFs [49]. Such proteins with PDZ domains are able to act as a scaffold between PTH1R and NaPi-IIa, and mediate PTH-signaling.

NHERF1, expressed in multiple tissues, including bone and kidney, has two PDZ domains and a merlin-ezrin-radixin-moesin (MERM) binding domain. Originally identified as a regulator of sodium-hydrogen exchanger type 3, it has been shown to bind to other proteins that contain PDZ-binding motifs, including PTH1R [50]. The MERM domain is involved with interacting with the cytoskeleton as it mediates binding with proteins such as Ezrin, an actin-associated protein. NHERF1 colocalizes with NaPi-IIa, and forms a complex through its PDZ domain [49], stabilizing the expression of NaPi-IIa at the apical membrane via its MERM domain. PTH treatment disrupts this complex by stimulating the phosphorylation of NHERF1, which leads to the dissociation and subsequent endocytosis of NaPi-IIa [51, 52]. PTH-regulation of NaPi-IIa internalization and interaction with NHERF1 is most likely mediated by the PLC-PKC pathway, as NHERF1 is able to bind PLC isoforms [53], and decoupling of PTH1R to PLC was observed in NHERF1-deficient mice [54]. In patients with abnormal renal phosphate reabsorption, NHERF1 mutations were identified, and in kidney cells transfected with mutant NHERF1, cAMP generation and inhibition of phosphate uptake was increased with PTH treatment [55**]. This suggests an regulatory role for NHERF1 in downstream signaling of PTH, which is similar to that previously observed, in which expression of NHERF1 reduces PTH-induced cAMP generation, whereas the absence of NHERF1 increases the cAMP response in cultured cells [50]. These data suggest that NHERF1 functions as a mediator of PTH-regulation of renal phosphate reabsorption, as well as an inhibitor of the PTH-activated PKA pathway. Most recently, it was shown that induction of NHERF1 expression in rat osteosarcoma cells inhibited PTH1R desensitization by blocking dissociation of PTH1R from Gα proteins [21**], thereby acting as a positive regulator of PTH1R. Thus, it appears that apart from its role in regulating NaPi-IIa expression at the BBM, NHERF1 is also involved in PTH-signaling at many levels in different tissues

Calcium reabsorption primarily takes place in the distal tubules and connecting tubules [56]. From the tubular lumen, calcium ions cross the apical membrane via TRPV5, a highly selective calcium channel, and are then transported across the basolateral membrane into the

blood system by the sodium/calcium-exchanger 1 (NCX1) and the plasma membrane ATPase [57]. Compared to control rats, parathyroidectomized rats had lower expression levels of renal calcium transport proteins, such as TRPV5 and NCX1, and displayed hypocalcemia due to reduced calcium reabsorption [3]. TRPV5 is regulated through the PKC-signaling pathway by extracellular calcium-sensing receptors [58]. PTH regulation of TRPV5 also occurs through PKC as it was recently shown that PTH-dependent increase in TRPV5 current density in cultured cells was prevented by PKC inhibitors [4*]. In kidney, PTH regulates calcium reabsorption at both transcriptional and post-translational levels by regulating the expression of calcium transport proteins as well as their activity, yet PTH-regulation of the promoter of related genes such as TRPV5 has not been reported.

Conclusion

PTH is able to activate multiple signaling pathways in cells that express PTH1R and even those that do not via indirect regulation in a paracrine manner; however as the work summarized here indicates, there are preferences for different pathways depending on cell type and function. In bone, the AC-PKA pathway is the primary pathway utilized by PTH, particularly in its anabolic responses. In kidney, both PKA and PKC pathways are activated by PTH in the proximal tubules for regulation of phosphate reuptake, whereas calcium reabsorption in the distal tubules seems to be mainly regulated through PKC. Recent studies suggesting the implication of Wnt-signaling and multiple roles of NHERF1 downstream of PTH are very interesting, however they remain to be further investigated.

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