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Parathyroid hormone: anabolic and catabolic actions on the skeleton

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Abstract

Parathyroid hormone (PTH) is essential for the maintenance of calcium homeostasis through, in part, its actions to regulate bone remodeling. While PTH stimulates both bone formation and bone resorption, the duration and periodicity of exposure to PTH governs the net effect on bone mass, that is whether it is catabolic or anabolic. PTH receptor signaling in osteoblasts and osteocytes can increase the RANKL/OPG ratio, increasing both osteoclast recruitment and osteoclast activity, and thereby stimulating bone resorption. In contrast, PTH-induced bone formation is explained, at least in part, by its ability to downregulate *SOST*/sclerostin expression in osteocytes, permitting the anabolic Wnt signaling pathway to proceed. The two modes of administration of PTH, that is, continuous *vs.* intermittent, can regulate, in bone cells, different sets of genes; alternatively, the same sets of genes exposed to PTH in sustained *vs.* transient way, will favor bone resorption or bone formation, respectively. This article reviews the effects of PTH on bone cells that lead to these dual catabolic and anabolic actions on the skeleton.

Introduction

Parathyroid hormone (PTH) is an 84-amino acid peptide hormone synthesized in the chief cells of the parathyroid glands. It is essential for the maintenance of serum calcium concentration within narrow limits through direct actions on bone and kidney, and indirectly through actions on the gastrointestinal tract [1]. PTH also regulates phosphorus metabolism [2]. It decreases serum phosphorus levels through the inhibition of renal phosphate reabsorption in both proximal and distal tubules, although the proximal effect is quantitatively the more important [3].

PTH is released from parathyorid cells tonically, with circadian dynamics and in a stochastically pulsatile fashion. The synthesis and secretion of PTH are controlled by the calcium-sensing receptor (CaSR) expressed in the parathyroid cell membrane [4]. The signal for PTH production and secretion is a reduced extracellular ionized calcium concentration,

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while the signal for a reduction in PTH production and secretion is an increase in extracellular ionized calcium concentration. In these two situations, the signaling pathways triggered or inhibited by the CaSR are governed by the state of occupancy of CaSR by calcium ion. Of less importance, PTH secretion can also be stimulated by an increase in phosphorus levels either directly or through a stoichiometric reduction in calcium levels [3].

One of the key mechanisms by which PTH regulates calcium homeostasis is related to its actions to stimulate bone remodeling, a feat that is achieved by the direct actions of PTH on osteoblasts and osteocytes, and indirect effects on osteoclasts through its actions on osteoblasts and osteocytes. While PTH stimulates both bone resorption and bone formation, the final outcome on bone mass, either catabolic or anabolic, will depend on the dose and periodicity of the PTH signal. Continuous exposure to PTH result in catabolic effects on the skeleton, while intermittent, low doses of PTH result in osteoanabolic effects [5]. In human subjects, the catabolic effect of PTH is best represented by the classic disorder of PTH excess, primary hyperparathyroidism (PHPT). Even in the asymptomatic form of this disease, bone loss can be appreciated in both cortical and trabecular compartments of the skeleton [6,7,8•,9,10•]. Conversely, the foreshortened amino terminal peptide of PTH, teriparatide [PTH(1–34)] and the full length molecule [PTH(1–84)] are osteoanabolic when administered once daily in low doses for the treatment of osteoporosis [11,12].

PTH actions are mediated primarily by a PTH receptor known as PTH1R. The two modes of administration of PTH, that is, continuous *vs.* intermittent, can regulate, in bone cells, different sets of genes or, alternatively, the same sets of genes in a sustained *vs.* transient manner, favoring bone resorption or bone formation, respectively [13,14]. This article reviews the effects of PTH on bone cells that lead to these dual catabolic and anabolic actions on the skeleton.

PTH receptor and PTH signaling

The amino-terminal domain of PTH interacts with the PTH1R, a G-protein-coupled receptor encoded by a 14-exon gene located on chromosome 3. PTH1R is expressed on the surface of osteoblasts and osteocytes in bone, and tubular cells in the kidney [15,16]. Stimulation of the PTH1R leads to the $G\alpha_s$-mediated activation of the adenylyl cyclase/cyclic AMP (cAMP)/protein kinase A (PKA) signaling pathway [17]. The PTH1R is also coupled to $G\alpha_q$-mediated activation of the phospho-lipase/protein kinase C (PKC) signaling cascade [18,19]. While PTH modulates key genes that control bone remodeling through the cAMP/PKA signaling pathway [20,21], the PKC signaling is not required or may be inhibitory to the osteoanabolic actions of PTH [22,23]. The binding of PTH to the PTH1R also translocates β-arrestins to the cell membrane [24], which in turn downregulates PTH-induced cAMP activation, and stimulates the ERK1/2 signaling cascade [15]. PTH-induced translocation of β-arrestins to the cell membrane contributes to the anabolic action of PTH on bone, independent of the classic G protein signaling [25].

Catabolic actions of PTH: increased bone resorption

The PTH-induced increase in bone resorption is mediated, *in vivo*, by increased activity of the bone-resorbing cell, the osteoclast. However, *in vitro* and *in vivo* studies indicate that PTH does not directly activate osteoclasts; rather, the effect of PTH to enhance bone resorption appears to be indirect, through its actions on osteoblasts and osteocytes [26–29].

The OPG–RANKL–RANK system

The OPG–RANKL–RANK pathway plays a critical role in bone resorption induced by PTH. PTH modulates, in osteoblastic lineage cells and in osteocytes, the expression of the receptor activator of nuclear factor-kappa B ligand (RANKL) and its soluble decoy receptor osteoprotegerin (OPG), and thereby regulates osteoclastogenesis [30–32]. RANKL binds to the receptor activator of nuclear factor-kappa B (RANK) both on the surface of hematopoietic precursors of osteoclasts, promoting their differentiation and survival, and in fully formed osteoclasts, stimulating their activity. OPG inhibits RANKL-induced bone resorption by binding to RANKL and thereby preventing its access to the receptor RANK [33–36]. Osteoclastogenesis is then modulated by the balance between the concentration of RANKL and OPG [37].

Continuous infusion of PTH, known to cause catabolic effects on the skeleton, increases mRNA encoding for RANKL and decreases mRNA encoding for OPG in primary murine osteoblasts and in bone from rats, leading to an increased RANKL/OPG ratio, and consequently, enhanced osteoclastogenesis and bone resorption [30,38,39]. *In vitro* studies provide evidence that PTH increases the *Tnfsf11* gene encoding RANKL by activation of cAMP/PKA–CREB pathway, and that PTH inhibits mRNA encoding for OPG expression via a PKA–CREB–AP-1 pathway [20,40,41].

Recent studies have shown that PTH also stimulates RANKL production in osteocytes [42–44,45•]. Indeed, data from studies in mice suggest that osteocytes, and not osteoblasts, may be the main source of RANKL for osteoclastogenesis [46,47,48•]. Results from these studies [46,47] show that mice lacking the *Tnfsf11* gene encoding RANKL exclusively in osteocytes develop increased bone mass with age that is associated with reduced osteoclast number and bone resorption. Moreover, mice lacking RANKL exclusively in osteocytes have reduced bone loss due to secondary hyperparathyroidism induced by dietary calcium deficiency as compared to wild type animals [48•]. Accordingly, in mice with conditional deletion of the PTH receptor in osteocytes, PTH fails to increase RANKL expression, and thereby osteoclastogenesis [45•]. *In vitro* assays using a co-culture system of osteocytes embedded in collagen gel and osteoclasts show that the osteocyte-derived RANKL reaches osteoclast precursors in its membrane-bound form through osteocyte dendritic processes [49].

The OPG–RANKL–RANK pathway also appears to be a main mediator of the catabolic actions of PTH in human subjects. Circulating levels of RANKL are increased and positively correlated with bone resorption markers and rates of bone loss at the total femur in patients with mild PHPT [50]. Additionally, the RANKL/OPG ratio, as determined by mRNA analysis of iliac crest bone biopsies, decreased 1 year following successful parathyroid

surgery in 24 patients with PHPT [51]. Finally, circulating levels of RANKL, OPG and the RANKL/OPG ratio were higher in subjects with PHPT than in controls, and in patients with PHPT, the RANKL/OPG ratio reduced 1 year after parathyroidectomy or alendronate therapy, as compared to baseline [52].

The monocyte chemoattractant protein-1 (MCP-1)

The monocyte chemoattractant protein-1 (MCP-1), a potent chemokine for monocytes and macrophages, is another mediator of PTH-induced bone resorption. *In vitro* studies indicate that MCP-1 enhances bone resorption by increasing chemoattraction of pre-osteoclasts and RANKL-induced osteoclastogenesis [53]. Both continuous (catabolic protocol) and intermittent (anabolic protocol) exposure to PTH increased the expression of MCP-1 via the PKA pathway in rat osteoblastic cells and in femurs of rats [53]. The up-regulation of *MCP-1* mRNA levels was moderated but sustained in the catabolic protocol, favoring the increase in bone resorption over bone formation. In the anabolic protocol, the increased MCP-1 expression was more pronounced than in the catabolic protocol, but transient, suggesting that a transient increase in bone resorption may be necessary to the osteonabolic effect of PTH [53,54].

In agreement with these pre-clinical studies, MCP-1 serum levels were positively correlated with PTH concentrations in 43 subjects with PHPT [55]. Of note, in these patients, parathyroidectomy led to a significant decline in MCP-1 serum levels as early as 15 min after the removal of the parathyroid adenoma.

Anabolic actions of PTH: increase in bone formation

Pre-clinical studies have demonstrated that the intermittent administration of PTH has anabolic effects on the skeleton [56–58]. These observations led to the clinical investigation of the biologically active but foreshortened amino-terminal fragment of PTH, PTH(1–34) and, later, the full length hormone [PTH(1–84)] as an anabolic approach to the treatment for osteoporosis. In fact, PTH therapy was eventually demonstrated to be effective for the treatment of osteoporosis [11,12], constituting the only osteoanabolic therapy currently available for this disease.

Similar to continuous PTH exposure, treatment with intermittent PTH leads to an increase in bone turnover. However, in patients treated with intermittent PTH there is an early stimulation of bone formation without resorption (a bone modeling effect) followed later by a general increase in bone turnover (a bone remodeling effect). The period of time when PTH is maximally anabolic has been termed the “anabolic window” [12,59–61]. Studies of the kinetics of bone markers [12,60,61] and dynamic histomorphometric analyses of iliac crest bone biopsies [62–64] in patients treated with PTH have supported this concept of anabolic window. Histomorphometric studies of postmenopausal women indicate that PTH(1–34) initially stimulates bone formation in the absence of prior resorption, which appears to be more pronounced in the early stages of the therapy, since the proportion of modeling-based bone formation decreases over the course of the treatment, when bone remodeling is stimulated [63,65]. The modeling-based bone formation induced by PTH also occurs in areas of remodeling where there is overfilling of bone resorption pits with

extension of bone formation beyond the margins of the resorption cavity [62–64]. The concept of the anabolic window includes a period of time after the bone modeling effect is no longer prominent, because even when remodeling is stimulated, bone formation exceeds bone resorption. The sections below describe the mechanisms by which PTH leads to these anabolic actions on the skeleton.

PTH actions on osteoblasts

Receptors for PTH are found in preosteoblasts, osteoblasts, lining cells, and osteocytes [3]. Intermittent PTH administration directly acts on osteoblasts to promote osteoblastogenesis, reduce osteoblast apoptosis, and reactivates quiescent lining cells [66–68]. An increase in osteoblast differentiation rather than osteoblast proliferation appears to be the main mechanism by which PTH stimulates osteoblastogenesis. Indeed, PTH arrests the cell cycle progression of osteoblasts, increasing their commitment to a differentiated osteogenic fate [69]. In addition, PTH can promote osteoblast differentiation and osteoblastic lineage commitment from bone marrow-derived cells, primary calvarial cells, and periosteal cells, independent of its effects on the cell cycle [14,70,71]. The expression of genes that typically signal bone formation, such as the osteoblast-specific transcription factor *Runx2*, *Osteocalcin*, *Alkaline Phosphatase*, *Collagen type I alpha 1 (COL1A1)*, and the novel bone formation-related factor Tmem119 are all stimulated by PTH, as shown by *in vitro* and *in vivo* studies [13,14,71–74]. Bone morphogenetic protein (BMP) signaling has also been described as a mediator of the PTH-induced differentiation of bone marrow stromal cells into osteoblasts [75]. In this study, a single injection of PTH in mice enhanced, in bone marrow cells harvested 30 min after the injection, the BMP-stimulated phosphorylation of Smad1, which was mediated by a PTH-induced endocytosis of a PTH/LRP6 complex. Further experiments indicated that the PTH-enhanced BMP signaling stimulates the commitment of stromal cells to osteoblast differentiation [75].

PTH can also decrease osteoblast apoptosis, as observed in femoral and vertebral sections of mice treated with daily injections of PTH [76]. Additionally, PTH treatment of osteoblastic cells inhibits the pro-apoptotic effects of etoposide, dexamethasone, hydrogen peroxide induced oxidative stress, UV irradiation, serum withdrawal and nutrient deprivation [73,76,77]. The anti-apoptotic actions of PTH include phosphorylation and inactivation of the pro-apoptotic protein Bad, increased expression of survival genes like *Bcl-2*, increased expression of *Runx2*, downregulation of the apoptosis inducer CARP-1 (Cell Cycle and Apoptosis Regulatory Protein), and increase in DNA repair [76–78].

The differentiation of lining cells into active osteoblasts may also explain the PTH-induced increase in osteoblast number. Indirect evidence for this finding was provided by studies showing increased osteoblast number on the bone surface of rats treated with intermittent PTH associated with a decrease in the fraction of lining cells [79], and without an indication of increased osteoblast proliferation [79,80]. In agreement with these observations, a recent lineage tracing study in mice, using an inducible gene system that labeled mature osteoblasts, has confirmed that PTH can re-activate lining cells [68]. The results provide evidence that, in PTH-treated animals, labeled, cuboidal cells (active osteoblasts) can be detected on the periosteal surface, whereas in vehicle-treated mice, labeled cells appeared

flat. Compared to baseline, PTH treatment increased by 50% the thickness of osteoblastic descendants in the calvaria. Similar findings that were observed for periosteal osteoblasts in the tibia were confirmed by electron microscopy [68].

Mediators of PTH actions on bone formation

Sclerostin

Sclerostin is a secreted glycoprotein, primarily produced by osteocytes, that acts as an inhibitor of bone formation [81,82]. Reduced sclerostin concentration and/or activity in human subjects leads to two genetic diseases known as van Buchem's Disease and sclerosteosis, characterized by generalized and progressive overgrowth of bone and sclerosis of the skeleton [83–85]. In mice, deletion or overexpression of the *Sost* gene encoding sclerostin leads, respectively, to high bone mass or osteoporosis [43,86]. Of clinical interest, antisclerostin antibodies have demonstrated osteoanabolic effects in rodents and in human subjects [87–91,92•].

Studies have suggested that sclerostin inhibits bone formation by antagonizing the Wnt/β-catenin osteoanabolic signaling pathway, which modulates osteoblast proliferation, differentiation and survival, as well as, osteoclast-induced bone resorption [93–95]. Wnt ligands bind to a dimeric receptor complex formed by the frizzled (Fzd) receptor and LDL-receptor related protein (Lrp) 5 or 6, stimulating the canonical Wnt/β-catenin signaling. Sclerostin inhibits the canonical Wnt/β-catenin signaling by occupying the Wnt ligands binding site at the LRP5/LRP6 complex [21,96–99]. The interaction between sclerostin and Lrp5 was recently supported by studies in mice lacking *Sost* (*Sost*$^{-/-}$), *Lrp5* (*Lrp5*$^{-/-}$), or both (*Sost*$^{-/-}$; *Lrp5*$^{-/-}$) [100•]. The *Sost*$^{-/-}$ high bone mass phenotype was blunted, while the *Lrp5* deficiency-induced osteopenia was fully rescued in double knockout mice (*Sost*$^{-/-}$; *Lrp5*$^{-/-}$). Further studies indicated that Lrp6-induced Wnt/β-catenin signaling is the major pathway through which sclerostin exerts its function, as shown by the complete reversal of the high bone mass phenotype in both double knockout (*Sost*$^{-/-}$;/*Lrp5*$^{-/-}$) and *Sost*-deficient (*Sost*$^{-/-}$) mice treated with a pharmacological inhibitor of the Lrp6 activity [100•]. While the mechanism by which sclerostin inhibits bone formation has been questioned by other studies showing that Lrp5 does not function as a Wnt co-receptor in osteoblasts [101,102], it is clear that sclerostin is a key inhibitor of bone formation.

Based on the observation that osteocytes express the PTH1R, further studies explored the hypothesis that the osteoanabolic action of PTH could be mediated by sclerostin [16]. In fact, PTH proved to be an inhibitor of sost/sclerostin, and this PTH-action was essential for the increased bone formation mediated by this hormone [43,45•,103–108]. The PTH-induced inhibition of *Sost* mRNA levels *in vitro* appears to be mediated by the activation of the cAMP signaling pathway downstream to the PTH1R [21,103,105]. In rodents, both continuous and intermittent PTH treatments decrease *Sost*/sclerostin levels [103,105]. Accordingly, transgenic mice overexpressing a constitutively active PTH1R specifically in osteocytes have decreased *Sost* expression associated with increased bone mass [43]. Supporting the idea that the down regulation of sclerostin in osteocytes is required for the anabolic effect of PTH, when *Sost* was concomitantly overexpressed in osteocytes, the increase in cortical bone area, periosteal bone formation rate, and cancellous bone volume

was abolished [43]. Mirroring these data, intermittent PTH treatment failed to suppress *Sost*/sclerostin expression in mice with an osteocyte-selective PTH1R ablation [45•,104].

In human subjects, serum sclerostin levels are lower in patients with PHPT than in euparathyroid or hypoparathyroid controls, and there is a negative correlation between circulating sclerostin and PTH levels [107–110]. In healthy men, circulating sclerostin levels decline within 6 hours following an acute PTH infusion [111]. Similarly, intermittent PTH therapy decreases serum sclerostin levels in postmenopausal women [106]. In patients with PHPT, a cross-sectional study showed that circulating sclerostin levels were lower in 60 subjects with active PHPT than in 74 individuals that had undergone parathyroidectomy [112]. Moreover, in a small series of 27 patients followed for up to a year post-parathyroidectomy, circulating sclerostin levels normalized after the surgery, and remained normal throughout the follow-up period [112]. These analyses help to confirm the antisclerostin effect of PTH.

Dickkopf1 (Dkk1)

Dickkopf1 (Dkk1) is a secreted protein, expressed in cells of the osteoblast lineage. Similar to sclerostin, it interacts with Lrp5/6 and interferes with Wnt binding, inhibiting the Wnt anabolic signaling and bone formation [113,114]. Studies of osteoblastic cells and parathyroidectomized rats treated with continuous infusion of PTH(1–38) for 1, 3, 6 and 24 hours have shown that PTH reduces Dkk1 mRNA levels in a time-dependent manner [115]. Accordingly, PTH administration to osteoblastic cells led to stabilization of β-catenin and functional activation of the canonical Wnt pathway [115]. Similarly, acute treatment with PTH reduces Dkk1 mRNA levels on bone explants [116]. In order to evaluate whether the canonical Wnt signaling is required for the PTH action *in vivo*, transgenic mice overexpressing Dkk1 exclusively in osteoblasts were exposed to distinct models of hyperparathyroidism. As expected, the overexpression of Dkk1 blunted the PTH-induced bone formation in these animals, but did not prevent the activation of Wnt signaling in bone [116]. In contrast, Yao et al. [117] showed similar increases in bone mass upon intermittent PTH administration to wild type animals and transgenic mice with overexpression of Dkk1 selectively in osteoblasts, indicating that inhibition of Dkk1 is not required for the anabolic action of PTH. Of note, the same study demonstrated that, in mice, daily PTH(1–34) injections reduce Dkk1 mRNA levels in bone [117]. Different from preclinical studies, both postmenopausal women with PHPT and those treated with intermittent PTH have increased Dkk1 serum levels [118,119]. These results are controversial, and further studies are necessary to elucidate the role of Dkk1 as a mediator of the PTH actions on bone formation.

EphrinB2/EphB4

EphrinB2 is a membrane-tethered ligand that interacts with its receptor EphB4, resulting in a two-way signaling between two adjacent cells [120]. PTH induces the expression of EphrinB2 in osteoblasts, stimulating Ephrin-mediated interaction between two osteoblastic cells, and thereby increasing PTH-induced bone formation [121]. EphrinB2 is also expressed in osteoclasts, and the EphrinB2/EphB4 signaling between osteoblasts and osteoclasts stimulates osteoblast differentiation and impairs osteoclastogenesis [120]. A recent study showed that the inhibition of EphrinB2/EphB4 signaling in mice treated with a PTH

anabolic regimen increases bone resorption, through, at least in part, increase in RANKL expression, impeding the PTH anabolic effect [122•]. Thus, PTH stimulates EphrinB2/EphB4 signaling, which not only mediates PTH-induced increased bone formation, but also limits the ability of osteoblasts to promote osteoclastogenesis.

T-cells play a permissive role in anabolic and catabolic actions of PTH

T lymphocytes express the PTH1R, and may have a role in both the catabolic and anabolic actions of PTH in bone [123,124]. Continuous PTH treatment of mice lacking T cells failed to increase osteoclast formation, bone resorption and cortical bone loss [125]. The lack of PTH-induced bone resorption in these mice appeared to be mediated by the CD40 ligand, a surface molecule present on activated T cells. This surface molecule induces the CD40 signaling in stromal cells, that stimulates RANKL/OPG production ratio, increasing osteoclastogenesis [125,126]. Accordingly, the deletion of T cells or T cell-expressed CD40 ligand reduced bone marrow stromal cell number, RANK/OPG ratio and osteoclast activity [125]. The PTH-induced bone loss and osteoclastic expansion are also inhibited when PTH1R is deleted in T cells [127].

T cells also play a permissive role in the anabolic effect of intermittent PTH. Intermittent administration of PTH increases the T cell expression of Wnt10b, a molecule that stimulates osteoblastogenesis [123]. As a result, the PTH-induced bone formation is reduced in mice lacking T cells or in those with a specific disruption of Wnt10b production by T cells [123]. Indeed, a conditional deletion of the PTH1R in T cells attenuates the intermittent PTH-induced T cell production of Wnt10b and the increase in osteoblastogenesis and bone formation in mice [128]. A recent study in mice has shown that the PTH-induced T cell production of Wnt10b and the inhibition of osteocyte-derived sclerostin by PTH have an additive effect to increase bone mass [129].

Is bone resorption required for the PTH-induced bone anabolism?

Evidence from pre-clinical and clinical studies suggests that osteoclastic resorption is required for the osteoanabolic effect of PTH [54,130,131]. In contrast, studies of Rhee et al. [132•] suggest that PTH-induced bone formation may be distinctly affected by bone resorption depending upon the bone compartment. In this study, transgenic mice with increased bone mass due to activation of PTH receptor signaling in osteocytes were either treated with alendronate to block resorption-dependent bone formation, or crossed with mice overexpressing the Sost/sclerostin, in order to specifically inhibit bone formation. While the suppression of bone resorption did not affect PTH-induced bone formation on the periosteal surface of cortical bone, a combination of both resorption-dependent osteoblast activity and Wnt driven bone formation modulate bone formation on the endocortical surface. Thus, depending on the bone compartment, PTH receptor signaling in osteocytes can increase bone accrual through modeling- or remodeling-based bone formation mechanisms [132•].

A study in postmenopausal women supported the findings from animal studies that PTH-induced bone formation may occur independently of bone resorption [133•]. In this study, the combination of the antiresorptive agent denosumab with PTH(1–34) for 12 months was

more effective to increase BMD at lumbar spine and hip sites than either therapy alone. These results might be related to the fact that Denosumab is a potent RANKL inhibitor, so that it blocks the main mechanism by which PTH increases bone resorption — the RANKL–OPG–RANK signaling pathway. As a result, PTH would preferentially signal through the anabolic Wnt/β catenin signaling pathway, amplifying the PTH-induced bone formation.

Conclusion

This review has focused on the catabolic and anabolic actions of PTH on the skeleton. Direct effects of PTH on osteoblasts and osteocytes, and indirect actions on osteoclasts, promote both bone formation and bone resorption, and the final effect on bone mass, either anabolic or catabolic, appear to depend on the duration and periodicity of the PTH exposure. While PTH stimulates bone remodeling overall, bone resorption predominates when continuous exposure to high levels of PTH ensues, whereas administration of low, intermittent doses of PTH leads to a net increase in bone mass. The two forms of PTH exposure, continuous or intermittent, regulate, in bone cells, different sets of genes or, alternatively, affect the same sets of genes in a sustained *vs.* transient manner, the first favoring bone resorption and second bone formation.

PTH receptor signaling in osteoblasts and osteocytes can increase the RANKL/OPG ratio, which appears to be the main mechanism by which PTH stimulates bone resorption. In contrast, PTH-induced bone formation is explained, at least in part, by its ability to downregulate SOST/sclerostin expression in osteocytes, unleashing the anabolic Wnt signaling pathway. Thus, the current concept is that PTH utilizes both catabolic (OPG/RANKL/RANK) and anabolic (SOST/sclerostin) pathways. Further studies are necessary to elucidate a means to control molecular pathways that are regulated by PTH, so that the skeletal action of PTH is maximally anabolic.

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• of special interest

•• of outstanding interest

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