Future of Parathyroid hormone and its analogues in dentistry

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Introduction

Bone remodeling is a highly coordinated physiological process orchestrated by cross talks between various cells, pathways and signaling molecules that are required to repair damaged bone and maintain mineral homeostasis. Bone regeneration is a complex physiological process that aims to restore the original function and architecture of bone lost in cases of trauma, fracture, abnormal bone healing etc. To achieve this goal of bone regeneration, various bone substitutes like bone grafts, osteogenic stem cells, osteoconductive scaffolds, growth factors, barrier membranes have been used with mixed results. Recently there has been a change in paradigm; the focus is shifting towards targeting the pathways involved in bone formation. Thus the focus has been redirected to four main hormones: calcitonin, PTH, vitamin D_3 (1,25 Vit D_3) and oestrogen. Each of these has an important role to play in bone remodeling by various mechanisms. The purpose of this review is to discuss parathyroid hormone and its analogues which have gained vast attention lately.

Endogenous human parathyroid hormone (PTH) is an 84 amino acid peptide (PTH 1–84) a key endocrine regulator of calcium homeostasis. Intact PTH 1–84 is secreted by parathyroid cells in response to reduced ionized calcium in the blood and, with its cleavage products (providing the N-terminus is preserved and at least 31 amino acids remain), activates the PTH/PTHrP receptor found in key target organs. The receptor is expressed (among other cells) by osteoblasts, osteocytes and

bone-lining cells, and activates distinct G protein signalling cascades by coupling with either adenylate cyclase, phospholipase C or cAMP/protein kinase A depending upon the cell type [1-4]. The parathyroid cell is sensitive to changes in extracellular calcium concentrations, with small increases in extracellular calcium inhibiting secretion of PTH. Conversely, a decrease in extracellular calcium leads to a rapid increase in PTH secretion[5]. It is possible to synthesize either the whole PTH molecule or specific fragments by recombinant technology and hence PTH and its analogues (Teraparatide) have found their application as osteopromotive agent extensively. To understand its varied applications, it's important to understand actions of this hormones and its analogues on the osteoblasts and the bone forming pathways.

Mechanism of action

The continuous exposure to parathyroid hormone (PTH) has been found to be associated with catabolic effects, whereas intermittent exposure to low doses of PTH is associated with anabolic effects and this has been proved experimentally by **Kroll,2000[6]**. Intermittent PTH prolongs osteoblast survival by mechanisms that involve activation and proteolytic degradation of Runx2. PTH's ability to orchestrate a dynamic range of signaling cascades that determine osteoblast fate may explain both its catabolic and beneficial actions on the skeleton [7]. By controlling osteoblast function, PTH increases bone formation on cancellous, endocortical, and periosteal bone surfaces. Intermittent PTH promotes osteoblast differentiation, in part, by its ability to promote exit from the cell cycle, to activate Wnt signaling in osteoblasts, and to inhibit the Wnt antagonist sclerostin in osteocytes. Insulin-like growth factor-1 is also required for the actions of PTH to increase osteoblast numbers. Parathyroid hormone-related protein receptor has been identified as a crucial mediator of both bone-forming and bone-resorbing actions of PTH, and they underline the complexity and heterogeneity of the osteoblast population and/or their regulatory microenvironment [8]. Another mechanism proposed for its bone building activity is that intermittent administration of PTH stimulates bone formation not by increasing the proliferation of osteoblast precursors, but by preventing osteoblast apoptosis[9], thereby prolonging the time spent in performing their matrix synthesizing function[11]. Clinical and

animal studies have shown that bisphosphonates, inhibitors of bone resorption can blunt the anabolic response to PTH, suggesting that active bone resorption enhances the anabolic actions of PTH [12, 13]. Based on the fact of active resorption involvement to enhance the anabolic effect, it was suggested in an experimental study by **Xin Li (2007)[14]** that PTH-induced osteoblastic expression of MCP-1 is involved in recruitment and differentiation at the stage of multinucleation of osteoclast precursors. Parathyroid hormone also significantly affects osteoblast function by altering gene expression. Neuron-derived orphan receptor-1 (NOR-1) has been identified as a PTH-induced primary gene in osteoblastic cells. NOR-1, Nurr1, and Nur77 comprise the NGFI-B nuclear orphan receptor family and Nurr1 and Nur77 are PTH-induced primary osteoblastic genes[15].

Teriperatide

Two forms of recombinant human PTH are available: full-length PTH (PTH 1-84; Preotact 1, approved in the EU only) and the 1-34 N-terminal active fragment of PTH (teriparatide, Forteo™, Forsteo™)[16,17]. Teriparatide (Forsteo® or ForteoA®, Eli Lilly), a biosynthetic human parathyroid hormone, which consists of the first 34 amino acids of parathyroid hormone, is an anabolic agent[18]. The pharmacologic activity of teriparatide is similar to the physiologic activity of PTH. Teriparatide mediates its biological effects via specific, G-protein-dependent, high-affinity membrane cell-surface receptors which are expressed on osteoblasts and renal tubular cells; both these molecules bind to the receptors with the same affinity and exert the same physiological effects on bone and kidney. It has been suggested that ligand binding induces a cascade that activates protein kinase-1, cyclic adenosine monophosphate, protein kinase C and phospholipase C. The activation of these pathways results in an increase in the number of active osteoblasts, a decrease in osteoblast apoptosis and probably, recruitment of bone lining cells as newly formed osteoblasts, thereby increasing bone strength, mass and diameter, and bone structural integrity, as well as increasing serum and urinary levels of markers of bone formation and resorption [19].

Pre clinical and clinical trials suggesting role of PTH in bone formation

A large number of pre clinical trials have been conducted to determine the optimal dose of parathyroid hormone which would have anabolic effect without initiating the bone resorptive cycle.

Turner (2007) [20] examined the dose-response effects of intermittent PTH on cancellous bone in hindlimb unloaded rats (HLU). 344 rats were HLU and treated with vehicle or recombinant human PTH(1-34) at 1, 5, 20, or 80 microg/kg/day for 2 weeks. The bone response was measured by microCT analysis of bone structure, histomorphometric analysis of static and dynamic bone parameters and Northern blot analysis of mRNA levels for bone matrix proteins. The findings of the study suggested that therapeutic dose of PTH (1 microg/kg/day) prevented disuse-induced trabecular thinning, whereas high-dose PTH (80 microg/kg/day) increased trabecular thickness compared with normal weight-bearing rats. Dosage of 60 µg/kg/day or 200 µg/kg/day has been associated with increased mechanical strength, increased volume of callus of healing fractures, and increased bone mass of both cortical and cancellous bones[21,22]. **Sheyn et al (2013)**[23] in an animal trial on rats compared the healing of calvarial bone defects with allografts with and without PTH. Bone formation was evaluated with the aid of fluorescence imaging (FLI) and microcomputed tomography (µCT) as well as histological analyses. Reverse transcription polymerase chain reaction (RT-PCR) was performed to evaluate the expression of key osteogenic and angiogenic genes. Osteoprogenitor differentiation, bone mineralization process, osteogenic genes osteocalcin (Oc/Bglap) and integrin binding sialoprotein (Ibsp) were upregulated in the allograft + PTH treated animals. The results suggested that PTH treatment enhances osteoprogenitor differentiation and augments bone formation around structural allografts .There are a plethora of studies suggesting crucial role of parathormone on bone formation and resorption, thus maintaining a regulatory microenvironment.

Role of teraperatide in bone formation

Teraperatide has been used as an anabolic agent in fracture healing[24], in the treatment of hypothyroidism[25], hyperthyroidism[26], osteoporosis and also for conditions like osteoradionecrosis of the jaw[27]. Teriparatide is licensed for use at a dose of 20 mcg/ day for approximately 18 months and no longer than 24 months[28]. It stimulates periosteal apposition, which leads to an increase in cortical area, cortical thickness, and causes an overall increase in cross-sectional area[24]. **Valderrama, 2010**[29] tested the role of teraparatide in tissue engineering by creating defects in dog mandibles and concluded that binding PTH

covalently to a synthetic, RGD-modified poly ethylene glycol (PEG) hydrogel marginally significantly improved bone formation at 2 weeks of healing compared to the use of PEG alone. Bone regeneration within the defects increased in all groups at week 4 of healing without statistically significant differences. A study by Bashutski JD**,2010** [30] has suggested that Teriparatide, as compared with placebo, is associated with improved clinical outcomes, greater resolution of alveolar bone defects, accelerated osseous wound healing in the oral cavity and thus offers greater therapeutic potential for localized bone defects in the jaw . **Magda, A (2010)** [31]had conducted a study to assess the effects of teriparatide(20 μg) on the radiographic linear measurement of alveolar bone level. Secondary objectives included clinical variables, bone turnover markers in serum and oral fluid, systemic bone density and quality of life in chronic periodontitis patients. The radiographic resolution was significantly higher after teriparatide than after placebo, starting already at 6 months, with a median growth at 1 year of 29% vs. 3% and hence it was concluded that teriparatide may offer a therapeutic potential for oral bone lesions in periodontitis. Another recent study suggetsed that teriparatide at doses of 20 μg or 40 μg showed statistically significant results which were associated with the improved quality of non-vertebral cortical bone and improved geometry and distribution of the trabeculae within the bone. However, the effect of PTH on effective bone remodeling and stimulation of osteoblasts gradually wanes between 18 to 24 months, thus suggesting an ideal course of treatment at around 6-12 months [32].

Conclusion and Future prospects

The basic bone forming mechanisms are involved in bone regeneration and that comprises of osteogenesis, osteoinduction, osteoconduction. To achieve bone regeneration, a balance between these individual mechanisms are required. Parathormone and its analogues not only enhance the recruitment of osteoblasts but also promote the proliferation and differentiation of migrated cells. These compounds have shown their competency in the treatment of bone healing of fracture, skeletal abnormalities, osteoporosis. With the latest interest in implants, bone regeneration has gained more attention in the field of Periodontology. These compounds seem very promising for the purpose of bone formation, alveolar ridge augmentation and increase in bone

mineral density at sites of insufficient bone volume . These could be used a local delivery agents, or incorporated in scaffold be used to treat various bony defects. However long term trials are required to determine the accurate dose, mode of delivery, duration of action in a localized site as that of oral cavity.

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