

Parathyroid hormone – possible future drug for orthopedic surgery

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Key words: parathyroid hormone, orthopedics.

Summary. Parathyroid hormone naturally secreted by the parathyroid glands is a potent anabolic agent for bone. Parathyroid hormone is primarily thought of as a catabolic protein involved in the physiologic release of calcium from bone. Whereas during recent years, a number of animal studies and clinical trials have demonstrated that intermittent parathyroid hormone administration induces anabolic effects on both cancellous and cortical bone, enhances bone mass and increases mechanical strength of the bones. Most of the studies, both animal and human, have addressed the treatment of osteoporosis and parathyroid hormone represents an important new advance in the therapy of osteoporosis. Few studies have investigated the effect of intermittent parathyroid hormone treatment in the field of orthopedics on fracture healing and fixation of orthopedic implants. The results of those studies indicated an enhancement of fracture healing, faster bone repair and better fixation of the implant. Recently there were few animal studies started to investigate the effects of parathyroid hormone treatment on bone formation in regenerated and surrounding bone of distracted callus during limb lengthening. Distraction osteogenesis is a technique for bone lengthening that is widely used clinically and experimentally. Newly forming bone during distraction osteogenesis is expected to be an appropriate pattern for parathyroid hormone anabolic effect. Preclinical studies as well as clinical trials suggest that parathyroid hormone might be useful as a stimulator of bone formation whereas a lot of questions regarding parathyroid hormone therapy remain unanswered and require further experimental studies and investigations.

Introduction

The hormone naturally secreted by the parathyroid glands is a parathyroid hormone (PTH), which is a major regulator of calcium and phosphate homeostasis. The main function of PTH is to maintain the calcium – ion concentration of the extracellular fluids within physiological limits (1). The overall effect of parathyroid hormone action is to increase and conserve serum calcium level by enhancing gastrointestinal absorption of calcium, increasing renal calcium reabsorption and liberating calcium from the skeleton through a process of enhanced bone resorption (2). Highly purified extract from parathyroid glands have a direct action on both kidney and bone, as well as on the gastrointestinal tract and lactating mammary gland (1).

Numerous experimental and clinical studies showed that PTH is a major regulator of bone metabolism. It was first demonstrated by H. Selye in 1932 that PTH has anabolic effects on the skeletal metabolism.

He found an anabolic effect of PTH in rats receiving one daily injection of parathyroid extract. In these rats the bone became macroscopically denser than in the untreated controls. When the hormone was administered in larger doses, however, there was a bone resorptive response (3).

Different methods were used to evaluate the anabolic effects of PTH on rat bone: biochemical serum markers of bone formation and bone resorption, measurements of bone density, histomorphometric analysis of bone architecture, mechanical testing of bone material and structural strength (4–7).

T. T. Andreassen et al in 1999 were first to show that intermittent administration of PTH (1–34) also could enhance callus volume and the mechanical strength of fractures in normal adult rats. Recent studies done by R. Skripitz (8, 9) showed that PTH increases the density of regenerating bone and enhances the fixation of steel implants dose- and time-dependently.

Parathyroid hormone fragments

The native PTH secreted by the parathyroid glands, PTH (1-84), consist of 84 amino acids. The anabolic properties of PTH are associated with the N-terminal part of the native PTH (1-84). In fact, PTH-fragments consisting of the amino acids PTH (1-31), PTH (1-34), and PTH (1-38) have the same potency and pharmacological profile as the full length hormone PTH (1-84) (10–16) whereas PTH (1-30) is unable to increase cancellous bone mass in ovariectomized rats (16).

PTH (1-31) and PTH (1-34) have similar effects on bone formation parameters. Recently the PTH (1-34) is mostly used in experimental studies (2, 8, 17–22) as well as synthetic analogs such as RS-66271 (23), LY333334 (20).

Possible mechanisms of PTH action

It has been shown that PTH has dual action and acts as an anabolic and catabolic hormone (24). PTH has been recognized as a bone anabolic agent when administered intermittently (2, 8, 9, 17–20, 22, 25–27, 29), while continuous exposure to PTH results in a dominant activation of osteoclastic bone resorption and likely inhibits osteoblast function (27, 29) so continuous exposure to PTH results in bone resorption. The cellular mechanism responsible for the anabolic actions of intermittent PTH treatment is not fully known (9, 29, 30).

PTH may act through several possible mechanisms (30). Since PTH binds to more than one receptor it is possible that different receptors mediate the anabolic and catabolic responses (30). Bone cells like osteoblasts, bone lining cells and bone marrow stroma cells, which can differentiate into the osteoblast cell lineage, have PTH receptors. Recent studies by P. H. Watson have shown that parathyroid hormone and PTH-related peptide (PTHrP) in bone (and many other tissues) have a well-documented nuclear localization (28). Evidence indicates that nucleolar PTHrP interacts with RNA and regulates cell function (28). The same authors demonstrated (28) that the type 1 PTH/PTHrP receptor (PTHR) could be localized to the nucleus of cells within the rat liver, kidney, gut, uterus and ovary.

PTH binds to its parathyroid hormone 1 receptor (PTH1R) in osteoblastic cells to regulate bone remodeling and calcium homeostasis (31). In bone the PTH receptor (PTH1R), a seven transmembrane domain receptor coupled to G-proteins, exists in cells of the osteoblast lineage (31). The rapid increase in bone formation induced by intermittent PTH doses does

not require cell proliferation and seems to be the result of activation of pre-existing bone lining cells to osteoblasts (32, 33).

It is revealed by different experimental procedures (31) that PTH significantly changes the expression levels of many hormones, cytokines and growth factors produced by osteoblastic cells and modifies the way the osteoblastic cells respond to many signaling factors (31). PTH (through different mechanisms) among many others is a regulating factor of bone formation. Parathyroid hormone – related peptide (PTHrP) and the PTH/PTHrP receptor are involved in the regulation of chondrocyte differentiation (34). The process of endochondral bone formation provides bone formation and growth by cells differentiation and proliferation and this process must be properly coordinated (34).

Microarray analysis performed by L. Qin (2003) presents a list of 125 genes that are regulated by PTH in osteoblastic cells. These genes belong to more than ten protein families based on their function and are involved in many signal transduction pathways (31).

Parathyroid hormone (PTH) is a multifunctional molecule that, in bone, can either initiate bone turnover through the activation of bone metabolic units (BMUs), with the end result being the net resorption of bone, or directly activate the formation of new bone, not necessarily via the bone metabolic units (BMU) (27). While prolonged exposure to PTH causes increased bone resorption, intermittent injections of PTH have an anabolic effect on bone (31).

Another idea is that fragments of PTH harbor different activities at bone sites (35). Yet another hypothesis is that two distinct secondary messenger systems each directing different responses are activated by PTH (36). It is noteworthy that PTH acts through dual signaling pathways in bone cells, with the osteoblast being the principal cellular target (30).

Bone growth and development is mediated by growth factors including the insulin-like growth factors (IGF-I and IGF-II) (29) and transforming growth factor TGF-beta-1. Osteoblasts produce and secrete IGF-I (29, 37) and possess type I receptor for IGF. Therefore it has been suggested that IGF-I is an autocrine and/or paracrine regulator of osteoblast function. It was established by P. Watson (1995) that IGF-I mRNA and peptide present in both periosteal and endosteal (trabecular) osteoblasts and in chondrocytes of the growth plate (29, 37) and PTH among several other factors including growth hormone, estrogen, vit D. and prostaglandin regulate osteoblast IGF-I

gene expression (29). Furthermore their findings suggested that IGF-I is the local mediator of PTH-induced bone formation in estrogen-deficient rats (29). Intermittent treatment with PTH in the rat elevate osteoblast expression of insulin-like growth factor – I (IGF-I) (27). PTH increases both osteoblast number and activity, but it is suggested that augmentation of cancellous bone density is probably due primarily to an increase in osteoblast number (27, 38).

Also PTH may stimulate bone marrow osteoprogenitor cells to proliferate, migrate and differentiate into osteoblasts if the bone tissue is loaded normally. PTH and mechanical loading might act synergistically on bone formation (39). The study performed by J. Li et al (2003) indicate that treatment with PTH enhanced load-induced bone formation by 53% and 76% on the endocortical and periosteal surfaces, respectively. The same conclusion was reached by Y. Ma et al (1999) in their study on bone mass and architecture after immobilization induced osteopenia, that when PTH was combined with mechanical loading, a synergistic anabolic effect on periosteal bone formation occurred (40).

Anabolic effect of PTH

Intermittently administered PTH is a strong anabolic agent (9, 25). According to various experimental studies, it is shown that in normal adult rats intermittent PTH treatment increases bone volume, bone formation and bone mass, leading to increased compressive strength, whereas continuous administration decreases bone mass (9, 41).

The concept of an anabolic agent is based upon a physiologic process entirely different from inhibition of bone resorption, namely stimulation of bone formation (30, 35). All currently approved therapies for osteoporosis in the United States are antiresorptive in mechanism, acting primarily to inhibit osteoclast-mediated bone loss (30, 35). PTH as a potential anabolic agent tends to increase bone mass to a far greater extent than antiresorptives. The potential of anabolic agents to improve bone density more substantially than antiresorptives, in addition, suggests that they might reduce fracture risk to a greater extent than the antiresorptives (30, 35, 42).

Animal studies with intermittent PTH have demonstrated a significant increase in cancellous bone mass at several sites, with either no change in cortical bone or a slight decline with time. The PTH effect to improve bone mass has been noted in rats, monkeys, dogs and rabbits (9, 17–20, 22, 25, 27, 29, 32, 38, 43–

46). Mechanical strength in the femur and vertebrae also increases with intermittent treatment. Cortical bone formation when ovariectomized rats were administered PTH for 36 weeks was increased, especially at the endocortical surface (47). PTH has also been administered to animals in combination with different antiresorptive agents. Recently, animal studies with a bisphosphonate and PTH have also been undertaken with an enhancement in cancellous bone mass, connectivity and strength, with modest increases in cortical bone sites as a result of the antiresorptive component (30, 35).

Recently, large, randomized, placebo-controlled clinical trials have been performed with PTH alone and in combination with other agents (30, 35). The principal finding common to all studies in both men and women is a substantial increase in spinal bone mineral density (BMD) with PTH. This increase in BMD is greater than the increase commonly observed after 1 year of antiresorptive therapy (30, 35).

Along with the increase in cancellous bone mass, there is the fear of cortical bone loss, or a ‘cortical steal’ phenomenon (30, 35). But histomorphometric analysis of osteoporotic men and women treated with PTH did not reveal a loss of cortical bone or an increase in cortical porosity. In fact, a distinct anabolic effect on cortical bone was observed at the endosteal surface, with significant increases in the width of bone packets and reduced endocortical resorption (30). PTH treatment resulted in greater periosteal circumference and cortical area and increased biomechanical strength. These observations provide evidence that PTH is anabolic for cortical bone (30).

PTH represents an important new advance in the therapy of osteoporosis. As an anabolic agent, its potential might be substantially greater than the antiresorptives. Clear evidence in human trials now documents the ability of PTH to stimulate cancellous bone formation and to reduce the frequency of fractures. Since the antiresorptives and PTH clearly work by completely distinct mechanisms of action, it is possible that the combination of agents could be significantly more potent than either agent alone (30). More studies are needed to document an anabolic effect on cortical bone (30).

Skeletal site specificity of PTH action

The reasons for skeletal site specificity of PTH action are unclear. Skeletal site specificity in response to PTH is well known in humans, where the anabolic effect of PTH is first detected in the spine, followed

by the hip and then – total body (42). There seem to be differences in the responsiveness of different skeletal sites to PTH in humans and rats. PTH is more responsive in the lumbar spine than the femoral neck in humans (42). A. Iida-Klein et al (2002) in their experiments showed that the BMD response to PTH was more rapid in the long bones, tibia and femur than in the lumbar vertebrae in rats. Detailed analysis showed that the initial anabolic rates were significantly higher in the tibia and femur than those at the lumbar vertebrae. A detectable PTH-stimulated increase in BMD in the lumbar vertebrae was slower and only significant after 7 week of treatment. This confirms skeletal site specificity in the responsiveness to PTH (25). Overall there appeared to be no significant difference in the anabolic action of PTH between tibia and femur. Thus it can be concluded that PTH exerts its anabolic action most rapidly and profoundly in the long bones, perhaps related to weight bearing (25). Possibly, the skeletal site where the most mechanical stress or weight bearing occurs may be the primary target of anabolic action of PTH (25). In support of this observation, recent studies have shown synergy between the effects of PTH and mechanical stress (40).

The difference of the initial target site of PTH anabolic action between mice (long bones) and humans (spine) may be caused by the difference in posture (25).

Recently, J. Li et al (1999) have examined the site-specific effects of PTH according to the differences in marrow composition using young and old OVX rats and have shown that PTH (80 µg/kg per day for 6–10 weeks) stimulates cancellous bone formation at all skeletal sites regardless of marrow composition (38).

A study to determine whether any skeletal site specificity exists for the PTH anabolic action at the molecular level is currently in process (25).

PTH and fracture model

The most prominent histopathological observation in a fracture model with PTH was the difference in the ossification of the fracture callus between the PTH and the vehicle treated group (8). These changes were consistent with increased bone strength and density. This increase in bone formation in the fracture callus, in the surrounding periosteum, and within the marrow cavity may represent an enhanced anabolic response to PTH compared with the bone response at nonfractured skeletal sites.

At present, only a few experiments have studied

the effects of PTH treatment on healing fractures (2, 17, 48, 49).

There was an experimental study, done by T. T. Andreassen et al (2001) in the University of Aarhus, Denmark, in which the effects of intermittent administration of parathyroid hormone (PTH (1-34)) on callus formation and mechanical strength of tibial fractures in 27-month-old rats after 3 and 8 weeks of healing were studied. PTH (1-34) was administered in 200 µg/kg/day dose daily during both periods of healing, and control animals with fractures were given vehicle. They reached the conclusion that PTH treatment increases callus formation and mechanical strength of healing fractures in 3-months-old rats according to the experimental results, which are obvious and statistically significant: at 3 weeks, PTH treatment increased maximum load and external callus volume by 160% and 208%; at 8 weeks, by 270% and 135%. It also enhanced callus bone mineral content (BMC) by 190% and 388% (3 and 8 weeks). From week 3 to week 8, callus BMC increases by 60% in the vehicle-injected animals, and by 169% in the PTH-treated animal. In the contralateral intact tibia, PTH treatment increased BMC by 18% and 21% (3 and 8 weeks). Recent experiment has shown that PTH induces only a modest periosteal bone formation in intact diaphyseal bone. According to the results of a study, they made a conclusion, which says that “since PTH increases callus deposition and mechanical strength, the treatment may positively influence the management of impaired healing, particularly in situations with reduced callus formation” (18).

In the earlier experimental study the same authors (17) have studied the influence of PTH (1-34) on callus formation and mechanical strength of tibial fractures in rats using doses in 60 µg/kg/day, and 200 µg/kg/day of PTH (1-34) after 20 and 40 days of healing. According to the results the dose of 200 µg/kg/day increased the ultimate load and the external callus volume of the fractures by 75% and 99% respectively, after 20 days of healing and by 175% and 72% respectively, after 40 days of healing. The dose of 60 µg/kg/day did not influence either ultimate load or external callus volume of the fractures after 20 days of healing, but the ultimate load was increased by 132% and the external callus volume was increased by 42% after 40 days of healing. The callus bone mineral content (BMC) increased in all groups. After 40 days of healing, the callus BMC was increased by 108% in the 200 µg/kg/day of PTH group and by 76% in the 60 µg/kg/day of PTH group. Both doses of PTH

(1-34) steadily augmented the contralateral intact tibia bone mineral content and bone mineral density (17).

PTH and orthopedic implant fixation

The anabolic effect of PTH seems stronger on regenerating bone than on normal bone (8, 9).

The results of study by R. Skripitz (2001) indicate that intermittent PTH treatment might be useful to enhance early fixation of orthopedic implants. Also the results suggest that intermittent parathyroid hormone treatment can enhance early implant fixation by enhancing the density of surrounding bone and by increasing the implant bone contact (8, 9). Their findings of a higher trabecular density and the enhancement of mechanical fixation of implants via PTH comply with the concept that intermittent PTH treatment acts by enhancing recruitment and proliferation of osteoprogenitor cells (9). The reason for increased pull-out strength might be a change in the mechanical properties of the cancellous bone due to increased mass (8, 9).

It is believed that PTH could have a similar effect to bisphosphonates, which inhibit osteoclastic activity (50) and in the early postoperative period by stimulating new bone formation, thereby decreasing the risk of late loosening (8, 9). It is well known that postoperative migration of a total joint replacement as little as 0.2 mm predicts late loosening (51, 52). Initial stability of an implant is crucial since once an implant is stabilized, it does not migrate later. Intermittent PTH treatment might therefore be considered as a possible drug for postoperative prophylaxis of late loosening and PTH was also able to improve the attachment strength between polymethylmethacrylate (PMMA) cement and bone (8, 9).

In conclusion PTH dose- and time-dependently increases the density of regenerating bone, enhances the fixation of steel implants, and enhances attachment of bone to a cement surface.

PTH and bone lengthening model

Distraction osteogenesis is a technique for bone lengthening that is widely used clinically and experimentally for leg lengthening and for the bone transportation in the treatment of fractures and non-unions. The formation of new bone in distraction osteogenesis is not well understood and it has been widely investigated by different methods. Newly forming bone during distraction osteogenesis is expected to be an

appropriate pattern for PTH anabolic effect when understanding the mechanisms of PTH action to bone cells. The main problem with the leg lengthening method is that the time until full recovery may be up to a year, partly because of the time needed for the new formed bone to consolidate and become strong enough for weight bearing (53). Recently there was an experimental study performed by C. Seebach et al (2003) on rats investigating whether intermittent parathyroid hormone (PTH (1-34)) could accelerate the consolidation of new formed bone after distraction osteogenesis. The results indicate increased ultimate load, stiffness, total regenerate callus volume, callus BMC and histologic bone density compared to untreated distraction osteogenesis specimens with addition that contralateral femur also became stronger, stiffer and denser under PTH (1-34) treatment, but to a lesser degree (53). This study suggests that PTH (1-34) might be useful as a stimulator of bone formation in order to improve regenerated bone stability while consolidation occurs (53).

Summary and clinical perspectives

In conclusion, during recent years, a number of animal studies have demonstrated that intermittent parathyroid hormone (PTH) administration induces anabolic effects on both cancellous and cortical bone. In parallel with the enhanced bone mass, enhanced amount of new mineralized bone, increased mechanical strength of the bones has been found. Treatment with parathyroid hormone (PTH) in animal models of fracture healing and fixation of orthopedic implants increases the bone density dose dependently, leading to faster repair and better fixation. Also in delayed fracture healing PTH (1-34) has been found to induce an anabolic effect and concomitant enhanced fracture strength. Further, in an experimental bone lengthening model it was found the acceleration of the consolidation of new formed bone after distraction osteogenesis due to intermittent PTH treatment. Therefore intermittent PTH treatment might be considered as a possible drug for postoperative prophylaxis of late orthopedic implant loosening, as a therapy for stronger and faster callus formation after fractures and used clinically to strengthen distracted bone and to shorten healing time (consolidation period) after distraction osteogenesis. Otherwise the development of systemic drugs requires a high degree of specificity thus a lot of further clinical and experimental studies are needed to document the required specifications.

Paratiroidinis hormonas ir jo vartojimo galimybės chirurgijoje

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Raktažodžiai: paratiroidinis hormonas, ortopedinė chirurgija.

Santrauka. Paratiroidinis hormonas (paraskydinų liaukų hormonas) turi stiprų anabolinį poveikį skeleto kaulams. Anksčiau manyta, kad šis hormonas yra katabolinis proteinas, kuriam veikiant kalcis pašalinamas iš kaulų. Tačiau per pastaruosius 70 metų atlikta daugybė eksperimentinių tyrimų ir klinikinių studijų, kurių duomenimis, protarpinis gydymas paratiroidiniu hormonu sukelia ir žievinio, ir akytojo kaulo anabolinių pokyčių, padidindamas kaulo masę ir kartu sustiprindamas kaulo tvirtumą. Dauguma tyrimų, tiek eksperimentinių, tiek klinikinių atlikti siekiant nustatyti šio hormono poveikį osteoporozėi, o teigiami rezultatai tapo reikšmingi jos gydymui. Nemaža eksperimentinių tyrimų dalis skirta ortopedijai. Buvo tiriamas protarpinio gydymo paratiroidiniu hormonu poveikis kaulų gijimo procesui ir ortopedinių implantų fiksacijos kokybei. Šių tyrimų duomenimis, kaulų lūžiai gijo greičiau, kaulinis rumbas buvo tvirtesnis, greičiau vyko kaulo remodeliacijos procesai, pastebėta stabilesnė ortopedinio implanto ir jį gaubiančio kaulo fiksacija. Jau pradėti eksperimentiniai tyrimai, kuriais siekiama nustatyti paratiroidinio hormono gydymo poveikį besiformuojančiam kauliniam rumbui po kaulų ilginimo operacijos. Manoma, kad paratiroidinis hormonas stipriausiai veikia kaulų čiulpų kamienines ląsteles, skatina jų proliferaciją, migraciją bei diferenciaciją į osteoblastus, todėl protarpinis gydymas šiuo hormonu gali turėti stiprų stimuliuojantį anabolinį poveikį besiformuojančiam naujam kaului distrakcijos metu. Tačiau į daugybę klausimų apie gydymą šiuo hormonu dar neatsakyta, todėl dar reikalingi tyrinėjimai bei studijos.

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Received 22 April 2004, accepted 28 June 2004

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