Perspective

Parathyroid hormone—a drug for orthopedic surgery?

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ABSTRACT Whereas continuous exposure to PTH results in bone resorption, administration at intermittent doses results in bone formation by increasing osteoblast number and activity. The anabolic action of PTH has also been demonstrated in clinical trials, in which PTH increased the bone mass and reduced fracture rate in patients with osteoporosis. In animal models of fracture healing and fixation of orthopedic implants, PTH increases the bone density in a dose-dependent manner, leading to faster repair and better fixation. The effect appears to be stronger on the new forming bone than on pre-existing bone. Based on these preclinical studies, we suggest that intermittent PTH treatment may also benefit fracture healing and implant fixation in patients.

Early research

Parathyroid hormone (PTH) is a major regulator of bone metabolism. Its main function is to maintain the calcium-ion concentration of the extracellular fluids within physiological limits (Arnaud et al. 1967). PTH is also a primary determinant of intracellular calcium homeostasis (Rasmussen 1968). Under physiological conditions, the overall effect is to conserve calcium. Although seldom mentioned in textbooks, PTH also has anabolic effects on bone, as first demonstrated by Selye in 1932. He found an anabolic effect 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 (Selye 1932).

In the early 1970s, purified PTH became available, and an "osteosclerotic" effect of the hormone was described in thyro-parathyroidectomized rats (Kalu et al. 1970). This has led to extensive investigations into the anabolic effect of the hormone, especially in rats but also in dogs, primates, and humans (Rodan and Martin 2000).

In 1982, Tam et al. found histological evidence of increased trabecular bone mass in thyro-parathyroidectomized rats injected once daily with bovine parathyroid hormone 1–84 (bPTH(1-84)) (Tam et al. 1982). In a series of experiments during the 1980s, Hock and Gunness evaluated the anabolic effect of 12 days of treatment with PTH (1–34) on bone in rats by a simple but efficient method. After killing the rats, the trabecular and cortical bone of the distal femur was separated manually, and calcium, hydroxyproline, and extracted dry weight were measured. The anabolic effect of PTH (1–34) was found to be greater on cancellous than on cortical bone mass, and was suggested not to depend on vitamin D, prostaglandins, or gonadal hormones (Tam et al. 1982, Gunness-Hey and Hock 1984, Gera et al. 1987, Gunness-Hey et al. 1988, Hock et al. 1988). An initial episode of blocked resorption did not seem to abolish the anabolic effect (Hock et al. 1989). These first studies have been followed by studies using more detailed methods to evaluate the anabolic effects of PTH on rat bone: biochemical serum markers of formation and resorption, measurements of density, histomorphometric analysis of architecture and mechanical testing of architectural and material strength (Hock et al. 1989, Dempster et al. 1993, 1995). Concern-

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ing fracture repair, it was first shown in 1997 that the decrease in strength seen in healing fractures of ovariectomized rats could be partly prevented by giving the animals PTH intermittently (Kim et al. 1997). Andreassen et al. (1999) were first to show that intermittent administration of PTH (1-34) can enhance callus volume and also the mechanical strength of fractures in adult rats that have not been ovarectomized. We have shown that PTH increases the density of regenerating bone and enhances the fixation of steel implants in a dose and time-dependent manner (Skripitz et al. 2000a, Skripitz and Aspenberg 2001b).

Possible mechanisms of the anabolic effect

Intermittently administered PTH enhances bone formation by increasing the osteoblast number and activity (Dobnig and Turner 1995). In normal adult rats, intermittent PTH treatment increases bone volume and accretion rate, whereas continuous administration decreases bone mass. Even though bone deposition occurs with both forms of administration, bone resorption offsets bone deposition with continuous PTH.

The cellular mechanism responsible for the anabolic effects of intermittent PTH treatment is not fully known. The large increase in mineral appositional rate (Parfitt 1987) is probably due mainly to an increase in osteoblast number (Li et al. 1999, Watson et al. 1999). After infusion of [^{3}H]-thymidine to label all cells progressing through mitosis during PTH treatment, it was found that almost all osteoblasts induced by PTH treatment were unlabeled in 16-month-old rats (Dobnig and Turner 1995). Thus, it is believed that the increased number of osteoblasts is due to activation of resting bone lining cells to become osteoblasts (Dobnig and Turner 1995). This view agrees with the study by Leaffer et al. (1995) demonstrating rapid PTH-induced ultrastructural changes in lining cells consistent with a transformation of bone lining cells to osteoblasts. The finding that the osteoblasts originate predominantly from bone lining cells suggests that the magnitude of the skeletal response to PTH is limited by the existing cell number (Dobnig and Turner 1995). This explains the observation that PTH is less effective in severely osteopenic rats (Qi et al. 1995). Within a week after withdrawal of PTH, the cancellous bone surfaces may again be covered mainly by lining cells (Leaffer et al. 1995).

Also in vitro, the way by which PTH is administrated profoundly influences the effect: continuous exposure to PTH inhibits, but transient exposure stimulates collagen type I synthesis by osteoblasts (Canalis et al. 1989, Canalis 1993). As a general note on in vitro studies, it seems that the response of different osteoblast cultures to PTH is variable and depends on factors such as the cell line used, age of the source cells, and initial degree of cell differentiation (Dempster et al. 2001).

In young rats, PTH is also thought to increase the differentiation of osteoprogenitor cells into osteoblasts. In 2-month-old rats, PTH stimulates the proliferation and differentiation of osteoprogenitor cells in the bone marrow (Nishida et al. 1994, Onyia et al. 1995). The bone marrow cells from PTH-treated rats were seen to form colonies of fibroblastic cells more readily than bone marrow from rats treated with vehicle alone (Nishida et al. 1994). PTH binds to receptors on osteoblasts and osteocytes and leads to increased expression of the early genes c-fos, c-myc, c-jun, and IL-6. These early genes are known to be involved in cell proliferation (Onyia et al. 1995, Liang et al. 1999).

Intermittent PTH not only initiates modeling but also postpones osteoblast apoptosis (Jilka et al. 1999). Daily injections of PTH attenuate osteoblast apoptosis in mice, thereby increasing osteoblast number, bone formation rate and bone mass; but they do not affect osteoclast number (Bellido et al. 2003). In contrast, sustained elevation of PTH did not affect osteoblast apoptosis but increased osteoclast number. The authors concluded that the self-limiting nature of PTH-induced survival signaling might explain why intermittent administration of the hormone is required for bone anabolism.

The mitogenic PTH effect may be mediated by regulators of bone remodeling such as Transforming Growth Factor β (TGFβ), which is known to be a potent mitogen for bone cells and which is regulated in part through PTH (Centrella et al. 1988). PTH may also interact with insulin-like growth factor I (IGF-I) (Dempster et al. 1993). PTH enhances the IGF-I synthesis and the secretion of IGF-1 binding proteins in osteoblast-like cells, and IGF-I antibody decreases PTH-induced collagen synthesis (Canalis et al. 1989, McCarthy et al.

1989). That IGF-I may be the local mediator of PTH-induced bone formation is also suggested by an experiment in PTH-treated rats where enhanced IGF-I gene expression was found in trabecular osteoblasts by in situ hybridization (Watson et al. 1995). Local co-infusion of PTH and IGF-I increased the cancellous mineral appositional rate, but there was no effect when each hormone was infused separately (Spencer et al. 1989). It has been suggested that a lack of detectable IGF peptide after continuous PTH infusion may explain the absence of increased bone formation, even though both intermittent and continuous treatment with PTH activate osteoblast recruitment and development (Watson et al. 1999). On the other hand, it might be possible that a continuous elevation of PTH could exert anabolic effects on skeletal tissue if its catabolic component could be minimized via estrogen repletion (Shen et al. 2000).

The non-uniform skeletal response to PTH

Clinical trials measuring bone mass have shown that the proximal femur appears to be less responsive to the anabolic actions of PTH than the lumbar spine (Hodsman et al. 1997, Cosman and Lindsay 1998). This could be explained by the greater anabolic effect on cancellous bone compared with cortical bone (Dempster et al. 1993). Furthermore, the lumbar spine has predominantly red (hematopoietic) marrow, whereas in adult humans the proximal femur has yellow (fatty) marrow. Because the vascularity and baseline rate of bone turnover are relatively low at skeletal sites with yellow marrow (Van Dyke 1967, Wronski et al. 1981), such skeletal sites might respond less to PTH. In most rat studies of PTH, histological observations were limited to skeletal sites with high turnover. A strong anabolic effect has been detected in the femoral neck of rats (Sogaard et al. 1994), but, in contrast to elderly humans, this skeletal site also has predominately red marrow in rats 15–18 months of age. PTH causes a smaller increase in bone mineral density in the caudal vertebra than in the lumbar vertebra, distal femur, and proximal tibia in rats (Kishi et al. 1998). Because the caudal vertebra contains mainly yellow marrow, this finding supports the idea that such skeletal sites may be less sensitive to the bone anabolic effects of PTH. In contrast, Li et al. (1999) demonstrated that, even though the magnitude of the anabolic response varies within the skeleton, PTH stimulates bone formation regardless of marrow composition.

The effects of PTH on cortical bone formation may also be dependent on the region of bone examined. PTH increased bone formation in rats at the tibio-fibular junction but not at the tibial midshaft (Halloran et al. 1997). This suggests that some regions of bone may be less responsive than others. Unloading also increases the responsiveness of cortical bone (Halloran et al. 1997). In a study on beagle dogs, PTH treatment was more efficacious in the trabeculae located adjacent to the mechanically loaded cortex than the less loaded, centrally located trabeculae of the lumbar vertebral body (Zhang et al. 1997). Andreasssen et al. (1999) found increased callus formation in a rat fracture model with a high dose of PTH (200 µg/kg/day). This treatment not only affected callus formation but had a positive effect on bone mineral density at the contralateral side as well, although smaller. PTH treatment also caused a fivefold increase in bone density within a bone conduction chamber, which represents an area of new bone formation with a high turnover but no mechanical stimulation (Skripitz et al. 2000b). In contrast, only a 20% increase was found in the vertebra and the femur of the same rats. On the whole, the effect of PTH appears to be strongest on repairing, cancellous, loaded bone with hematopoietic marrow. These 4 determinants are all related to remodeling rate, and probably reflect the available number of cells responsive to PTH.

Clinical use in osteoporosis

PTH has recently been released for the treatment of osteoporosis, and its anabolic action has been studied in clinical trials—of which many were performed at a time when little animal work had been performed (Reeve and Mosekilde 1996). In fact, pioneering groups have performed animal and human experiments concurrently, e.g. a group from the Helen Hayes Hospital in New York (Shen et al. 1992, 1993, 1995, Lindsay et al. 1993, 1997, Meng et al. 1996). The first small uncontrolled clinical trial (4 patients) showed increased calcium isotope incorporation in the skeleton after PTH treatment (Reeve et al. 1976a, b). In a multicenter trial of 21 patients, it was found that the trabecular bone

volume in the iliac crest also increased after treatment for 6–24 months, without increasing the calcium balance (Reeve et al. 1980). The unchanged calcium balance led to the suspicion that PTH increases the bone mass of the axial skeleton at the expense of peripheral cortical bone (Reeve et al. 1980). PTH injections in 6 osteoporotic patients in a calcium kinetic study revealed only minimal increases in bone accretion rate (Slovik et al. 1981). To address concerns regarding calcium absorption, a study was performed injecting osteoporotic men and women with 0.5–1.0 µg/kg/day PTH (1–34) and it was found that spinal bone density increased for 6–12 months (Neer et al. 1993). Thereafter, the bone mass did not increase further in patients treated for 2 years. In two controlled studies, PTH (1–34) increased vertebral bone mass with no effect on cortical skeletal bone mass (Lindsay et al. 1993, Neer et al. 1993). It is therefore believed that PTH may increase the bone mass of the axial skeleton without decreasing the bone mass of the peripheral (cortical) bone (Reeve et al. 1991). Combining PTH with estrogen for 2 years also increases spine and radius density and the calcium balance (Reeve et al. 1990, 1991). In a randomized controlled trial treating osteoporotic women for three years, an increase in spinal bone mineral content was found. There were also indications of reduced vertebral deformation, suggested to be due to a reduction of fractures (Lindsay et al. 1997). After PTH treatment has been stopped, the bone mass may be maintained by the use of bisphophonates. In a placebo-controlled randomized clinical trial, once-daily administration of PTH (1–34) (20 and 40 µg) for a median of 19 months significantly increased BMD at most skeletal sites and substantially reduced the risk of fractures (Neer et al. 2001). In yet another trial, it was shown that PTH could lead to an increase in bone mass of up to 13% within 1 year of therapy, and protected against osteoporotic fractures without adverse effects (Body et al. 2002). Again, no adverse effects, but substantially increased lumbar bone mineral densities, were found in a randomized prospective dose study of 220 patients given 60 µg PTH (1–34) only once per week for 48 weeks (Fujita et al. 1999).

Fracture repair and implant fixation

Intermittent treatment with PTH (1–34) increases callus formation and mechanical strength in experimental fracture healing (Andreassen et al. 1999, Holzer et al. 1999, Nakajima et al. 2002). A daily 200 µg/kg dose of PTH was more effective in enhancing callus formation and mechanical strength than a dose of 60 µg/kg in rat tibial fractures (Andreassen et al. 1999). Mechanical analyses in this model showed substantial differences in ultimate load, absorbed energy at ultimate load, and ultimate stress. The most prominent histopathological observation in a rat fracture model with PTH was the difference in the ossification of the fracture callus between the PTH-treated group and the group receiving vehicle alone (Holzer et al. 1999). Due to the results of the histological examinations and the biomechanical testing, the authors came to the conclusion that PTH should be tested as a systemic treatment for fractures that are slow to heal. In a low-dose (10 µg/kg) rat study, callus formation was accelerated by the early stimulation of proliferation and differentiation of ostoprogenitor cells, increased production of bone matrix proteins, and enhanced osteoclastogenesis during the remodeling phase (Nakajima et al. 2002). These changes were consistent with increased bone strength and density in the fractured femurs and led to the conclusion that PTH may have a more profound effect on the skeleton during bone repair. In a rat bone chamber model, which is used to study new bone formation, we were also able to demonstrate such a difference in response to PTH treatment of different skeletal sites (Skripitz et al. 2000a, b). Within the chambers, we found a linear correlation between the bone density and the log PTH doses of 15, 60 or 240 µg/kg. The cancellous density increased from 48% to 60%, and to 73% at 2, 4 and 6 weeks of intermittent PTH treatment (60 µg/kg), respectively, whereas without treatment cancellous density decreased from 44% to 24%, and to11% over the same time. These effects within the chambers were much more dramatic than in the vertebra or femur of the treated animals. The increase in bone formation in the chamber may therefore represent an enhanced anabolic response to PTH at a site undergoing repair.

In ovariectomized rats, intermittent treatment with high doses of PTH (1–84) (150 µg/kg body

weight) showed morphometrically and mechanically improved fracture healing when compared to placebo-treated or estrogen-treated rats (Kim and Jahng 1999, Jahng and Kim 2000). In old rats PTH enhanced fracture strength, callus volume, and callus bone mineral content after 3 and 8 weeks of healing (Andreassen et al. 2001). The external callus consisted of more dense trabeculae, more woven bone, and had a higher total bone volume. A PTHrP analog was tested as systemic therapy for the impaired bone healing in corticosteroid-treated rabbits (Bostrom et al. 2000). At 6 weeks, 9 of 10 ulnae from PTHrP-treated rabbits achieved radiographic union, whereas only 2 of 10 limbs achieved union in control animals. In a rat distraction osteogenesis model PTH (1–34) at a dose of 60 µg/kg/d increased the strength, stiffness, bone mineral content, histological density and trabecular thickness of the distraction callus. The contralateral femur also became stronger and stiffer, but to a lesser degree (Seebach et al. 2004). Additional data from that study are consistent with the concept that PTH stimulates early bone formation once it has been initiated, but does not induce de novo bone formation.

With histological techniques, it was found that PTH administration enhanced bone formation and resorption in the early stage of healing, whereas net bone resorption was decreased later in the healing period (Andreassen et al. 1999). Like other osteogenic factors, PTH increased the osteoblast population in injured rat bone due to enhanced proliferation and differentiation of osteoprogenitor cells (Nishida et al. 1994, Li et al. 1999). Attenuated osteoblast apoptosis (Jilka et al. 1999) probably plays a role also during bone repair.

Insertion of an orthopedic implant into the skeletal system constitutes an injury, initiating bone repair. Thus, implant fixation may be considered to be the end result of a fracture healing response. With its capacity to enhance bone formation in the early stages of healing, PTH might be promising for the enhancement of orthopedic implant fixation. In a rat experiment, we were able to show that intermittent administration of PTH (1–34) at a dose of 60 µg/kg/d is able to enhance removal torque and pull-out strength of a stainless steel screw after 4 weeks (Skripitz and Aspenberg 2001b). Histological examination showed that the PTH-treated animals had less areas of soft tissue and more bone at the implant-tissue interface. In a time sequence study with similar implants, intermittent PTH treatment increased bone-implant contact as early as after 1 week and enhanced implant pullout strength twofold after 2 weeks (Skripitz and Aspenberg 2001a). In another rat study, we determined how intermittent PTH administration influences the tensile strength of the bone-cement interface (Skripitz and Aspenberg 2001c). Bone bonding was evaluated by a detachment test and PTH treatment significantly increased the median pull-away strength compared to that in the vehicle-treated rats. To our knowledge, these have been the only demonstrations that PTH may improve implant fixation to bone, and the dose level was similar to that used in rat models for osteoporosis treatment.

Clinical relevance of rat studies

In rat bone, collagen constitutes only about 60% of the organic matrix, as compared to 90% in humans (Andreassen et al. 1995). In rats, the cortical bone is subdivided into an outer zone of concentric lamellar bone and an inner zone of more irregularly oriented nonlamellar bone, with the outer lamellar zone first occurring at the age of 3 months (Danielsen et al. 1993). Haversian remodeling features sparsely in rats, and they do not have the same degree of neatly ordered cortical osteons. The low levels of Haversian remodeling in rats may not present a problem, however, when testing agents for their ability to build cancellous bone. Cancellous remodeling occurs in rats and a remodeling period (resorption and formation) of 31 days was measured in vertebral cancellous bone (Li et al. 1991), as compared to 3–5 months in humans. The cellular mechanisms inducing bone loss or bone gain are, however, the same in humans and in rats, and the rat skeleton provides an appropriate model when evaluating the principal effects of therapeutic agents on bone mass, bone structure, strength and composition (Frost and Jee 1992). It is, however, important to note that in general the rat has a stronger bone anabolic response to PTH than humans, and this may not be predictive of intraskeletal variations in the response of adult human bone to the hormone. In addition, healing capacity in patients might be depressed by metabolic dis-

eases, medication, tobacco etc. A larger animal as a model might, however, be more clinically relevant and closer to the human than the rat model.

Clinical possibilities

According to some authors, the risk of prosthetic loosening is determined during the first postoperative months. It has been shown that the early postoperative migration is related to bone resorption and thus to the cellular activities of the bone bed (Hilding et al. 2000). Immediately after implantation, the bone cells adjacent to the implant are likely to be dead due to necrosis, or perhaps apoptosis. This is a strong stimulus for bone resorption, and a race arises between osteoclasts threatening to undermine the mechanical support for the prosthesis and osteoblasts trying to replace it with new bone. If osteoclastic activity is inhibited, migration becomes reduced (Hilding et al. 2000). As it appears that the effect of PTH is strongest on repairing, cancellous, loaded bone with hematopoietic marrow and that such cells are more abundant at a repair site than the rest of the skeleton, one could expect PTH to have even stronger effect in orthopedic surgery than in the treatment of osteoporosis. PTH cannot induce bone formation from uncommitted cells, which appears to be an exclusive property of the BMPs. However, PTH can increase bone formation once it has been initiated, or in a repair process (Skripitz et al. 2000b). Thus, PTH cannot be expected to be useful in nonunions, for example, although it might speed up fracture repair. We therefore suggest that PTH could have an effect in the early postoperative period after osteosynthesis or joint replacement by stimulating new bone formation, thereby decreasing the risk of late loosening.

Based on preclinical studies and on clinical trails for osteoporosis treatment, we suggest that intermittent PTH treatment may benefit not only fracture healing, but also implant fixation.

No competing interests declared.

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