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Prostaglandins: Mechanisms of Action and Regulation of Production in Bone

L. G. Raisz, C. C. Pilbeam and P. M. Fall

University of Connecticut Health Center, Farmington, Connecticut, USA

Abstract. Prostaglandins (PGs), particularly PGE_2, are produced by bone and have powerful effects on bone metabolism. PGs have an initial, transient, direct inhibitory effect on osteoclast function. However, the major long-term effect in bone organ culture is to stimulate bone resorption by increasing the replication and differentiation of new osteoclasts. PGs also stimulate osteoclast formation in cell culture systems. Stimulation of osteoclastic bone resorption may be important in mediating bone loss in response to mechanical forces and inflammation. PGs have a biphasic effect on bone formation. At relatively low concentrations or in the presence of glucocorticoids, the replication and differentiation of osteoblasts is stimulated and bone formation is increased. This increase is associated with an increase in production of insulin-like growth factor-I (IGF-I). However, at high concentrations or in the presence of IGF-I, PGE_2 inhibits collagen synthesis. In osteoblastic cell lines this inhibition can be shown to occur at the level of transcription of the collagen gene. The stimulatory effect on bone formation has been demonstrated when PGs are administered exogenously, but it is not clear how endogenous PG production affects bone formation in physiological or pathologic circumstances. The production of PGs in bone is highly regulated. The major source appears to be cells of the osteoblast lineage. A major site of regulation is at the level of the enzyme PG endoperoxide synthase (cyclooxygenase or PGH synthase). PGE_2 production and PGH synthase mRNA are increased by PTH and interleukin-1 and decreased by estrogen. Glucocorticoids probably act by a different mechanism, decreasing either arachidonic acid or PGH synthase activity. Many other factors including mechanical forces and growth factors influence PG production in bone. Thus endogenous PGs are probably important local regulators of bone turnover, and abnormalities in their production could play a role in the pathogenesis of osteoporosis.

Introduction

The possibility that prostaglandins (PGs) play a role in bone metabolism was first recognized by Chase and Aurbach more than 20 years ago [1], when they found that prostaglandins E_2 (PGE_2) could mimic the effect of parathyroid hormone (PTH) to increase cyclic AMP production in skeletal tissue. On the basis of this observation, we examined the effect of PGE_2 in a fetal rat long bone culture system and found that it was a potent stimulator of bone resorption [2]. The possibility that PGs play a role in skeletal pathology was opened up by the studies of Tashjian and his associates [3,4] that demonstrated PGE_2 was the pathogenic factor responsible for hypercalcemia in two animal models of malignancy, as well as by our own finding that bone resorption mediated by complement and antibodies to cell surface antigens was PG-dependent [5]. Subsequently, many studies have been carried out to analyze the effects of PGs on bone formation and resorption which have clearly demonstrated biphasic effects. This, together with the fact that the regulation of PG production in bone is quite complex, has made it difficult to assign precise roles to PGs in the physiology and pathology of the skeleton, but many observations point to the probability that such roles exist and are important. Several reviews on PGs and bone metabolism are available [6–8].

Prostaglandins and Bone Resorption

Following the initial observation that PGE_2 itself could stimulate bone resorption, studies were carried out to assess the structure–activity relations for these compounds and their role in mediating the resorptive response to a wide variety of agents. These studies have shown that PGE_2 and PGE_1 are the most potent stimulators of resorption,

while PGI_2 and $PGF_{2\alpha}$ are less potent [9–11]. Moreover, the effects of $PGF_{2\alpha}$ may be mediated in part by its ability to stimulate the production of PGE_2 in the bone itself [12]. This ability to stimulate PGE_2 production is shared by many growth factors and cytokines [13–17]. PG-dependent bone resorption has been observed most frequently in the organ culture model using neonatal mouse calvaria, while in the fetal rat long bone model many of these same growth factors can produce PG-independent stimulation of resorption [18]. Recent studies on osteoclast formation and differentiation using bone marrow and spleen cell cultures indicate that PGs play an important role in the replication, differentiation and fusion of osteoclasts [19]. In some culture systems they appear to act as cofactors with 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$), while in others they appear to mediate cytokine effects on osteoclast generation. A number of studies suggested endogenous PGs are vital to osteoclast generation in co-culture systems of marrow and spleen cells with cells of osteoblast lineage or marrow stem cells [20,21].

The source of PGs in these systems has not been fully identified and it is likely that multiple cell types contribute. Moreover, it is difficult to assess the physiologic importance of these effects of PGs, since their production may be greatly enhanced in culture systems compared with the amounts produced in vivo. Indeed, a number of culture systems which do not produce detectable amounts of PG have been shown to generate osteoclasts quite normally. However, PGs could be involved in cell–cell interaction with high local concentration without producing detectable amounts in the medium.

The dual effect of PGs on osteoclastic bone resorption was first recognized by Chase and his associates who showed a powerful inhibitory effect of PGs on isolated osteoclasts [22]. This inhibition is similar to that seen with calcitonin and probably is due to the fact that PGs can stimulate cyclic AMP production in isolated osteoclasts just as calcitonin can. Careful studies in organ culture have demonstrated a small and transient inhibition of bone resorption with high concentration of PGs, but this is abolished when the cultures are pretreated with parathyroid hormone (PTH) [23,24]. In vivo, there is a transient decrease in serum calcium concentration after interleukin-1 (IL-1) injection which can be abolished by indomethacin [25]. Whether this is due to inhibition of bone resorption or some other effect on calcium transport has not yet been proven. It is difficult to develop a teleologic hypothesis for the dual effect of PGs on bone resorption. One possibility is that it is important in mediating the response to changes in mechanical force. There is evidence that both a decrease and an increase in mechanical force can stimulate PG production in bone [26–31]. Thus increased PGs at one sight might be important in stopping the resorptive process at that site, while at another site new osteoclasts could be recruited for activation of resorption.

Prostaglandins and Bone Formation

The dual or biphasic nature of the effects of PGs on bone formation was apparent from the earliest studies of PG effects on collagen synthesis in organ culture. PGs, particularly $OGF_{2\alpha}$, were found to increase collagen synthesis in cultured embryonic chick frontal bone [32], while high concentrations of PGE_2 were found to inhibit collagen synthesis in fetal rat calvaria [33]. Subsequent studies showed that the effect in fetal rat calvaria was biphasic [34,35]. A modest stimulation of collagen synthesis was seen with low concentrations of PGE_2 [6]. When bone formation was inhibited with glucocorticoids, the effects of PGE_2 were stimulatory at all concentrations. Cultures of osteoblastic cell lines have shown a variety of both stimulatory and inhibitory responses and variations in structure–activity relations which have further complicated our understanding [36–40]. Nevertheless, under most culture conditions PGE_2 is a potent mitogen for bone cells. These studies have suggested that there are multiple signal transduction pathways. While it is clear that signal transduction by pathways other than cyclic AMP must occur, the precise pathways have not been established.

Recent studies of the biphasic effects of PGs on bone formation suggest that the stimulatory effect seen particularly in the presence of glucocorticoids may be dependent on the production of endogenous growth factors. PGE_2 does increase the production of insulin-like growth factor-I (IGF-I) in bone [41,42], but other growth factors may be important, since we were unable to block the responses of PGE_2 in cultures containing a saturating concentration of IGF-binding protein-2 which can block the actions of both IGF-I and IGF-II in bone cultures (L. G. Raisz and P. M. Fall, unpublished observations). In contrast, PGs appear to have a direct transcriptional inhibitory effect on bone collagen synthesis in cell and organ culture, based both on inhibition of enzyme activity in cells transfected with collagen promoter chloramphenicol acetyltransferase reporter constructs (ColCAT) and on studies in transgenic animals bearing similar constructs [43].

There are now a large number of in vivo studies showing that administration of PGE_2 can stimulate bone formation [8]. In infants given PGE_1 infusions to prevent closure of the ductus arteriosus, prominent periosteal new bone formation was observed radiographically. The new bone appeared to be architecturally sound since it was incorporated into the cortex of the growing appendicular skeleton when PGE_1 infusion was stopped [44]. Both periosteal and metaphyseal bone formation can be increased by PG administration in experimental animals [45]. While these studies strongly suggest that the major effect of PGs on bone formation is stimulatory, they do not really indicate whether endogenous PGs would have the same effect. Long-term studies of the role of endogenous PGs are difficult to carry out because of the biphasic [46] effects on PG synthesis to the nonsteroidal anti-inflammatory drugs (NSAIDs) used to inhibit PG synthesis, as well as their clinical side effects. Short-term studies using indomethacin and other NSAIDs have shown relatively little effect on normal bone turnover or on the anabolic response to PTH, but have been found to alter bone loss after oophorectomy and ectopic bone formation [47–49]. Moreover, the stimulation of periosteal new bone formation that can be

produced in isolated avian bones by mechanical impact is at least partially blocked by NSAID treatment [27].

Regulation of Prostaglandin Synthesis

The complex and multifactorial regulation of PG synthesis in bone provides strong support for the concept that PGs are important in the local regulation of bone turnover. There is direct and indirect evidence for the regulation of PG synthesis by mechanical forces. A complex pattern of increased PG production has been reported in cell cultures subject to stretch, while compression of bone organ cultures was found to increase PGE_2 and PGI_2 production [28,29]. Indirect evidence is provided by studies showing that indomethacin blocks the increase in resorption following tenotomy in rats [26], the periosteal response in avian bones [27], and the cyclic AMP response in osteoblastic cells subjected to the shear stress of flowing medium [50].

Almost all of the agents which have been shown to stimulate bone resorption also increase PG production in bone, although their relative potency as stimulators of resorption and of PG synthesis may be quite different. Few agents have been identified which can stimulate bone resorption only by increasing PG production. The most obvious of these is arachidonic acid, but this may also be true for bradykinin [51,52]. However, arachidonic acid may also have independent effects on bone cells [55]. Among the most important physiological and pathologic bone resorbers, IL-1 is characterized by a relatively large component of PG dependence, while PTH and $1,25(OH)_2D_3$ are relatively independent of PG synthesis [54–57]. Moreover, $1,25(OH)_2D_3$ is only a weak simulator of PG production in bone organ cultures, and it is possible that this effect is due to increased IL-1 production [57].

While the mechanisms by which PG production are regulated are not fully understood, a number of studies have now been carried out in cell and organ culture suggesting that a major site of regulation is the transcriptional control of prostaglandin H (PGH). PGH synthase mRNA levels have been shown to increase in response to IL-1, PTH and growth factors [56,58]. Release of arachidonic acid (AA) is another control mechanism which is affected by a variety of factors. For example, bradykinin can increase and glucocorticoids can decrease AA release. IL-1 and tumor necrosis factor alpha probably act by increasing both AA release and PGH synthase [58–60].

PG production can be increased by cyclic AMP in both bone cell and organ cultures [61,62]. Since PGE_2 itself increases cyclic AMP, this mechanism provides for autoamplification [63]. Such a mechanism could be important in enabling small physical strains to be translated into large changes in cellular function. The syncytium of osteocytes and osteoblasts is capable of producing PGs and is well adapted to sense these small perturbations, and the rapid movement of PGs both intra- and extracellular would provide a mechanism for spreading the signal from one part of syncytium of cells to another.

While it is not possible to assign a role to PGs in the pathogenesis of osteoporosis, the recent finding that estrogens and androgens can inhibit PG production can be inhibited by estrogen and increased by oophorectomy in older rats, and that estrogens and androgens can inhibit PG production in cultured neonatal mouse calvaria [64–66]. The association of estrogen withdrawal with an increase in both resorption and formation of bone and with a relative deficiency in the formation response is compatible with a PG-mediated mechanism. However, it seems likely that multiple factors are involved in the changes that occur in bone turnover at the menopause and with hormone replacement therapy.

One difficulty in assessing the role of PG production in local regulation has been the difficulty of obtaining valid measurements in vivo. Even in soft tissue studies the procedures involved in obtaining the tissue often result in substantial AA release and increased PG production. Thus, for example, the amount of PG produced by gingival tissue was found to be much smaller when the material was rapidly frozen in liquid nitrogen than when it was dissected and homogenized at 4°C [67]. New methods are needed to assess PG production in vivo and to study its regulation.

Conclusions

Despite the large amount of information concerning the effects of PGs on bone metabolism and the regulation of PG production in skeletal tissue, their importance in the physiology and pathology of bone is still far from established. Indeed, it may be that the complexity and contradictions in the data currently available have led to an underestimation of the potential relevance of this class of compounds. The fact that many agonists alter PG production but also have their own independent effects suggests that PGs may play an ancillary role in bone cell regulation. On the other hand, the potential for regulating PGE_2 production both in terms of pharmacologic manipulation of the relevant enzymes and the use of a variety of agonists and antagonists has great potential and should be explored further.

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