

PERSPECTIVES

Selective Prostaglandin Agonists as Anabolic Agents

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Abstract

Although the ability of prostaglandins to stimulate bone formation was demonstrated more than 30 years ago, it has been difficult to develop clinical applications, largely because of the multiplicity of prostaglandin actions. The development of selective agonists for prostaglandin receptors, particularly the prostaglandin E₂ receptors, EP2 and EP4, has made it possible to characterize the anabolic pathway and to explore these agonists as therapeutic agents. Studies in experimental animals suggest that both agonists might be used locally to accelerate fracture repair or heal skeletal defects or systemically to stimulate bone formation in osteoporosis. *BoneKEy-Osteovision*. 2006 July;3(7):15-20.
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Introduction

An effect of prostaglandins on bone was first suggested by Chase and Aurbach (1), who showed that prostaglandin E₂ (PGE₂) stimulated cAMP production in bone similar to parathyroid hormone (PTH). Organ culture studies by Klein and Raisz (2) showed that PGE₂ stimulated bone resorption. Just as for PTH, there was less emphasis initially on the possible anabolic effect of PGE₂ (3). The concept that prostaglandins could be anabolic was first suggested by the work of Blumenkrantz and Sondergaard in chick organ cultures (4). This was reinforced by clinical studies showing that infusions of PGE₁ could produce hyperostosis (5) and the finding that PGE₂ treatment could stimulate new bone formation in experimental animals (6-8). However the effect is biphasic. *In vitro* PGE₂ and PTH can inhibit collagen synthesis when applied continuously to bone cell cultures (9;10), but both agonists can increase osteoblastic activity through effects on replication and differentiation of osteoblast precursors (11-13).

While clinical application of the anabolic effect of PTH has been highly successful, similar applications using the prostaglandin

pathway are just beginning to be developed. Part of the reason for this is undoubtedly the much wider distribution of prostaglandin receptors and actions. This is due both to the multiplicity of prostaglandins produced and the multiple receptors present. There are four receptors for PGE₂, two of which, EP2R and EP4R, can increase cAMP production in bone cells and are presumed to be the mediators of both the anabolic and resorptive effects.

Following the identification of the different PGE₂ receptors, knockout animals were developed allowing studies that demonstrated that both EP2R and EP4R could play a role in osteoclastogenesis (14;15). Studies using a selective EP4R antagonist supported a role for this receptor in the stimulation of bone formation in a marrow ablation model (16;17). During the last decade there have been successful efforts to develop increasingly selective agonists for the PGE₂ receptors (14;18;19). EP2R and EP4R agonists have now been shown to be anabolic in cell and tissue culture and in animal models. These agonists have been used both systemically and locally, and both as sole agents and as combined treatments with other agents. Moreover a critical role for EP4R has been

suggested by the observations that haploinsufficiency of this receptor decreases both the anabolic and resorptive response to PGE₂ (20;21). The following is a summary of some recent findings.

EP4 Receptor Selective Agonists

The first series of highly selective agonists was developed by Ono Pharmaceutical Company (22;23). The effects of these and other PGE₂ agonists were examined in mice in models of local infusion and in mice lacking the individual EP receptors. Animals lacking EP4R showed osteopenia and an impaired response to PGE₂. In addition, the EP4R selective agonist was effective in inducing local bone formation (24). Systemic administration of the EP4R agonist prevented bone loss in ovariectomized and immobilized rats by stimulating bone formation (25). A number of subsequent studies confirmed the anabolic efficacy of these selective agonists, both *in vitro* (26) and in a variety of *in vivo* models including skeletal repair (27), fixation of implants (28) and mechanical loading (29). Combination therapies have also been tested. For example, the EP4R agonist can enhance the local effects of bone morphogenetic protein-2 (BMP-2) (30;31). Moreover BMP-2 was found to act in part by inducing prostaglandin synthesis (32;33). The combination of an antiresorptive, risedronate, with the EP4R agonist was found to produce additive increases in BMD and bone strength in ovariectomized rats (34). The EP4R agonist was also found to accelerate healing and prevent wound complication in a model of sternotomy in diabetic rats (35).

Most recently, investigators at Pfizer have developed a selective EP4R agonist that has potent anabolic activity (36;37). This compound produces a dose-related increase in bone formation and bone strength in ovariectomized rats similar to that observed with PGE₂, without producing obvious side effects, such as diarrhea, that occur with PGE₂ treatment.

EP2 Receptor Selective Agonists

Selective EP2R agonists have not been as extensively studied as those for EP4R,

perhaps because they are less effective as anabolic agents (38). However, in a rat calvarial organ culture model, an Ono EP2R agonist, as well as Butaprost, a weaker agonist, were effective in stimulating collagen synthesis (26;39). A selective agonist developed by Pfizer has been used to stimulate bone formation locally (40;41). This compound can accelerate fracture healing and the closure of critical defects in both canine and rat models. This approach is currently being examined in early clinical trials to accelerate bone healing (David D. Thompson, personal communication).

Other Prostanoids

Many other prostanoids, as well as leukotrienes, are produced by bone cells and could play a role in skeletal regulation. PGF_{2 α} may affect bone both directly and indirectly through its ability to induce cyclooxygenase as well as fibroblast growth factor (42;43). Prostaglandin F derivatives have anabolic activity in rats but have not been further developed, possibly due to unwanted side effects on other organ systems (44).

The prostaglandin D pathway may also be involved. The effect of mechanical loading to induce cyclooxygenase and increase prostaglandin production may result in not only increased production of PGE₂ but also PGD₂. The latter can be converted to a ligand for the peroxisome proliferator-activator receptor gamma, Δ 12-prostaglandin J₂ (45). Moreover Δ 12-prostaglandin J₂ has been shown to stimulate bone formation when applied locally (46).

Conclusions

While it is clear that prostaglandins can be anabolic and that this is largely mediated by activation of the EP2 and EP4 receptors, it is still uncertain whether these effects can be harnessed therapeutically. Prostaglandin receptors are ubiquitous and adverse effects are likely to occur in many other tissues. Moreover, it may be difficult to separate the anabolic effect from the resorptive effect of prostaglandins. On the other hand, local

administration should be feasible. The current use of BMP-2 to stimulate local bone formation might be replaced by a less expensive, less immunogenic and possibly more effective agent in the form of a selective EP receptor agonist. Studies of the molecular mechanisms by which EP receptor agonists stimulate bone formation and comparisons of their effects with those of other anabolic agents such as PTH could increase our understanding of the regulation of bone formation. There are several known interactions between prostaglandins and other growth factors including not only BMP-2 and FGF₂ but also vascular endothelial growth factor, insulin-like growth factor and TGF- β (47-49). An exploration of these pathways could lead to new approaches to anabolic therapy in osteoporosis and other skeletal disorders.

Conflict of Interest: The author reports that he is a consultant for Pfizer and Procter & Gamble; receives research support from Servier International; and serves on a Data Safety and Monitoring Board for Novartis.

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