Fracture healing with an EP-2 agonist

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Healing of bone fractures is a synchronized molecular, biochemical, and cellular process. An essential component of bone healing involves the inflammatory phase where prostaglandins play a key role.

Prostaglandin E2 (PGE2) is a potent bone anabolic agent. PGE2, when delivered by subcutaneous (SC) injection, significantly increases bone formation and bone mass throughout the skeleton. However, PGE2 is not a practical therapeutic agent due to objectionable systemic side effects (vasodilatation, nausea, and diarrhea). When PGE2 is administered locally to the periosteum or marrow cavity of bone, increased bone formation is observed. The action of PGE2 is mediated by 4 distinct receptor subtypes: EP1, EP2, EP3, and EP4. Two of the subtypes, EP2 and EP4, signal via a cAMP pathway and are involved in mediating PGE2's bone anabolic effect. EP2-selective agonists when delivered locally to the periosteal surface or the marrow cavity of bones were shown to increase cortical and cancellous bone formation without the systemic side effects observed with PGE2.

CP-533,536 is a nonprostanoid agonist of the prostaglandin EP2 receptor subtype of prostaglandin E2 (PGE2) with significant local bone anabolic activity. CP-533,536 binds to the EP2 receptor with high affinity and selectivity. PGE2 has demonstrated significantly increased bone mass and bone strength when administered systemically or locally to the skeleton. However, due to side-effects including diarrhea, lethargy, and flushing, PGE2 is an unacceptable therapeutic option. CP-533,536 initiates cAMP (cyclic adenosine monophosphate) signaling via an EP2 receptor-mediated signaling pathway. In in vivo studies, CP-533,536 stimulated local bone formation when injected onto the periosteal surface and into the marrow cavity of long bones in rat models. In addition, CP-533,536 enhanced bone fracture healing in rat and dog fracture models. Furthermore, CP-533,536 induced new bone formation and healed critical-sized segmental defects of long bones in the dog. These data suggest that CP-533,536 may have utility in enhancing fracture healing and the healing of bone defects in humans.

References