Mini Review

Newer anabolic therapies in osteopororsis

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ABSTRACT

Osteoporosis is one of the top 10 global diseases of 21 st century. The altered bone turnover rate has been attributed to impaired activity of osteoblasts and over-activity of osteoclasts. Anti-resorptive and bone forming therapies are the two choices available for the treatment of osteoporosis. In the mini-review, we will discuss the experimental therapeutics of emerging osteoanabolic strategies

Key words: Anabolic therapies in osteoporosis

Introduction

According to WHO report, osteoporosis is one of the top 10 global diseases of 21st century attributed by an altered bone turnover rate due to impaired activity of osteoblast and over activity of osteoclast. Antiresorptive and bone forming drugs are two foremost choices available for the treatment of osteoporosis. Most of the antiresorptive therapies uncouple bone remodeling cycle causing an early increase in bone mass due to inhibition of resorption while osteoblasts continue to fill in the resorbed pits. This process could last maximum for two years after which osteoblast function declines. Hence, stimulating the function of osteoblast, so-called bone anabolic therapy is necessary to replace lost bone or rebuild new bone mass.

In this mini-review, we will discuss the experimental therapeutics of emerging osteoanabolic strategies. As osteoporosis therapy is likely to be long-term, the safety of any potential osteogenic agent requires serious consideration. Target-based drug development, established on firm mechanistic understanding should yield molecules with better safety profiles. Therefore, much stress is placed on various putative osteogenic candidate molecules and understanding of their modes of action and the context in which these molecules may become therapeutic targets.

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Intermittent parathyroid hormone (iPTH) is the only available bone anabolic therapy as it is capable of increasing bone mineral density (BMD), restoring trabecular microarchitecture and reducing fracture risk to a greater extent than the antiresorptive therapies.[1]However, iPTH has the following drawbacks: (1) FDA recommended carrying a black-box warning because it is associated with an increased risk of osteogenic sarcoma in rats, (2) daily injection negatively impacts treatment adherence, and (3) it can be given only once in a lifetime for a maximum of 2 years. Hence, there is a great need for new osteogenic drugs and better preparations of parathyroid hormone(PTH) to offer an improved option and a competitive environment.

Oral parathyroid hormonemimetics

Recently, a small molecule mimic of PTH, AH3960 has been developed by GlaxoSmithKline, which can stimulate cAMP*in vitro*. This compound has much less activity compared to PTH in cAMP production assay.[2]The major challenge of transient activation of osteoblast PTH receptor by the oral PTH mimetic remains as sustained activation will lead to increased bone loss by stimulating the production of osteoblastic Receptor activator of nuclear factor kappa-B ligand (RANKL).

Antagonizing the calcium-sensing receptor (CaSR)

The G protein coupled CaSR in the parathyroid gland critically regulates PTH release. Amino-alcohol-based small

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molecule (ronacaleret) could suppress the receptor function resulting in augmented release of PTH without giving rise to parathyroid gland hyperplasia. Thus, endogenously produced PTH could exert bone anabolic action. Human studies have shown that ronacaleret exhibits a modest anabolic action in postmenopausal women, but the effect was less than iPTH.[3]It appears that human parathyroid glands do not have the sufficient PTH store required for exerting the anabolic effect like iPTH.

Wnt pathway

The Wnt pathway involves a large number of proteins that can regulate the production of Wnt signaling molecules, their interactions with receptors on target cells and the physiological responses of target cells that result from the exposure of cells to the extracellular Wnt ligands. The Wnt binds to cell-surface receptors of frizzled family that interacts with a transmembrane protein called LRP 5/6 and activates dishevelled family proteins which in turn inhibits a second complex of proteins that includes axin, GSK-3 and protein adenomatous polyposis coli (APC) that otherwise promotes proteolytic degradation of β-catenin, an intracellular signaling molecule and ultimately affects its interaction with TCF/LEF family transcription factors to promote osteoblast specific gene expression. So, careful regulation of this pathway can leave us with handful solutions for osteoporosis as loss or gain of function mutations in LRP5 gene is associated with low and high bone mass phenotypes, respectively. Several inhibitors are known to regulate this pathway at various stages such as sclerostin, DKK-1, sFRP-1 and WIF-1. By neutralizing those inhibitors and increasing intracellular level of β-catenin via inhibition of kinase GSK-3β, we could get effective osteoanabolic outcome.[4]

Monoclonal antibodies against sclerostin and Dkk-1 showed marked anabolic effects in rodents. One clinical trial with human anti-Dkk1 neutralizing antibody (BHQ880) has been started by Novartis for bone loss associated with multiple myeloma.[5]Diverse classes of compounds have proved their anabolic effect *in vitro* and *in vivo* by regulating Wnt signaling as iminooxothiazolidines methyl ester inhibits sFRP-1, 2-aminopyrimidine, and naphthylpyrimidine act as Wntsignalling agonists, sulfonamides with bis-phenyl sulfone core disrupts binding of Wnt to sFRP-1. One more class bis-arylmaleimides acts by inhibiting GSK-3 and its preclinical observations for bone formation are promising, but it can be tumor-promoting since GSK3 suppresses hedgehog and notch pathways besides Wnt pathway.[6]

As proteosomal degradation pathway leads to reduced nuclear translocation of β-catenin via the canonical Wnt pathway, suppressing proteosome activity is considered an effective therapeutic strategy towards osteoanabolism. We have discovered novel orally active small molecule that accelerates fracture healing in rats by stimulating BMP-2 production by osteoblast and the effect is mediated by inhibition of proteosome activity.[7]

Polyphenolic Compounds

Phytoestrogens are typically considered as antiresorptive. Recently, our groups has isolated 6-*C*-b-d-glucopyranosyl-(2S,3S)-(+)-3',4',5,7-tetrahydroxyflavanol (GTDF), a novel flavonol-*C*-glucosidefrom stem bark of *Ulmuswallichiana*. GTDF stimulated osteoblast proliferation, survival, and differentiation but has no effect on osteoclast formation, suggesting a pure osteogenic effect. GTDF promotes modeling-directed bone growth as it increases parameters of peak bone mass achievement, including increased longitudinal growth, bone mineral density, bone-formation rate (BFR), cortical deposition, and bone strength in growing rats. Simultaneously, it restores trabecular osteopenia and increases L5 compression strength in osteopenic rats. This flavonol also reduces fracture risk as it restores drill holes injury in femurs of both Ovx and sham operated animals by filling new bone at a faster rate. It mediates this effect by stimulating cAMP production, which further enhances osteogenic gene expression. Based on these preclinical data, GTDF has been licensed to Kemxtree, NJ, USA for developing it as an orally active rapid fracture healing compound.[8]

Future Direction

An ideal bone anabolic agent will be the one that is orally administered and selectively stimulates osteoblast function without affecting that of osteoclast and hence maintains normal bone remodeling. Achieving this goal is in itself arduous. However, added to this challenge are added issues pertaining to safety such as potential for inducing osteogenic sarcoma and vascular calcification. In addition, the most desirable anabolic therapy will be the one that can effectively heal a fracture in osteopenic individuals.

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