Adiponectin Signaling Regulates Skeletal Physiology

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Abstract

Bone remodelling is important to maintain the skeletal physiology. Bone loss with aging and hormonal pathologies may be result of altered bone remodelling leading to osteoporosis. Even in presence of existing therapies, there is an unmet clinical need to look for ideal alternatives that would stimulate bone formation and keep resorption in check. Adiponectin and its derivatives could be a possible candidate for such therapy. Orally active small molecule AdipoR agonists may be a proposed solution for this.

Keywords: Adiponectin, AdipoR agonists, Osteoporosis, Osteoblasts, Osteoclasts.

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Introduction

Bone remodeling is the backbone of skeletal physiology. Weight-bearing bones, including the lumbar vertebra, femur, tibia, and radius maintain bone quality through remodeling. Bone remodeling is broadly comprised of five phases; a) activation phase, when pre-osteoclasts migrate to the site requiring remodeling (bone containing microdamage) and then fuse together to form multinucleated mature osteoclasts, b) resorption phase, when mature osteoclasts resorb bone mineral and matrix followed by their apoptosis; c) reversal phase when mesenchymal stem cells and preosteoblasts migrate to the resorption site and undergo proliferation and differentiation to mature osteoblasts; d) formation phase when mature osteoblasts fill the resorption pit with a non-mineralized matrix followed by the mineralization of bone matrix and e) quiescent phase when the recently concluded remodeling site becomes quiescent and lined by resting lining cells.[1] The remodeling cycle takes about 4 to 8 months, of which the formation phase is the longest. In healthy adult subjects, the amount of bones removed during remodeling is replaced by an almost equal amount of new bone. Menopause and aging mark the fall in gonadal hormones that negatively influence bone remodeling by the relative increase in resorption over formation resulting in net bone loss.[2]

The existing therapies to treat osteoporosis fall under a) remodeling suppressors (anti-resorptive) and b) remodeling enhancers (formation promoting/bone anabolics). The first line of osteoporosis therapy is represented by bisphosphonates that suppress resorption and bone formation. Denosumab, a human neutralizing antibody against the receptor activator of nuclear factor-kB ligand (RANKL) is also a strong remodeling suppressor. Peptide ligands of parathyroid hormone receptor 1 (PTH1R), including teriparatide (PTH1-34) and abaloparatide (PTH-related protein 1-36), stimulate bone formation. However, the anabolic effect is transient, given that the initial stimulation of bone formation is counteracted by stimulation of bone resorption at a later stage.[3] Sclerostin, a wnt inhibitor produced by osteocytes, inhibits osteoblast function and stimulates osteoclast function. Sclerostin levels are increased in post-menopausal women. A humanized neutralizing antibody against sclerostin also has a bone anabolic effect, albeit for a limited duration of line teriparatide.[4] A therapy that would stimulate bone formation and keep resorption in check is an ideal osteoporosis therapy and is an unmet clinical need.

Adiponectin is a major adipokine secreted by adipocytes. Adiponectin exists as a trimer (low molecular weight), hexamer (medium molecular weight), and 12 or 18mers (high molecular weight) in serum. Besides these forms, leukocyte-derived elastases cleave the oligomeric adiponectin to produce globular adiponectin (gAd), which consists of three c-terminal globular domains held together by the strong hydrophobicity of the trimer interior core. Adiponectin signal through adiponectin receptors 1 and 2 (adipoR1 and adipoR2). Adiponectin receptors (AdipoRs) have seven transmembrane passes, but unlike the G protein-coupled receptors, the C-terminal domain is extracellular, and the N-terminal domain is intracellular. In preclinical studies, reduced circulating adiponectin is associated with various metabolic disorders, including type 2 diabetes, obesity, and cardiovascular diseases. Conversely, administration of adiponectin or augmenting its expression is reported to ameliorate these pathological conditions.[5] Osteoporosis is

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a metabolic disease, and the role of adiponectin signaling is less understood.

Here, we studied the therapeutic effect of gAd in a rat model of post-menopausal osteoporosis model. This model was established by bilateral ovariectomy (OVX) of skeletally mature rats. Treatment of gAd started after the establishment of osteopenia, and teriparatide, and alendronate (a bisphosphonate) were used as standards-of-care comparators. The restorative effects of gAd in OVX rats assessed by bone mass, microarchitecture, and bone strength were better than alendronate and equivalent to teriparatide. Both osteoanabolic and anti-resorptive mechanisms led to the anti-osteoporosis effect of gAd. In cultured osteoblasts and bones, gAd increased a) AdipoR1 and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a) expression to promote mitochondrial respiration, which likely fueled osteoblast differentiation, b) suppressed sclerostin in a sirtuin1-dependent manner, and c) decreased (RANKL) to achieve its anti-catabolic effect.[6]

Besides gAd, we have shown that 6-C-β-D-glucopyranosyl (2S,3S)-(+)-3′,4′,5′,7′-tetrahydroxyflavanol (GTDF),[7-9] epigallocatechin gallate (EGCG), resveratrol,[10] isovitexin,[11] activate adiponectin receptors (AdipoRs) to stimulate osteoblast differentiation in vitro and bone formation in animal models of bone loss. Whereas isovitexin signals through both AdipoRs, GTDF is selective to AdipoR1. The downstream mechanism of AdipoR activation by these compounds involves activation of AMP-activated protein kinase, upregulation of PGC-1a, mitochondrial biogenesis, and ATP production by osteoblasts.

Our research concludes that orally active small molecule AdipoR agonists could stimulate osteoblast function by reprogramming mitochondrial respiration and concomitantly inhibit osteoclast function. Given their dual-action, we propose positioning these small molecules as a new class of anti-osteoporosis drugs for their development.

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