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Strontium signaling: Molecular mechanisms and therapeutic implications in osteoporosis

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ABSTRACT

Osteoporosis is an important age-related bone disease characterized by increased bone turnover with insufficient bone formation relative to bone resorption. According to the current understanding of this disorder, anti-resorptive and anabolic drugs have been developed for therapeutic intervention. Another therapeutic approach consists of dissociating bone resorption and formation. Preclinical and clinical studies provided evidence that strontium (in the form of ranelate) induces beneficial effects on bone mass and resistance in animal models of bone loss and in osteoporotic patients. These effects are mediated in part by the pharmacological actions of strontium on bone metabolism, by reducing bone resorption and maintaining or increasing bone formation. Current pharmacological studies showed that strontium activates multiple signaling pathways in bone cells to achieve its pharmacological actions. Notably, activation of the calcium-sensing receptor by strontium in osteoclasts or osteoblasts leads to activation of phospholipase Cβ, inositol 1,4,5-triphosphate, release of intracellular Ca^{2+}, and activation of MAPK ERK1/2 and Wnt/NFATc signaling. Strontium-mediated activation of these pathways results in the modulation of key molecules such as RANKL and OPG that control bone resorption, and to the regulation of genes promoting osteoblastic cell replication, differentiation and survival. This review focuses on the more recent knowledge of strontium signaling in bone cells and describes how the resulting pharmacological actions on bone metabolism have important therapeutic implications in the treatment of age-related bone loss and possibly other disorders.

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1. Introduction

1.1. Mechanisms of age-related bone loss

The skeleton is a unique tissue providing support and mineral balance for the organism. The skeletal tissue is formed during growth and is maintained during adult life by continual renewal of the matrix, a process called bone remodelling. Bone remodelling is ensured by two cell types: osteoclasts which resorb the calcified bone matrix and osteoblasts that are responsible for new bone matrix synthesis. During growth, bone formation exceeds bone resorption, resulting

Abbreviations: BMD, bone mineral density; CasR, Calcium sensing receptor; ERK1/2-MAPK, Extracellular-signal-regulated kinase ½—Mitogen-activated protein kinase; HA, Hydroxyapatite; MSC, Mesenchymal bone marrow stromal cells; NFATc, Nuclear factors of activated T-cells; OA, Osteoarthritis; OPG, Osteoprotegerin; OVX, Ovariectomized; PTH, parathyroid hormone; RANKL, Receptor activator of nuclear factor-kappaB ligand; SrRan, Strontium ranelate.

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in bone expansion. In the young adult, bone resorption is balanced by bone formation, resulting in the maintenance of bone mass. At menopause, an imbalance in bone resorption relative to formation results in a negative bone balance at the tissue level (Khosla & Riggs, 2005). This leads to an increased number of bone remodelling units, perforation of trabeculae and endocortical erosion, which is responsible for trabecular disconnection, alteration of trabecular microarchitecture and reduced bone strength (Raisz, 2005). Aging is also associated with decreased bone formation relative to bone resorption, thereby accentuating bone loss. These two conditions may lead to osteoporosis, a common skeletal disease characterized by reduced bone mass, deterioration of bone microarchitecture and increased susceptibility to fractures (Martin & Seeman, 2008).

Several mechanisms may contribute to the age-related increase in bone resorption. The decline in the bioavailable sex hormones with age leads to increased expression of receptor activator of nuclear factor-kappaB ligand (RANKL) by osteogenic stromal cells. RANKL binds RANK expressed on osteoclast precursor cells and thereby promotes signalling leading to increased osteoclast differentiation (Anderson et al., 1997; Li et al., 2000). Sex hormone deficiency also results in reduced expression of the RANK antagonist osteoprotegerin (OPG) by bone marrow stromal cells/osteoblasts and other cells (Hofbauer et al., 2000). These changes, in addition to the rise in the expression of local cytokines such as IL1, IL6, TNFα and IL17 result in increased osteoclastogenesis and bone resorption (Manolagas, 2000; Pacifici, 2012). The age-related decrease in bone formation is caused by several mechanisms (Kassem & Marie, 2011; Marie & Kassem, 2011a). Intrinsic causes that lead to defective bone formation include decreased pre-osteoblastic cell proliferative capacity and osteoblast function, possibly related to a local decrease in the production of anabolic factors such as Insulin Like Growth Factor-1 (IGF-1) or Transforming Growth Factor-β (TGF-β). Another cause is the increased lipid oxidation causing oxidative stress and activation of the transcription factor peroxisome proliferator-activated receptor-gamma-2 (PPARγ2) that governs adipocyte differentiation. This induces preferential differentiation of mesenchymal bone marrow stromal cells (MSC) into adipocytes and accelerated senescence of osteoblast precursor cells (Manolagas, 2010). Extrinsic causes involved in the defective age-related bone formation include the decline in physical activity, insufficient protein intake, excess alcohol and tobacco consumption and long term glucocorticoid treatment. Therefore, efficient therapeutic strategies in osteoporosis should target not only the increased bone resorption, but also the decreased bone formation associated with aging (Marie & Kassem, 2011b).

1.2. Mechanisms of action of anti-osteoporotic drugs

Based on the evidence that estrogen deficiency at menopause results in increased bone remodeling and bone resorption, pharmacological compounds targeting osteoclasts have been developed to decrease bone resorption for therapeutic intervention in osteoporosis (Riggs & Parfitt, 2005). Bisphosphonates act by inhibiting osteoclasts and inducing osteoclast death, resulting in decreased bone resorption and subsequently bone formation due to the coupling phenomenon during bone remodeling (Russell et al., 2008). This leads to the maintenance of bone mass and a reduction in fracture incidence in BP-treated osteoporotic patients. Denosumab, a fully human monoclonal antibody to RANKL that blocks its binding to RANK, acts by blocking osteoclast differentiation, resulting in decreased bone remodeling and a reduced risk of fractures in women with osteoporosis (Cummings et al., 2009). Cathepsin K expressed by osteoclasts plays a major role in bone resorption, and was therefore considered as a therapeutic target in osteoporosis. Current preclinical and clinical studies indicate that Odanatacib, a selective and reversible cathepsin K inhibitor reduces osteoclast resorption efficiency, resulting in increased bone mass in osteoporotic patients (Costa et al., 2011; Masarachia et al., 2012). Although being efficient at decreasing the bone remodelling activity, the long term effects of these anti-resorbing agents on bone properties remain unknown (Baron et al., 2011).

A major remaining challenge in the treatment of osteoporosis is to identify strategies that would induce a reversal of the age-related decrease in bone formation. To date, the number of anabolic agents that promote osteoblastogenesis is limited. The development of intermittent parathyroid hormone (PTH) administration as an anabolic treatment was a major advancement in the treatment of osteoporosis. Intermittent PTH increases bone formation in osteoporotic patients, resulting in increased trabecular bone mass and cortical thickness (Neer et al., 2001; Compston, 2007). However, this anabolic treatment has some limitations linked to the low half life and high cost of this molecule. Recently, a major observation led to the development of a novel anabolic agent. It was found that the genetic loss-of-function of sclerostin, the product of the SOST gene expressed by osteocytes (i.e., old osteoblasts embedded in the mineralized matrix), results in increased bone mass (Balemans et al., 2001). Sclerostin inhibits bone formation by antagonizing LRP5/Wnt signaling (van Bezooijen et al., 2004). This observation led to the development of a sclerostin antibody which has potent anabolic pharmacological effects in vivo. This compound increases bone formation and bone mass in a rat model of postmenopausal osteoporosis (Li et al., 2009) and in osteoporotic patients (Papapoulos, 2011).

Besides anti-resorptive and anabolic treatments, an alternative potential therapeutic strategy in osteoporosis consists in promoting bone formation while reducing bone resorption. There is ample experimental evidence that strontium, a trace element chemically close to calcium (Dahl et al., 2001), induces pharmacological actions on bone metabolism (Marie, 2010a, 2010b). A compound containing two atoms of strontium (strontium ranelate, SrRan) was found to act by dissociating bone resorption and bone formation in vitro through the activation of several signaling pathways in osteoclasts and osteoblasts. These pharmacological effects were shown to translate into beneficial effects on bone mass, bone quality and bone resistance in osteopenic models and in osteoporotic patients. This review focuses on the pharmacological effects of strontium on bone cell metabolism, and its therapeutic implications in osteoporosis and other bone diseases characterized by insufficient bone formation relative to bone resorption.

2. Pharmacological effects of strontium on bone cells

2.1. Strontium and osteoclastogenesis

Early studies provided pharmacological evidence that strontium (Sr) reduces osteoclast differentiation, activity and bone resorption in vitro (Baron & Tsouderos, 2002; Takahashi et al., 2003). More recent studies provided some mechanistic input into this effect. SrRan reduces the adherence of osteoclasts to bone by disrupting the actin containing sealing zone (Bonnelye et al., 2008). It also decreases the differentiation of osteoclasts by modulating the NFκB signaling pathway (Caudrillier et al., 2010), as well as the number and activity of cultured osteoclasts (Bonnelye et al., 2008) In addition, SrRan at higher dosage levels was found to increase apoptosis in isolated rabbit osteoclasts through the PKCβII pathway (Hurtel-Lemaire et al., 2009). The high doses that were effective at inhibiting osteoclast activity or survival in these assays are similar to those found in bone treated with SrRan since Sr is adsorbed at the bone surface (Dahl et al., 2001). In any case, it is clear that Sr induces pharmacological actions on osteoclast differentiation, activity and lifespan, resulting in reduced bone resorption observed in vitro.

2.2. Strontium and osteoblastogenesis

Strontium also induces pharmacological effects on bone forming cells in vitro. In rat calvaria organ culture, SrRan was initially shown