Materials Science and Engineering C 78 (2017) 1222–1230

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Review

Strontium and strontium ranelate: Historical review of some of their functions

M. Pilmane [a], K. Salma-Ancane [b,*], D. Loca [b], J. Locs [b], L. Berzina-Cimdina [b]

[a] Institute of Anatomy and Anthropology, Riga Stradins University, 16 Dzirciema Str., Riga LV 1007, Latvia
[b] Rudolfs Cimdins Riga Biomaterials Innovations and Development Centre of RTU, Institute of General Chemical Engineering, Faculty of Materials Science and Applied Chemistry, Riga Technical University, 3 Pulka Str., Riga LV-1007, Latvia

ARTICLE INFO

Article history:
Received 27 October 2016
Received in revised form 29 April 2017
Accepted 9 May 2017
Available online 9 May 2017

Keywords:
Strontium
Strontium ranelate
Physiology
Bone
Medicine

ABSTRACT

The review covers historical and last decade's scientific literature on the biological and clinical role of strontium (Sr) and strontium ranelate (Sr RAN). It enrols the description of the main effects of Sr on supportive tissue, its proven and possible morphopathogenetical mechanisms and the interaction with the bone, and especially focuses on the Sr ability to inhibit osteoclasts and affect the programmed cell death. The main experimental and clinical experience regarding the Sr RAN influence in the treatment of osteoporosis and the search for correct doses is also highlighted. The review gives insight into the role of Sr/Sr RAN on stem cells, apoptosis, animal and clinical research.

Contents

1. Biological role of Sr

Sr is a chemical element with atomic number 38, which had been discovered in lead mines [73]. Food is the main source for Sr uptake for humans, and some types of food like grains and seafood may contain up to 25 mg/kg of Sr. Also small amounts of Sr enter the human body through the skin and lungs. The common daily Sr balance has been established as follows: intake with food/fluid – 1.9 mg, secretion with urine – 0.34 mg, excretion with faeces – 1.5 mg, secretion *via* sweat glands – 0.02 mg and loss with hair – 0.2×10^{-3} [73].

The major chemical element found in the bone is calcium (Ca), but there are actually at least a dozen of other chemical elements in the bone and one of them is Sr. Although Sr is a bone-seeking element, most of it is absorbed in bones and teeth, thus demonstrating its excellent ability to bind with the mineral phase of bone – biological

* Corresponding author.
E-mail address: kristine.salma-ancane@rtu.lv (K. Salma-Ancane).

http://dx.doi.org/10.1016/j.msec.2017.05.042
0928-4931/

hydroxyapatite (HAp), which made this divalent cation interesting for the application in medicine [63,69,83]. 99% of the total amount of Sr in the body is deposited in the bone (36–140 mg/kg), preferably in the new trabecular bone and in "favourite" sites such as diaphysis of the femur, lumbar vertebra, and the iliac crest [33,97]. However, the total amount of Sr in the skeleton is small compared with that of Ca and displays only 3.5% of the Ca molar content [73] or accounts for 0.035% of the Ca content [15].

The Sr content in a new compact bone is calculated to be three to four times higher than that in an old compact bone, and approximately 2.5 times higher in a new cancellous bone than in an old one. This proportion is kept throughout the lifetime, partly because the bone turnover is higher in cancellous bone than in cortical bone, and the newly formed bone is more abundant in cancellous bone than in cortical bone [102]. It is well known that Sr has a unique mechanism of action increasing pre-osteoblast proliferation, osteoblast differentiation, type I collagen synthesis and bone matrix mineralization, while osteoclast differentiation and activation are inhibited [16,20].

2. Sr/Sr RAN and osteoporosis

In the last decade, extensive research has been done on the effects of Sr on bone, due to the development of the antiosteoporosis drug Sr RAN, which has attracted the most attention due to its promising physicochemical and pharmacokinetic characteristics [86]. Sr RAN is registered as a medication in over than 70 countries and has been used for postmenopausal osteoporosis in women and men for more than 10 years. Sr RAN as dual action agent simultaneously increases the osteoblast differentiation while osteoclast formation is inhibited [14]. Clinical trials have shown that SrR significantly improves bone mass and quality, and increases bone strength through changes in bone matrix properties and bone mineral density (BMD) in patients [68,100]. Moreover, Sr RAN remarkably reduces the risk of spine or hip fractures [84].

In spite of the unique mode of action and impressive clinical trials, Sr Ran is licensed for use in Europe, but is not approved by the US Food and Drug Administration (FDA) [19,30,63]. Taking into account the fact that Sr and Sr RAN possess a unique and similar mode of action, this review will mainly focus on the common description of Sr and Sr Ran functions as well as possible pathophysiological mechanisms (unless an exception is indicated further in the text).

Osteoporosis is a metabolic bone disease characterized by a high bone turnover, low bone mass, destruction of bone microstructure, and increased risk of bone fragility and fractures [32]. In patients with osteoporosis, osteogenesis regression and osteoclasts enhancement occur, also weakening the functionality of osteoblasts, resulting in affected bone spicules and decreased bone volume, and leading to the increased risk of fractures of supportive tissue. It is mainly believed to be an oestrogen-deficiency disease because the oestrogen deficiency increases the rate of bone remodelling which, in association with a negative remodelling balance (resorption exceeding formation), results in impaired bone architecture, mass and strength [68]. In addition, other genetic and epigenetic factors may play an important role in triggering of osteoporosis. Fracture prevention is the main goal of any therapy for osteoporosis. Sr Ran as an antiosteoporotic agent has the theoretical premises to promote fracture healing and osseointegration. Numerous clinical studies have demonstrated that the systemic Sr Ran treatment minimizes the risk of vertebral, nonvertebral and hip fractures in a wide range of post-menopausal women with documented osteoporosis [57,85,90].

3. General effects of Sr/Sr RAN on bone

The dual action of Sr Ran and Sr, promoting osteoblast-mediated bone formation and inhibiting osteoclast-mediated bone resorption, has been under extensive research both *in vitro* and *in vivo* [30,63]. The main effects of Sr/Sr Ran from *in vitro* and *in vivo* studies at the cellular and tissue level are summarized in Fig. 1.

Both Sr and Sr Ran enhance bone formation and slow down bone resorption. The resulting increase in bone mineral density (BMD) seems to be associated with the improved mechanical properties of the bone. Sr is generally believed to have a dual action of promoting osteogenic bone formation and inhibiting osteoclastic bone resorption [63]. Sr induces the higher expression of the osteoblastic genes – alkaline phosphatase (ALP), osteocalcin (OC) and bone sialoprotein, combined with increased bone nodules, and a reduction in the number of mature osteoclasts *in vitro* [14]. Several other authors also support the effects of Sr to induce pre-osteoblast proliferation and enhance osteoblast activity, as demonstrated by the increase in the expression of several early and late osteoblastic markers, such as type I collagen, ALP, bone sialoprotein, OC and, ultimately, bone matrix mineralization and nodule formation in bone marrow stromal cell cultures and immature osteoblasts [9,18,27]. Exactly the same – the presence of dual functions – is described for Sr RAN in the bone remodelling process, during which the bone is constantly being renewed [4]. Sr Ran is suggested to inhibit the bone resorption induced by osteoclasts as well as osteoclast differentiation/activation [10], and to stimulate the bone-forming function of the osteoblast and pre-osteoblast proliferation/differentiation.

Recently, Almeida et al. have demonstrated that Sr RAN enhances the expression of Type I Collagen and osteopontin (OPN), which are important components of the organic bone matrix [107]. Moreover, Sr RAN is able to promote the formation of large bone-like nodules in osteogenic cultures and accelerate the acquisition of the osteoblastic phenotype

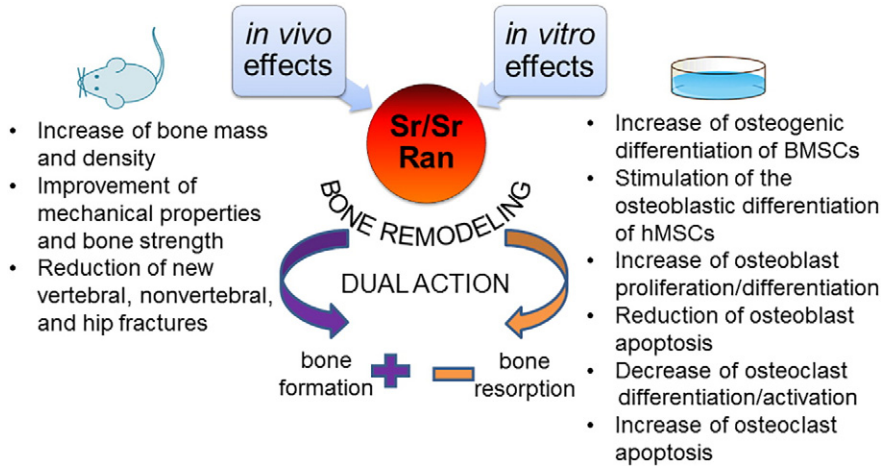

Fig. 1. *In vivo* and *in vitro* effects of Sr/Sr RAN. See the text for details.