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Strontium ranelate treatment improves oxidative damage in osteoporotic rat model

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Abstract:
Background: Osteoporosis is the most common skeletal disorder and is considered a risk of fracture. Most medication used for the treatment of osteoporosis is antiresorptive; however, strontium ranelate (Sr) therapy in postmenopausal women has shown a double effect on resorption and bone formation. In this study, the effect of Sr on status of the oxidative stress and antioxidant defence system was investigated.
Methods: Twenty-one adult albino female Wistar rats were used. The animals were randomly assigned into three groups, control (sham operated rats, received saline), OVX (ovariectomized rats), OVX + Sr (4 months later ovariectomy, strontium ranelate treatment was begun and continued for 120 days) each containing 7 animals. Strontium ranelate (500 mg/kg/day) and placebo (saline) were administered *via* oral gavage. At the end of the treatment, liver and kidney of rats were removed and malondialdehyde (MDA) level, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) activities were determined by biochemical analysis methods.
Results: In liver, MDA levels were significantly higher in the OVX and OVX + Sr groups than the control group. GSH-Px activity decreased in OVX group and increased in OVX + Sr group compared with values of control group. CAT activity was increased in the OVX + Sr group when compared to control group. In kidney, MDA level was increased in OVX group. SOD activity was decreased in the OVX + Sr group. GSH-Px activity decreased in OVX group and increased in OVX + Sr group compared with control group. CAT activity increased in the OVX + Sr group when compared to control.
Conclusion: According to our results, Sr has preventive effect on oxidative damage in ovariectomized rats.

Key words:
strontium ranelate, osteoporosis, oxidative stress, ovariectomy, rat

Abbreviations: CAT – catalase, GSH-Px – glutathione peroxidase, MDA – malondialdehyde, NBT – nitroblue tetrazolium, OVX – ovariectomized, SOD – superoxide dismutase, Sr – strontium ranelate

Introduction

Osteoporosis is characterized by a generalized and progredient bone loss, leading to low bone mass and microarchitectural deterioration with subsequent bone fragility [9]. The use of strontium in the treatment of osteoporosis dates back over half a century [14, 23]. Strontium is a trace element defined as a bone-seeking agent. It has been shown to affect bone cells and bone metabolism *in vitro* as well as *in vivo* in a dose dependent manner. In contrast to radioactive strontium, which has toxic effects on bone cells, the nonradioactive element influences bone remodeling by inhibiting bone resorption and stimulating bone formation [5, 12, 25].

Strontium ranelate (Sr) is composed of an organic moiety (ranelic acid) and of two atoms of stable non-radioactive strontium. The chemical name applied to Sr is 5-[bis (carboxymethyl)amino]-2-carboxy-4-cyano-3-thiophenacetic acid strontium salt. It is currently under development by the Institut de Recherches Internationales Servier (IRIS) for the treatment and prevention of osteoporosis [21].

Free radicals are molecules with at least one unpaired electron in the outermost shell, unstable, highly reactive, having short half life and low molecular weight. Oxidative stress is defined as imbalance between antioxidant systems in the body and free radical production caused the lipid peroxidation into lipid bilayers of cells. Antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) play an important role in scavenging reactive oxygen species produced under oxidative stress [3].

The ovariectomized rat model is used in this study to show postmenopausal osteoporosis. The ovariectomized rat is the most frequently used model for osteoporosis [6, 7, 16, 18]. To the best of our knowledge, the antioxidant system and lipid peroxidation effect of Sr has not yet been studied on ovariectomized rats. Therefore, the aim of this study was to investigate the effect of strontium ranelate on status of the oxidative stress and antioxidant defence system.

Materials and Methods

Animals

Twenty-one adult albino female Wistar rats weighing 200–250 g were used in this study. The animals were acclimatized for 1 week to our laboratory conditions prior to experimental manipulation and were exposed to a 12-h light and 12-h dark cycle at a room temperature of 22°C. They had free access to standard laboratory chow and water *ad libitum*. The animals were randomly assigned into three groups: control (sham operated rats, received saline), OVX (ovariectomized rats) and OVX + Sr (4 months later ovariectomy, strontium ranelate treatment was begun and continued for 120 days) each containing 7 animals. Strontium ranelate (500 mg/kg/day) and placebo (saline) were administered *via* oral gavage. All animal procedures used were in strict accordance with the National Institutes of Health Guidelines on the Care and Use of Laboratory Animals, and the approval of the ethic committee of the School of Medicine, Mersin University was obtained prior to the study.

Surgical procedures and treatment

Under ketamine (50 mg/kg, Ketalar, Eczacibasi İlaç Sanayi ve Ticaret A.Ş., İstanbul, Turkey) and xylacine (8 mg/kg, Rompun, Parke-Davis/Pfizer) anesthesia, 14 animals in OVX and OVX + Sr groups underwent bilateral ovariectomy by ventral incisions and 7 were sham-operated (control). At the end of the experiment, animals in all groups were sacrificed and liver and kidney tissues were removed. The liver and kidney of rats were quickly excised, rinsed in ice-cold 0.175 M KCl/25 mM Tris HCl, pH 7.4, to clean the blood, weighed, finely minced in the same solution, and homogenized in a homogenizer with a Teflon pestle. Homogenates were centrifuged at 10,000 × g for 15 min and supernatants were used for lipid peroxidation and antioxidant enzymes assay.

Biochemical assays

Lipid peroxidation

The levels of homogenized tissue malondialdehyde (MDA), as an index of lipid peroxidation, were determined by thiobarbituric acid reaction according to Yagi [26].

Enzyme assay

SOD activity was measured by the inhibition of nitroblue tetrazolium (NBT) reduction by O_2^- generated by the xanthine/xanthine oxidase system. One unit of SOD activity was defined as the amount of protein causing 50% inhibition of the NBT reduction rate [24].

CAT activity of tissues was determined according to Aebi [1]. The decomposition of H_2O_2 can be followed directly by the decrease in absorbance at 240 nm, resulting from enzymatic decomposition of H_2O_2. The difference in absorbance per unit time was a measure of catalase activity. The enzyme activities were given in U/mg protein.

Activity of GSH-Px was measured spectrophotometrically at 340 nm. The method was based on the changes in absorbance resulting from the conversion