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Iron-sulfur nitrosyl complexes as potential therapeutic agents for anti-aging pharmacology and radiation medicine

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Motivation and Aim: It is well known that many of the age-related dysfunctions, including cardiovascular and Alzheimer diseases and the dysfunctions in renal and immune systems, to name just a few, stems from the age-dependent violations in the regulatory functions associated with the nitric-oxide (NO) radical [1–5]. The functional disorders in the NO system are also observed after the organism has been subjected to ionizing radiation. In this regard, iron-thionitrosyl complexes, as the long-living reservoirs and transport remedies of NO, may be of interest for anti-aging therapy and anti-radiation medicine. Here, we present the evidences of geroprotective effects of the iron-sulfur nitrosyl complex, $Na_2[Fe_2(S_2O_3)_2(NO)_4]\bullet 4H_2O$ (FeSNO), as the novel NO donor for anti-aging therapy.

Methods and Algorithms: The thionitrosyl iron complex FeSNO was synthesized in the Institute of Problems of Chemical Physics, RAS [5]. Experiments on the studies of geroprotective and radioprotective effects of FeSNO were performed in the Institute of Gerontology, NAMS. Wistar male rats, the adult animals (7–8 month age) and the old animals (24 month age at the beginning of the experiments), were daily administered intraperitoneally with FeSNO for 14 days. In the experiments on the studies of radioprotective effects of FeSNO, the adult animals were exposed to X-ray irradiation. Experiments on measuring the intensity of free-radical lipid peroxidation, i.e. the levels of malonyldialdehyde (MDA) and thiobarbituric acid, and the levels of activity of the antioxidant enzymes, i.e. superoxide dismutase (SOD), catalase (Cat), glutathione peroxidase (GPO), and glutathione reductase (GR) in liver, heart, and brain of the animals, as well as measurements of the stable NO-metabolites (NO_2^-, NO_3^-) in blood plasma and homogenates of heart and aorta tissues and the measurements of glucose, hemoglobin and glycated hemoglobin in erythrocytes were performed by the standard methods.

Results: The prolong service testing, for 605 days, has proved that the administration of rats with FeSNO gives the reliable effect of the lifespan prolongation, 30 percent extension, as compared to the control animals. In addition, the FeSNO administration restores the age-related changes in the levels of MDA as well as the changes in activities of the antioxidant defense enzymes (SOD, Cat, GPO, GR) in liver, heart and brain tissues of the animals. Furthermore, the rats of 7–8 months age were subjected to X-ray irradiation (5 Gy, sublethal dose), after which the irradiated animals were daily administered with FeSNO for 30 days. Again, it was revealed that FeSNO restores the negative impacts of the radiation on activities of the antioxidant protection enzymes, SOD, Cat, GPO and GR, and prevents the activation of peroxidation of lipids in tissues of the irradiated animals. Besides, FeSNO positively impacts on the nitric oxide

metabolism in blood plasma, heart, and aorta of the irradiated animals, as well as on the functional indexes of metabolism of carbohydrates.

Conclusions: Thus, FeSNO exhibits the remarkable geroprotective effect as well as the remarkable radioprotective effect. The geroprotective effect evidences that this compound is low toxic. It means that the nitrosyl complexes of iron with the functionalized sulfur-containing ligands, as the NO donors, hold considerable promise as potential agents in creating the novel drugs for anti-aging pharmacology as well as the drugs for radiation medicine, in part, the radiomitigators for minimization of consequences of radiation damages of healthy tissue cells in clinical oncology.

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