Salen-Manganase Complexes, EUK-8 and EUK-134, Protect Against Protein and Lipid Oxidative in Neuroblastoma Cells and Rat Liver Homogenates in vitro

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Abstract: Oxidative damage to proteins and lipids leads to severe failure of their biological functions with subsequent final effects on cells functions in various tissues especially liver and brain. In this study, researchers investigated the protective effects of two salen-free radical scavengers namely EUK-8 and -134 and also a standard antioxidant (catechin) in two different models of oxidative stress. In the first study, researchers used Fe²⁺/Ascorbate Model as a well-validated system for production of ROS in rat liver homogenates and the protective effects of EUK-8, EUK-134 and catechin against this system were evaluated. In the second study, the protective capabilities of these compounds against the free-radical damaging effects of hydrogen peroxide (H₂O₂) on SK-N-MC cell line were evaluated in term of attenuation of intracellular lipofuscin level. Results of the first study indicated that the simultaneous addition of Fe²⁺/ascorbate and EUK-8 and/or EUK-134 at different concentrations (5, 10, 25 and 50 μM) to the liver homogenate significantly decreased the extent of PCO, LPO and ROS while the level of PB-SH increased relative to the control group. Results of the second study also showed that pretreatment of the cells with EUK-8 and -134 (25 μM) followed by exposure to H₂O₂ restored the viabilities of cells relative to the H₂O₂-treated cells. In addition, each of the compounds significantly and time-dependently reduced the intracellular level of lipofuscin pigments among the H₂O₂-treated cells.

Key words: Lipofuscin, liver, neuron, oxidative stress, ROS level, salen-manganase complexes

INTRODUCTION

Oxidative stress is believed to be involved in the initiation and propagation of a variety of diseases including aging, neurodegeneration, carcinogenesis, coronary heart disease, diabetes and hepatic diseases (Dalle-Donne et al., 2003; Bishop et al., 2010). These complications usually result due to enhanced level of endogenous Reactive Oxygen Species (ROS) (Farber, 1994; Halliwell, 1999). ROS include hydroxyl (OH), peroxyl (RO₂⁻) and superoxide anion (O₂⁻) radicals and nonradical species such as hydrogen peroxide (H₂O₂). Despite the beneficial roles as second messengers in some signal transduction pathways at low concentrations, these species become highly toxic to a variety of cells and tissues at evaluated levels (Farber, 1994; Halliwell, 1999). The most pronounced events associated with the ROS-mediated injuries include peroxidation of lipids and oxidation of proteins and DNA. Peroxidation of lipids leads to the production of 4-Hydroxy-2-Nonenal (HNE) and Malondialdehyde (MDA) which act as highly reactive cross-linking agents. One of the recognized outcomes of these oxidative processes is the formation and accumulation of aggregates known as lipofuscin (Brunk and Terman, 2002). Lipofuscin as a histological index of aging is mainly made of oxidized protein (30-60%) and lipids (20-50%) and accumulates mostly in post-mitotic cells such as neurons, cardiac myocytes, skeletal muscle fibers, retinal pigments and epithelial cells (Brunk and Terman, 2002; Jung et al., 2007). Many studies have revealed that lipofuscin pigments could induce neurotoxicity through the ROS generation (Brunk and Terman, 2002; Szewo et al., 2002). These effects at the low levels are usually counteracted by the endogenous antioxidant defense elements such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione, vitamin C, E and uric acid. However under oxidative stress condition, the efficiency of this defense system is declined resulting in ineffective scavenging of free radicals (Fridovich, 1999; Yazdanparast et al., 2008). Under these conditions, exogenous natural or synthetic antioxidants are usually prescribed by physicians (Cerillo, 2003). These antioxidants can delay and/or prevent the oxidation processes through simple or complex mechanisms including suppression of oxidation chain reactions, chelation of transitional metal ion catalysts, breakdown of peroxides and scavenging radical (Ames et al., 1993). In

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