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Modification of premature cell aging in vitro and oxidative stress in cellular models of neurodegenerative diseases by selected antioxidants

Abstract

My doctoral dissertation consists of four papers published in the journals *Aging*, *International Journal of Molecular Sciences, Polymers* and *Acta Biochimica Polonica.* They concern the study of the effect of antioxidant substances on changes caused by oxidative stress in fibroblasts stress induced premature senescence (paper no. 1) and cellular models of neurodegenerative diseases (paper no. 2, 3). The last publication complements the previous ones and concerns research related to the biocompatibility of the nanoparticles (paper no. 4).

Oxidative stress was induced by the use of chemical compounds with pro-oxidative potential such as hydrogen peroxide (H_2O_2) and 6-hydroxydopamine (6-OHDA) as well as through aggregation of pathological forms of proteins, e.g. tau protein in neuroblastoma cells, which is responsible for the occurrence of many neurodegenerative diseases.

The obtained results argue against the mediation of secondary reactive oxygen species in processes related to premature aging of cells caused by hydrogen peroxide. Antioxidants used in the experiments showed a slight protective effect, probably due to their influence on the mitochondria. The effect depended on the type of the tested compound, its concentration, time of incubation but also on the type of the cells.

The published results partly explain the mechanism of action of the low concentrations of 6-hydroxydopamine, which leads to an increase in the level of reduced glutathione in the cells. This is probably due to the adaptive response of cells to oxidative stress and related to the increased activity of glutathione metabolism enzymes (glutathione *S*-transferase, γ-glutamyl-cysteine ligase, glutathione reductase, and glutathione peroxidase) dependent on the transcription factor Nrf2. Activation of genes coding for these enzymes can be induced not only by 6-OHDA, but also by some nitroxides, e.g. 4-amino TEMPO, which significantly contributes to the reduction of oxidative stress in mammalian cells. This effect is also observed in the case of oxidative stress caused by tau protein aggregation. Interestingly, nitroxides unlike other antioxidants, are non-toxic even in high concentrations. However their low molecular mass and

short half-life limit their application in therapies. An interesting alternative may be amphiphilic nitroxide-containing polymers which show better antioxidant properties compared to free nitroxides. In addition, they are safe for use in therapies due to the lack of hemolytic and toxic effects with respect to normal cells