Abstract

Results of many studies demonstrate a significant role of oxidative stress in the pathogenesis of many illnesses including cardiovascular diseases. Free cellular iron plays significant role in development of oxidative cell damage; it catalyzes formation of hydroxyl radicals. Hydroxyl radicals belong among the most reactive and toxic forms of reactive oxygen species (ROS). Hence, iron chelators can be used as preventive agents against the development of oxidative damage of tissues. This study deals with confirmation of ability of the iron chelator salicylaldehyde isonicotinoyl hydrazone (SIH) to prevent this damage and with the study of properties of new aroylhydrazone chelators derived from SIH. Protective effects against a model oxidative stress and own toxicities of individual agents were evaluated *in vitro* using rat cardiomyoblast cell line H9c2, the viability of cells was determined by neutral red uptake assay.

A 24-hour incubation of H9c2 cells with 200 μM tert-buthyl hydroperoxide (t-BHP) evoked dramatic changes of cellular morphology and was followed by cell death. Co-incubation with all chelators dose-dependently reduced or abolished cell damage. The replacement of salicyl aldehyde in SIH with a methyl ketone led to an amplification of protective properties of this ligand, this chelator is (1-(2-hydroxyphenyl)ethylidene) isonicotinohydrazide - 2-HAF-INH (SIH: EC_{50} = 18.2 μM; 2-HAF-INH: EC_{50} = 11.4 μM). In comparison with SIH, where following a 24-hour incubation a 45% reduction of cell viability was observed, 100 μM 2-HAF-INH did not show any acute toxicity. After 72-hour incubation the toxicity of 2-HAF-INH was higher (88% reduction of cell viability) than SIH (68%). The IC_{50} value was determined as 29.7 μM for SIH and 12.2 μM 2-HAF-INH. From the series of other eight differently substituted aroylhydrazones, the best ratio of cytoprotective and toxic properties showed 1-(2-hydroxy-7-oxo-7,8-dihydronaphthalen-1-yl)ethylidene) isonicotinohydrazide (AHC-INH).

This study confirms a key role of free cellular iron in peroxidative cell damage and significant protective ability of new original aroylhydrazone iron chelators, which deserve further investigation.