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Long-term effects and some mechanisms of protective action of antimutagens of 1,4-dihydropyridine series in animals and human cells

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Some antioxidants of 1,4-dihydropyridine (1,4-DHP) series were tested as modifiers of chemical and radiation mutagenesis in different test-systems. Such events as DNA damages, point mutations, chromosome breaks and aberrations, cell survival, etc. were analysed. Ethyl methanesulfonate (EMS) was mainly used for simulation of chemical mutagenesis. In these experiments, frequencies of chemically induced injuries were successfully reduced by antimutagens in somatic cells, e.g. in mouse micronucleus test, but the response of germ cells to their action varied depending on experimental conditions.

The most demonstrative results were obtained in *Drosophila* assays where antimutagens inhibited EMS-muta- and clastogenicity under larval treatment, which was much before exposure of adult males to EMS. Nevertheless, namely in this case antimutagens displayed their protective potential in a wide range of concentrations and their efficiency was high. Positive effects disappeared or even were inverted when adult males were exposed to an antimutagen and the mutagen step by step.

The sufficient differences in results of larval and adult treatment with antimutagens allowed the assumption that chemicals were unlikely to interact with each other in organism but rather to interfere into electrophile-detoxifying pathways or DNA repair. Indeed, antimutagens fed to females promoted maternal repair of DNA lesions induced by EMS in spermatozoa. Pre-treatment of adult males with antimutagens decreased EMS-mutagenicity in premeiotic germ cells as opposed to mature sperm. Repair deficiencies reduced sensitivity of germ cells to antimutagens.

Thus, antimutagens of this series are able to modulate DNA repair involved in chemical mutagenesis. It is of great interest that antimutagens affected maternal repair systems in oocytes inhibited EMS clastogenicity in sperm cells stored in females for 14 days. So long-term effects may indicate triggering type of their action, possibly by modulating expression of appropriate genes. Predominant indirect

mechanisms of antimutagenic action were confirmed when studying impact of some 1,4-DHP derivatives on heat shock protein (HSP) system. One of them has been shown to induce the HSP puffs in the third polytene chromosome of salivary glands in *Drosophila* larvae of normal and temperature-sensitive lines.

Radioprotective effects of 1,4-DHP derivatives were found in human lymphocytes *in vitro* by comet assay as well as in carps from ponds contaminated by Chernobyl radionuclides. In the latter case, long-term effects, especially by impact on malformations in fry, were also observed. Here we put forward a hypothesis that antimutagens trigger the host protective mechanisms and control expression of responsible genes.