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ANTIMUTAGENIC EFFECTS OF SOME 1,4-DIHYDROPYRIDINE DERIVATIVES DUE TO MODULATING DNA REPAIR IN GERM CELLS

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The efficient antimutagens (AMs) were earlier found among 1,4-dihydropyridine (1,4-DHP) derivatives, which reduced the rate of spontaneous mutations by 50–85% in *Drosophila* germ cells and inhibited chemical mutagenesis in different test-systems including mouse micronucleus test. In *Drosophila* assays, antimutagenic activity of the compounds was shown to correlate with their antioxidant ability. When studying their influence on mutagenesis induced by ethyl methanesulfonate (EMS), the inhibitory effects did not appear to be due to the antioxidant properties of 1,4-DHP derivatives.

Among possible mechanisms, we focused our attention on modulating DNA repair involved in chemical mutagenesis. To study this problem, different approaches were used, i.e. the maternal effect, alternative repair capacity of pre- and post-meiotic germ cells in males, repair-deficient mutants such as *mei-9*^{L1} or *mei-9*^{a}. In the first experimental set, effects of some AMs of 1,4-DHP series on maternal repair of DNA primary lesions induced in mature sperm were tested. For this purpose, AMs (usually at the dose of 10mM) were fed to females including excision repair-deficient ones, whereas males were exposed to EMS (10–25mM). Embryonic and postembryonic dominant lethality (EL and PEL) caused by chromosome breaks was estimated in F_1; sex-linked recessive lethals (SLRLs) presented predominantly by point mutations were analysed in F_2 and verified in F_3. AMs administered to repair-proficient females reduced the rates of lethal chromosome breaks and SLRLs induced by EMS in spermatozoa. The level of protection ranged from 20% to 35–70% respectively.

The response of repair-deficient females to the same AMs was unstable or even absent. In the second experimental set, adult males were treated with AM (5–10mM) and EMS (10mM) step by step and then a series of broods was carried out. SLRL frequencies were tested at different spermatogenesis stages, namely, in repair-inert spermatozoa (in the first brood) and repair-active pre-meiotic cells (in the fourth and fifth broods). It should be emphasised that the protective effect was

observed in pre-meiotic repair-proficient germ cells only. In the third experimental set, male larvae were pre-treated with AMs (10–30mM), whereas adults were exposed to EMS (10–25 mM). In this case, the AMs tested sufficiently decreased the level of EMS-induced dominant lethality, sex-chromosome losses and SLRLs in repair-proficient males, but not in repair-deficient ones. In all approaches, repair-proficient germ cells were sensitive to the AMs, with chemically induced mutational events of any kinds being reduced.

The deficiencies in excision repair systems led to decreased sensitivity of both oocytes and male germ cells to the antimutagenic action. All the mentioned data indicate that 1,4-DHP derivatives are able to modulate repair processes involved in chemical mutagenesis in germ cells.