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Factors affecting the induction of micronuclei at low doses of X-rays, MMS and dimethylnitrosamine in mouse erythroblasts

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Abstract

In erythrocytes from mouse bone marrow the time schedule of micronucleus formation in relation to the last DNA synthesis was investigated by [^{3}H]thymidine labelling in the autoradiographic technique.

The results suggest that micronuclei can be produced both in the G 2 and S periods by X-irradiation. Furthermore, X-rays had a delaying effect on the cell cycle leading to a pronounced under-estimation of the doseâ€"effect curve at higher dosages. Even when the cells were harvested as late as 30 h after irradiation, the full effect had most likely not yet appeared at dosages over 100 rad. Combined treatment with caffeine did not influence the doseâ€"effect curve of X-rays, indicating no influence of a caffeine-sensitive repair mechanism.

The induction of micronuclei by MMS, in contrast with the effect of X-rays, seems to have been restricted, at least predominantly, to the period of DNA synthesis. The doseâ€”effect relation of MMS was characterized by a threshold giving a weaker effect than expected at low doses. Pretreatment with caffeine enhanced the effect of MMS at high but not at low doses, suggesting an error-free repair process operating at low doses and an error-prone and caffeine-sensitive repair at higher doses. The extent of alkylation in the bone-marrow cells was linear with respect to injected dose of MMS both in the presence and absence of caffeine.

Pretreatment with phenobarbital reduced the effect of MMS sixfold, which can be explained by a reduction of alkylation found in the bone marrow. This result is in agreement with the enhanced excretion of MMS or its metabolites into urine and bile after pretreatment of the mice with phenobarbital. DMN had no measurable effect on the frequency of micronuclei. However, in the presence of caffeine a significant effect was observed, which was roughly of the same magnitude for the two dosages used. Pretreatment with phenobarbital also indicated a synergistic effect between DMN and phenobarbital. The treatment with DMN, phenobarbital and caffeine together gave a frequency of micronuclei not different from the control level, suggesting some antagonistic action between phenobarbital and caffeine.

The indication that DMN is caffeine-sensitive at low dosages, whereas MMS is not, might be related to the difference in the alkylating properties of these chemicals.

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Abbreviations

DMN, dimethylnitrosamine; LEC, lowest effective concentration; MMS, methyl methanesulphonate; MNNG, *N*-methyl-*N*â€²-nitro-*N*-nitrosoguanidine; PB, phenobarbital

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