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Comparative characteristics of in vitro micronucleus test and conventional chromosomal aberration test in CHL cells

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We examined the in vitro micronucleus (MN) test as an alternative method for the conventional chromosomal aberration (CA) test in the early drug development stage. In a preliminary study, the clastogenic activity of mitomycin C or cyclophosphamide was evaluated by the in vitro MN test in the presence or absence of the cytokeratin inhibitor cytochalasin B (Cyt-B). Cytotoxicity was assessed using a cytokinesis-block proliferation index in the presence of Cyt-B and ATP assay in the absence of Cyt-B. As a result, the significant MN induction with the same magnitude of cytotoxicity was observed under both conditions. Based on these results, we selected the method without Cyt-B to avoid the interaction of test compounds with Cyt-B. Afterward, the characteristics between the in vitro MN test and conventional CA test was compared among twelve compounds which were synthesized in our company. In the conventional CA test, five structural aberration inducers, one polyploidy inducer, three structural abnormality and polyploidy inducers, and three non-inducers were classified. These results were completely consistent with those of the in vitro MN test (concordance rate: 100%). Although the action of specific polyploidy inducers was not considered to be detected in the MN test, some of the compounds employed showed significant MN induction. In addition, the MN inducing dose in the in vitro MN test was clearly lower than the polyploidy inducing dose in the CA test. The above results suggest that the in vitro MN test may detect aneugenetic activity of the compounds identified as a polyploidy inducer in the CA test.

In vitro小核試験と染色体異常試験の特性比較
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Induction of chromosome aberrations by a combination of sodium nitrite and antioxidants in cultured Chinese hamster cells

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Keywords: Sodium nitrite; Antioxidants; Chromosome aberrations; Synergistic effect

It is well known that the secondary or tertiary amino compounds and nitrite react under acidic conditions to form nitrosamines. It is also known that ascorbic acid or phenolic antioxidants such as catechol inhibit the formation of nitrosamines. On the contrary, a long-term administration of ascorbic acid or catechol in a combination with sodium nitrite induced hyperplasia or papillomas in a forestomach of rats. To clarify mechanisms of this forestomach carcinogenesis, synergistic effects of sodium nitrite and ascorbic acid were cytogenetically investigated in Chinese hamster CHL cells. Simultaneous short-term treatment with sodium nitrite and ascorbic acid induced chromosome aberrations considerably, in spite of the fact that no chromosome aberrations were observed in the cells after treatment with sodium nitrite or ascorbic acid alone. A similar experiment was performed with sodium nitrite and catechol. Catechol induced chromosome aberrations to the cells at a low frequency by itself, but it enhanced an incidence of the aberrations significantly when combined with sodium nitrite. These findings suggest that the induction of chromosome aberrations by the combination of nitrite and the antioxidants is probably one of the factors that result in forestomach cell proliferation in rats.

チャイニーズハムスター培養細胞を用いた亜硝酸ナトリウムと抗酸化剤の複合処理による染色体異常誘発
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