CYTOGENETIC ACTION OF ASPIRIN IN A HUMAN LYMPHOCYTE CULTURE

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In human lymphocyte cultures treated with aspirin in concentrations of 10, 100, 200, and 300 μg/ml in the G_0 stage of the cell cycle and in concentrations of 10, 50, 100, 500, and 1000 μg/ml for 1 h in the S stage the frequency of induced chromosomal aberrations was significantly higher than in the control. After treatment with aspirin in the G_1 stage a significant difference was found only with aspirin concentrations of 50 and 500 μg/ml, and if treated in the G_2 stage, in concentrations of 10, 50, and 100 μg/ml. No linear relationship could be found between the cytogenetic effects of aspirin and its dose.

KEY WORDS: aspirin; chromosomal aberrations.

Previous clinical investigations showed that aspirin significantly increases the number of chromosomal aberrations in the lymphocytes of patients with rheumatic fever [1].

The object of the present investigation was to make an experimental analysis of the frequency of chromosomal aberrations in lymphocytes in stages G_0, G_1, S, and G_2 of the cell cycle in order to establish a possible dose dependence of the cytogenetic effect of aspirin.

EXPERIMENTAL METHOD

Blood was cultured in the usual way [2]. Blood from clinically healthy donors aged 27-29 years and from three patients with allergic diseases of the heart aged 28-30 years was used. Culture continued for 58 h. Chromosomal aberrations were analyzed in the metaphase stage; aberrations of chromatid and chromosome types were counted. Before the investigation, the preparations were numbered and their identity disclosed only before the final analysis of the results. Statistical analysis of the results was carried out by the χ^2 method.

EXPERIMENTAL RESULTS

Aspirin in concentrations of 10, 100, 200, and 300 μg/ml, if acting on the G_0 stage without rinsing, induced chromosomal aberrations in the proportions of 2.6, 3.3, 3.3, and 3.8%, significantly higher than the control level of 1.4% ($P < 0.05$). In the G_1 stage (12 h after the beginning of cultivation, exposure for 1 h then rinsing off) aspirin in concentrations of 10, 50, 100, and 500 μg/ml also induced chromosomal aberrations to the number of 2.4, 4.1, 3.8, and 5.8% respectively; a significant excess over the control (1.6%) was obtained with concentrations of 50 and 500 μg/ml ($P < 0.05$). In the S stage (28 h after the beginning of culture, exposure for 1 h, rinsing off) aspirin in concentrations of 10, 50, 100, 500, and 1000 μg/ml induced chromosomal aberrations in 3.8, 2.9, 2.8, 3.5, and 3.6% of cases; the excess over the control (1.3%) was significant ($P < 0.05$). In the G_2 stage (54 h from the beginning of cultivation, without rinsing) aspirin in concentrations of 10, 50, 100, and 500 μg/ml induced chromosomal aberrations in numbers of 3.7, 3.3, 3.6, and 2.9%, significantly higher than the control (1.4%) with doses of 10, 50, and 100 μg/ml. In these experiments, with aspirin concentrations close to the therapeutic level (100-200 μg/ml), chromosomal aberrations

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were induced at the G_0 and S stages, and their level was statistically significantly higher (3-4 times) than the control. The frequency of chromosomal aberrations in a culture of lymphocytes from a healthy donor and from patients with allergic diseases of the heart was the same ($P > 0.05$). Of the 316 aberrations detected, 70.9% were chromatid breaks, 28.2% were isochromatid breaks, and 0.9% were aberrations of the exchange type, i.e., the principal type of chromosomal aberrations induced by aspirin were chromatid breaks. The fact that the frequency of chromosomal aberrations did not depend on the dose of aspirin can be attributed to its effect on the permeability of the cell membranes. It can be concluded from these findings that the effect of aspirin in a dose of 10 μg/ml differs only slightly from its effect in a dose of 1000 μg/ml. Evidently 10 μg/ml is the minimal concentration of aspirin at which the membrane permeability is sharply reduced, preventing further penetration of the drug into the cell and the nucleus. This hypothesis requires further detailed investigation, for the solution to this problem could shed light on the fine mechanisms of action of aspirin (including the mechanisms of its antiinflammatory action). The results of the present experiments, demonstrating the weak mutagenic action of aspirin, agree with data obtained by other workers who have studied the cytogenetic activity of aspirin in cultures of lymphocytes [3] and of skin fibroblasts of healthy donors [4].

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