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제 목	Effects of indomethacin and arachidonic acid on sister chromatid exchange induction by styrene and styrene-7, 8-oxide		
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1. Introduction

Styrene is converted to styrene-7,8-oxide, an activated metabolite, by oxyhemoglobin and cytochrome P-450 species. The metabolism of styrene is known to involve glutathione S-transferase-catalyzed conjugation of styrene-7,8-oxide with glutathione.

The purpose of the present paper was to study the possible role of prostaglandin endoperoxide synthase(PES) in the metabolism of styrene and styrene-7,8-oxide-induced sister chromatid exchanges(SCEs). If PES favors the formation of styrene glutathione adducts, styrene-induced SCEs would be expected to be enhanced by indomethacin and suppressed by arachidonic acid.

2. Materials and Methods

Heparinized whole-blood from a health male donor(28 yr, smoker) was used for the lymphocyte cultures in the present study.

Whole-blood lymphocyte cultures were applied as described by Norppa et al.(1985). Briefly, 0.3 ml of heparinized whole-blood was injected into a sterilized 30-ml screw-capped glass bottle containing 6 ml of growth medium. Immediately after adding blood to the cultures, the cells were treated with 0.5 or 1 mM styrene, or 50 or 100 μM styrene-7,8-oxide as final concentrations. 75 or 150 μM indomethacin or the same concentrations of arachidonic acid was injected into some of the cultures simultaneously with styrene or styrene-7,8-oxide. After the treatment, the cells were incubated, caps tightly closed, for 72 h. Colchicine was injected into the cultures at 2.5 h before harvest. The harvested cells were fixed, and were kept at -20℃ overnight. Slides were stained by the fluorescence-plus Giemas method.

The number of SCEs was counted in 25 harlequin-stained cells from each of the duplicate cultures on coded slides. ANOVA was employed for the comparison of SCE frequency between the treatments.

3. Results

As expected, both styrene(0.5 and 1 mM)and styrene-7,8-oxide(50 and 100 μM) induced SCEs in a dose-dependent manner. Indomethacine or arachidonic acid did not affect the frequency of SCEs at any concentrations used.

Simultaneous treatment with indomethacin at 75 and 150 μM slightly but significantly enhanced SCE induction(by 16-32%;$p<0.05$- $p<0.001$) at both concentrations of styrene tested, in comparison with styrene alone. The higher concentration of indomethacin was more effective than the lower in promoting styrene-induced SCEs, the difference between the two concentration being statistically significant($p<0.05$) at 1 mM styrene. Similar findings were obtained with styrene-7,8-oxide, although the enhancing effect of indomethacin on styrene-7,8-oxide-induced SCEs was statistically significant($p<0.01$-0.001) only at 150 μM indomethacin; the difference between the two concentrations of indomethacin was statistically significant($p<0.05$) at 50 μM styrene-7,8- oxide.

SCEs induced by styrene and styrene-7,8-oxide were decreased by simultaneous treatment with arachidonic acid. The effect was statistically significant($p<0.01$) only at 150 μM arachidonic acid with 1 mM styrene and 100 μM styrene-7,8-oxide, with a 15-20% reduction in SCEs.

4. Discussion

An enzyme system that could influence the genotoxicity of styrene is PES which has been reported to be involved in the *activation of a number of genotoxic compounds.* Accordingly, indomethacin effectively prevented mutagenicity of benzene, diethylstilbestrol, benzo[a]pyrene(BP), and 7,12-dimethylbenz[a]anthracene(DMBA). Arachidonic acid, on the other hand, potentiated SCE induction by PB and DMBA.

In the present study, indometnacin promoted and arachidonic acid suppresed SCE induction by both styrene and styrene-7,8-oxide. Consequently, our results also indicate the involvment of PES in the metabolism of styrene and styrene-7,8-oxide. However, the present results do not support a role for PES in the metabolic activation of styrene. On the contrary, the observation that styrene-induced SCEs are potentiated by indomethacin but suppressed by arachidonic acid lends support to an *inactivating* role of PES in styrene metabolism.