SENSITIVITY OF EMBROYONIC LUNG TISSUE OF A AND C57B1 MICE IN ORGAN CULTURES TO TRANSPLACENTAL ACTION OF URETHANE

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The transplacental action of urethane in a dose of 80 mg was studied in organ cultures of embryonic lung tissue from mice of lines A (high cancer incidence) and C57B1 (low cancer incidence). Preadenomatous changes were found in the experimental lung tissue culture of A mice: diffuse hyperplasia of the epithelium (36.2%), focal hyperplasia (32.8%), and adenomas (15.5%). Diffuse and focal hyperplasia of the epithelium developed in 39.6 and 8.0% of cases, respectively, in embryonic lung tissue cultures of C57B1 mice, but no adenomas appeared. The results indicate correlation between the sensitivity of the embryonic lung tissue of these strains of mice to the transplacental carcinogenic action of urethane in experiments in vivo and in vitro. Organ cultures can thus be used as a model to study transplacental carcinogenesis in the lungs.

Adenomas of the lungs were shown previously [1] to appear and develop in organ cultures of embryonic lung tissue of mice of line A in response to the transplacental action of urethane. Later, the writer and other workers observed the development of various hyperplastic growths of the epithelium in response to the transplacental action of carcinogens in organ cultures of embryonic lung tissue of other animals with a varied predisposition to the development of lung tumors [2-5, 7]. Experimental data and clinical observations indicate that young animals and, in particular, embryos, are more sensitive to carcinogenic agents. The question thus arises of the effects of transplacental action of a carcinogen on the embryo of insusceptible animals, with a low incidence of spontaneous carcinoma, during organ cultivation.

To study this problem the transplacental action of urethane was compared in organ cultures of embryonic lung tissue from mice of lines A and C57B1, with high and low incidence of spontaneous carcinoma, respectively.

EXPERIMENTAL METHOD

Pregnant mice of lines A and C57B1 were given subcutaneous injections of urethane in the last third of pregnancy for 3 days before explantation of the embryonic lung tissue for organ culture. The total dose injected was 80 mg per mouse. Cultures of the lungs of intact mice of the corresponding lines acted as the control. Full details of the method were described previously [1]. Altogether 114 experimental cultures (56 from line C57B1 and 58 from line A) and 167 control cultures (112 from line C57B1 and 55 from line A) were studied.

EXPERIMENTAL RESULTS

The morphological picture and dynamics of growth and differentiation of control cultures of the embryonic lung tissue in the C57B1 mice were approximately the same as those of line A mice in this

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series of experiments and in those described earlier [1]. However, the survivial rate of the cultures was higher than for line A. During cultivation for 19 days, whereas some explants of embryonic lung tissue of line A mice retained their normal structure, 29 of the 55 cultures (52.7%) showed degenerative changes, compared with 37 of the 112 cultures (33.0%) from line C57B1 similarly affected. The difference was statistically significant ($P<0.01$).

In the experimental cultures of embryonic lung tissue of the C57B1 mice hyperplasia of the epithelium developed in the course of 12 days: diffuse in 22 (39.6%) and focal in five (8.0%) cases. Degenerative changes were observed in 19 (33.8%) of the 56 cultures; i.e., their frequency was the same as in the control.

In experimental cultures of embryonic lung tissue of line A mice this same dose of urethane induced the development of diffuse hyperplasia of the epithelium in 21 (36.2%) and focal hyperplasia in 19 (32.8%) of the 58 explants. Adenomas and adenomatous proliferation developed in nine explants (15.5%). In one case an adenoma was found as early as on the second day of cultivation, i.e., 3 days after the first injection of urethane into the pregnant animal. In the experimental cultures, degenerative changes were completely absent. This indicates the marked growth-stimulating action of urethane. A similar effect has been observed previously by the author and other workers as a result of the transplacental action of various carcinogens in organ cultures of embryonic lung and kidney tissues of mice, rats, and golden hamsters [4, 7, 8]. It must be emphasized that neither adenomas nor preadenomatous growths were observed in cultures of embryonic lung tissue of C57B1 mice.

The comparative study of organ cultures of embryonic lung tissue of these two lines of mice thus showed that the embryonic lung tissue of intact C57B1 mice is cultivated more successfully than embryonic lung tissue of A mice. This is perhaps explained by some special feature of the lung tissue of these lines which, in turn, determines their sensitivity to the carcinogenic action of urethane. The sensitivity of the embryonic lung tissue of C57B1 mice to the transplacental carcinogenic action of urethane was much lower than that of the A mice. This was reflected, first, in the absence of a growth-stimulating action of urethane in the experimental C57B1 cultures and its presence in the A cultures. Second, the carcinogenic effect of urethane in the A cultures was much greater than in the C57B1 cultures. It will be noted that the first and least specific stage of tumor development [6], i.e., diffuse hyperplasia, occurred in the C57B1 cultures at a frequency comparable with that in the A cultures, whereas the second state – focal hyperplasia – was observed in only solitary cases. No adenomas developed in the C57B1 cultures.

During organ cultivation the embryonic lung tissue of line A mice thus proved to be more susceptible to the transplacental carcinogenic action of urethane than the corresponding C57B1 tissue. Because of this correlation between the sensitivity of the lung tissue to the action of the carcinogen in experiments in vivo and in vitro, organ cultures can be used with success as a model with which to study transplacental carcinogenesis.

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