EFFECT OF ESTROGEN ON THE UTERUS OF VARIOUS STRAINS OF MICE

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1,2-Dimethylhydrazine (DMH) induces the appearance of sarcomas of the uterus in a high percentage of CBA mice, whereas in C57BL/6 and C3HA mice, under the same conditions, these tumors arise only occasionally or not at all [4]. Definite interlinear differences therefore exist in sensitivity to this agent. It has been shown that these tumors are hormone-dependent: injection of estradiol dipropionate (ED) accelerated the appearance of sarcomas of the uterus induced by DMH in CBA mice [3]. It was also shown that injection of DMH into CBA mice caused persistent estrus, whereas in C57BL/6 and C3HA mice persistent estrus was not observed; on the contrary, prolonged diestrus was observed in these strains [2]. The persistent estrus arising in CBA mice under the influence of DMH indicates a constant, and not cyclically changing level of endogenous estrogens, which evidently would promote the development of sarcomas of the uterus, but predominance of the diestrus phase in C3HA and C57BL/6 mice after exposure to this carcinogen indirectly indicates a low level of endogenous estrogens, which may perhaps partly determine the resistance of mice of these strains to the development of uterine sarcomas.

All these facts suggest significant differences in the response of these lines of mice to estrogen. The aim of this investigation was to study the reaction of the uterine tissue of CBA mice, which are sensitive to induction of sarcomas of the uterus by DMH, and of C57BL/6 and C3HA mice, resistant to induction of sarcomas of the uterus, to ED.

EXPERIMENTAL METHOD

Female CBA, C57BL/6, and C3HA mice aged 12 weeks underwent bilateral ovariectomy, after which the vaginal smears were studied for 2 weeks. Animals whose cycle had ceased were used in the experiments. Mice of each strain were divided into four groups with 6-10 mice in each group. Group 1 was the control, whereas groups 2, 3, and 4 received ED in olive oil by subcutaneous injection of a dose of 0.02, 0.01, and 0.05 μg/10 g body weight respectively for 3 days. In all the animals vaginal smears taken in the morning at the same time of day were tested from the first day of injection of ED. The mice were killed with ether at the time of maximal reaction of the vaginal mucosa to EP; the uterus was removed, freed from fat, washed free from blood with 0.9% NaCl, and weighed. The relative mass of the uterus (in % of the animal's body weight) was determined To compare the relative mass of the uterus of the different strains of mice, for all of which the control relative mass of the uterus was known, this value was expressed as a ratio of its own control (average mass). The statistical analysis was carried out by the Wilcoxon—Mann—Whitney method.

EXPERIMENTAL RESULTS

EP in a dose of 0.05 μg/10 g body weight after only 3 days caused the appearance of abundant scales in the vagina of 100% of CBA and C57BL/6 mice and 89% of C3HA mice (Fig. 1). The relative mass of the uterus was higher ($p < 0.01$) than in the control in mice of all the different strains, However, the degree of this increase was significantly ($p < 0.01$) greater (0.4389) than in the C57BL/6 (0.2570) and C3HA (0.2698) mice (Table 1).

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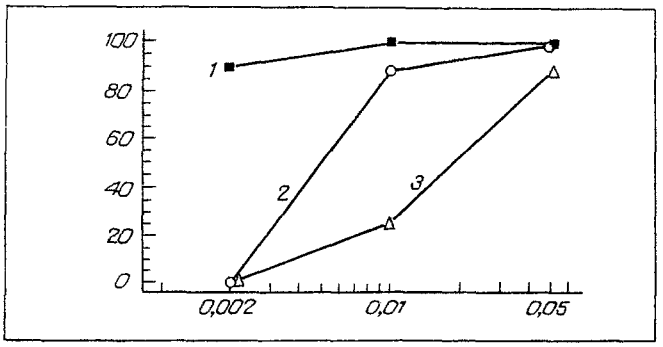

Fig. 1. Appearance of pseudoestrus after injection of estrogen in different doses into mice of different strains. Abscissa, dose of ED (in μg/10 g body weight); ordinate, number of mice with pseudoestrus (in %). 1) CBA; 2) C57BL/6; 3) C3HA.

TABLE 1. Changes in Relative Mass of Uterus (in % of body weight) after Injection of ED (M ± m)

Strain of mice	Control	Dose of ED, µg/10 g body weight		
		0,002	0,01	0,05
CBA	0,1096± 0,0244	0,1705± 0,0302*	0,3984± 0,0733*	0,4389± 0,1219*
C57Bl/6	0,0904± ±0,0148	0,0711± ±0,0084	0,1578± ±0,0339	0,2570± ±0,0514*
C3HA	0,0829± ±0,0198	0,0989± ±0,0260	0,1657± ±0,0264	0,2698± ±0,0615*

Legend. Asterisk indicates values for which $p < 0.01$ compared with corresponding control.

With a dose of 0.01 μg/10 g body weight, the greatest number of scales was observed on the 4th day after the beginning of the experiment in 10% of CBA mice and in 8970 of C57BL/6 mice, whereas in C3HA mice, estrus appeared in only 25% of the animals (Fig. 1). ED in this dose also caused a significant ($p < 0.01$) increase in the relative mass of the uterus in all strains of mice studied. However, just as in the case with a dose of 0.05 μg, the relative mass of the uterus in the CBA mice was significantly higher ($p < 0.01$) than in resistant strains (0.3984 compared with 0.1578 and 0.1657).

After injection of ED in a dose of 0.002 μg/10 g body weight no vaginal scales appeared on the 3rd and 4th days. They first appeared on the 6th day in 90% of the CBA mice, whereas no vaginal scales could be found at the times tested in any of the C57BL/6 and C3HA mice (Fig. 1). The relative mass of the uterus showed the same picture: only in CBA mice did the estrogen induce a significant ($p < 0.01$) increase in the relative mass of the uterus compared with intact CBA (0.1705 and 0.1096) or compared with experimental C57BL/6 (0.0711) and C3HA (0.0989) mice. In the C57BL/6 and C3HA mice the relative mass of the uterus was indistinguishable from their own control (Table 1).

These results are evidence of significant differences in the response of the uterus of CBA, C57BL/6, and C3HA mice to administration of ED. These differences were manifested as the greater reactivity of the uterus of CBA mice than that of the other two strains, and which was expressed, first, as a lower threshold of sensitivity of CBA mice to ED, a sharper increase in weight of the uterus in response to equal doses, and second, a lower threshold of onset of pseudoestrus under the influence of ED.

These results agree with those of chronic experiments on induction of sarcomas of the uterus by DMH in the mice of these same three strains: under identical conditions they appeared in 40.7% of CBA mice, in 2.7% of C57BL/6 mice, and not at all in C3HA mice [4]. Meanwhile, in mice of these same strains no difference was found in the frequency of induction by DMH of tumors of the large intestine and skin [4], i.e., differences in the frequency of sarcomas of the uterus are evidently associated, not with a difference in the sensitivity of the mice to DMH, but with local differences in the hormonal

status, most probably a higher level of estrogen receptors in the uterus of CBA mice than of CBA57BL/6 and C3HA mice It has also been shown that injection of DUH into the sensitive CBA strain raises the level of estrogen receptors [1], which also increases the sensitivity of the uterus to tumor development in the present of additional injection of ED.

Our results thus suggest that the uterine tissue of CBA mice is significantly more sensitive to estrogen than the uterus of C57BL/6 and C3HA mice, and this may be one cause of induction of hormone-dependent sarcoma of the uterus in CBA mice, and also of the significant potentiation of this induction by injection of exogenous hormone.

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DYNAMICS OF PROLIFERATIVE ACTIVITY OF ORGANOTYPICAL EPITHELIAL-MESENCHYMAL RECOMBINANT CULTURES FROM EMBRYONIC LUNGS OF INTACT AND URETHANE-TREATED MICE

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Transplacental exposure of the developing organism to chemical carcinogens takes place against the background of active intercellular and intertissue interaction, regulating the processes of morphogenesis, proliferation, and differentiation. In normal ontogeny the mesenchyme is an inducer of development of the epithelial anlage and, in particular, of the lungs [6, 10]. The role of epithelial-mesenchymal interaction and of each of these tissue components in induced carcinogenesis of the lungs and other organs is unknown. To study this problem we developed an experimental model, consisting of a culture of organotypical epithelial-mesenchymal recombinance, obtained from dissociated lungs of intact and experimental mouse embryos, receiving a pulmonotropic carcinogen transplacentally [4, 7, 9]. One of the early stages of induced adenoma of the lungs is an increase in proliferative activity of the epithelial cells [2, 5, 8]. We used this criterion to study epithelial-mesenchymal interactions and the role of each of these tissue components in the realization of transplacental carcinogenic effects.

This paper describes a study of the dynamics of proliferative activity of cells in cultures of organotypical epithelial-mesenchymal recombinants, formed from dissociated embryonic lungs of line A mice, either intact or receiving urethane transplacentally.

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