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SUPPRESSION OF EXPERIMENTAL LIVER TUMORS BY ESTROGEN TREATMENT OR CASTRATION IN MALE RATS

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It has been reported that the incidence of liver cancer in human is markedly sex-differentiated, with a much higher frequency in men than in women. In experimental animals, male have higher incidence of liver tumor than female in carcinogen-induced tumors as well as spontaneous tumors. Our studies were investigated to examine the modifying effects of sex hormone in the diethylnitrosamine (DEN)-induced liver tumor model. One hundred twenty male F344 rats were randomly divided into experiment I and experiment II. Animals of each experiment were divided into four groups. For induction of liver tumors, mini-osmotic pump providing a continuous infusion (0.5$\mu\ell$/hour for 2 weeks) of DEN dissolved in dimethyl sulphoxide (DMSO) at a dose level of 47.5μg (50$\mu\ell$) or 23.75μg (25$\mu\ell$) /pump was implanted into the abdominal cavity of each animal in experiment I and experiment II, respectively, under ether anesthesia at 6 weeks of age. At 5 weeks of age, the animals of group 1 were having sham-operation and the animals of group 2 were having castration. Silastic tube (Silicon Medical Tube No. 2, 100-2N, Keneka Medix Corporation, Japan; internal diameter 2mm) containing 1μg or 10μg estradiol-3-benzoate (EB; CAS No. 50-50-0, Sigma E8515) was implanted subcutaneously in each animal of group 3 and group 4, respectively and it was change every 4 weeks until sacrifice. All animals were killed at 26 weeks after DEN treatment. Body weights of the animals of group 2, 3, 4 in each experiment had significant lower value compared with those of group 1 ($p<0.05$). Comparing with group 1, the animals of group 2, 3, 4 in each experiment had the decrease weight of liver, prostate, seminal vesicle and coagulating gland ($p<0.05$), but had the increase weight in adrenal gland and pituitary gland ($p<0.05$). In experiment I, incidences of liver tumors in group 1 (DEN alone), group 2 (DEN +castration), group 3 (DEN +EB 1μg) and group 4 (DEN +EB 10μg) were 100% (15/15), 93.3% (14/15), 85.7% (12/14) and 66.7% (10/15), respectively,

showing that value of group 4 was significantly different from that of group 1. Tumor multiplicities of group 1, 2, 3 and 4 were 5.47±0.73, 2.80±0.51, 2.07±0.41 and 1.67±0.46, respectively, showing castration or EB treatment reduced number of liver tumors significantly ($p<0.001$). In experiment II, incidences of liver tumors in group 1 (DEN alone), group 2 (DEN +castration), group 3 (DEN +EB 1μg) and group 4 (DEN +EB 10μg) were 33.3% (5/15), 6.7% (1/15), 0% (0/15), 6.7% (1/15), respectively and tumor multiplicities of group 1, 2, 3, and 4 were 0.33±0.13, 0.07±0.07, 0, 0.07±0.07, respectively, also showing castration or EB treatment reduced liver tumors. In estrogen receptor (ER) α expression detected by immunohistochemistry and Western blotting, ERα expressions were existed in normal adjacent liver cells but were lost in tumor cells, and it seemed that the loss of ERα may be associated with liver tumor development. Together with these results, we conclude that the modulation of sex hormones by surgical castration or EB treatment decrease the DEN-induced liver tumors, and it suggests that liver tumors may be inhibited by estrogen but may be promoted by androgen, and liver carcinogenesis may be associated with the loss of ERα.

keyword : Carcinogenesis, Liver tumor, Diethylnitrosoamine (DEN), Castration, Estrogen