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THE INFLUENCE OF HYPER- AND HYPOTHYROID STATES ON THE INCIDENCE OF 3-METHYLCHOLANTHRENE-INDUCED TUMOR IN DDY MICE.

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ABSTRACT

In female DDY mice, the incidence of 3-methylcholanthreneinduced skin tumors was increased in the hypothyroid state produced by the administration of Endojodin or 1-methyl-2-mercaptoimidazole ($p < 0.01$) and decreased in the hyperthyroid state produced by L-thyroxine administration ($p < 0.05$) compared with controls. The calorigenic effect or the direct action of thyroid hormones may correlate with tumor induction in mice.

Key words: Skin tumor- Tyroid hormone-DDY mice

INTRODUCTION

Several investigators have reported that various hormones influence the development of tumors in animals. Particularly, thyroid hormones, sex hormones and prolactin are of critical significance in the inducation of tumors. Kellen (1972) had mentioned that the evidence concerning hyper- and hypothyroidism in relation to cancer growth is even more controversial, and no general conclusion seems possible.[1)] The finding that the incidence of carcinoma in hyperthyroid patients in less than that in normal patients led to an experiment of thyroid hormone therapy. It was of interest, therefore, to determine the incidence and growth rate of carcinomas influenced by the different hormonal environments.

We present here that the incidence of skin carcinoma in mice produced by 3-methylcholanthrene increased in the hypothyroid state induced by Endojodin or methylmercaptoimindazole treatment, but in the hyperthyroid state induced by L-thyroxine administration the incidence decreased.

MATERIALS AND METHODS

358 DDY female mice, 12 weeks of age at the start of the experimental period, were divided into 4 groups as noted in Table 1 and maintained on a regular diet (Oriental Yeast Co., Tokyo) for 12 weeks. Hyperthyroid state was produced by giving L-thyroxine (T_4, 200 g/dl)

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of drinking water ad libitum and hypothyroid state was produced by intraperitoneal injection of 0.06 ml of Endojodin (Hexamethyl diaminoisopropanol-diiodide concentration iodide 0.118 g/ml, Bayer Co. Ltd) (20 w/v% solution) every other day or by giving 1-methyl-2-mercaptoimidazole (MMI) (20 mg/dl) of drinking water.

0.05 ml of 3-methylcholanthrene (MCA) (3 mg was dissolved in 1 ml of acetone) was administered by painting the skin on the shaved back of each mouse twice a week for 3 months.

The observation period to determine the tumor incidence was 3 months. Then all animals were killed and weighed, but these which died during the experiment were deleted from the final result. The tumors were extirpated, weighed and examined histopathologically.

Blood samples were collected by ocular sinus puncture under light ether anesthesia and were centrifuged. The sera thus obtained were frozen and stored until assayed. Serum triiodothyronine (T_3) and thyroxine (T_4) levels were determined by a double antibody radioimmunoassay technique using a commercial kit (Dainabbott Laboratories).

RESULTS

A retardation of body growth of mice was observed in Endojodin, MMI and L-T_4 treatment (8% decrease in mice treated with Endojodin, 14% in those with MMI and 19% in those with L-T_4, as compared with control mice). Histologically, all the skin tumors developed in the mice were found to be of squamous cell carcinoma.

The animals which received Endojodin or MMI showed a significant increase in the incidence of skin cancers at both the 2nd and 3rd month, as compared with the control animals. On the contrary, the slight decrease in incidence of the tumor was observed in mice receiving L-T_4, for 2 months, but 3 months after L-T_4 treatment there was no significant difference in tumor incidence between T_4 the animals treated with T_4 and the control animals. In this experimental period, hyper- or hypothyroid state gave statistically no significant effect on the tumor growth compared with the control (Table 1).

DISCUSSION

There are many reports that calorigenic effects of various thyroid states influence the incidence and the rate of growth of breast cancer which is hormone dependent. Jull *et at.*, (1960),[2] Eskin *et al.* (1968),[3], and Chen *et al.* (1977)[4] indicated the increment in mammary tumor growth, accompanied by the significant elevation of serum prolactin levels, and this tumor growth was inhibited by 2-bromo-α-ergocryptine (CB-154) which blocked prolactin release from the anterior pituitary. From our observation about skin cancer produced by MCA, it was evident that the hypothyroid state shortened the latent periods in induction of tumors, while the hyperthyroid state was contrary. However tumor incidence was not always parallel with serum thyroid hormone level (Table 1, 2).

Baker and Yaffe (1975)[5] have reported that in hyperthyroid rats fewer chemically induced tumors developed which were hormone-independent. Thus, the other mechanism for tumor induction or growth, namely the calorigenic effect or the direct action of thyroid hormones, can not be completely ruled out.

Table 1. Incidence of MCA induced Skin Tumor in mice given Endojodin, MMI and T_4

Treatment	No. of mice		No. of mice with tumors		Tumor weight (g) Mean ± SD.
	Initial	Effective	2 months	3 months	
Control	110	109	41 (38%)	64 (59%)	0.77 ± 0.996
Endojodin	140	135	88* (65%)	131^{4}* (97%)	1.45 ± 1.306
MMI	35	30	19^{2}* (63%)	25^{5}* (83%)	1.06 ± 1.153
T_4	60	54	13^{3}* (24%)	37 (69%)	0.76 ± 0.704

a ~ e: Statistically Significant $\left\{ \begin{array}{l} *, {}^{4}*, {}^{5}* : p < 0.01 \\ {}^{2}* \quad : p < 0.02 \\ {}^{3}* \quad : p < 0.05 \end{array} \right\}$ (Student's t-test) as compared with control.

Table 2 Serum T_3 and T_4 Levels in mice Receiving Endojodin, MMI and L-T_4.

Treatment	T_3 (ng/dl)	T_4 (μg/dl)
Control (n = 25)	108.3 ± 4.1	3.4 ± 0.2
Endojodin (n = 9)	93.4 ± 5.7*	2.2 ± 0.3^{4}*
MMI (n = 16)	83.3 ± 11.1^{2}*	1.6 ± 0.2^{5}*
T_4 (n = 16)	230.8 ± 46.3^{3}*	11.4 ± 1.9^{6}*

Each. value represents mean ± SE.

a ~ f: Statistically Significant $\left\{ \begin{array}{l} * \sim {}^{4}* : p < 0.05 \\ {}^{5}*, {}^{6}* : p < 0.01 \end{array} \right\}$, as compared with the control, respectively (Student's t-test).

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