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EFFECT OF THYMIC AND PINEAL POLYPEPTIDE FACTORS ON RADIATION CARCINOGENESIS

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KEY WORDS: radiation carcinogenesis; thymic factor; pineal factor; antitumor effect.

During tumor growth *in vivo* the reactions of cellular immunity and functional activity of T lymphocytes are depressed [11, 13]. If the disturbed function of the T lymphocytes is restored by means of certain drugs such as levamisole, phenformin, or epithalamin in some cases growth of both spontaneous tumors and tumors induced by chemical carcinogens is inhibited [2, 7, 8, 12]. Data showing the important role of the thymus in regulation of T lymphocyte function and in antitumor immunity [11, 13] indicate the urgent importance of a study of the effect of the active factors (hormones) of the thymus on the development and growth of neoplasms.

The object of this investigation was to study the effect of a polypeptide thymic factor (thymarin), which specifically restores disturbed T lymphocyte function and reactions of cullular immunity [10], and also of pineal polypeptide factor (epithalamin), whose stimulating effect on immunity is evidently realized through its varied influence on the neuroendocrine system [4], on radiation carcinogenesis.

EXPERIMENTAL METHOD

Experiments were carried out on 148 noninbred female albino rats bred at the Research Institute of Radiation Hygiene, Ministry of Health of the RSFSR, aged 3 months, and subjected to whole-body x-ray irradiation in a single dose of 4 Gy (400 rads, RUM-17 apparatus, voltage 200 kV, current 15 mA, filters 0.5 mm Cu + 1 mm Al, focus distrance 50 cm, exposure dose rate $0.23 \cdot 10^{-3}$ A/kg (54 R/min). The animals were divided into three groups. Starting from the third week after irradiation they received 10-day courses, once a month throughout life, of 0.2 mg thymarin [10] or epithalamin [8] in 0.2 ml 0.9% NaCl solution, or the same volume of solvent (control) subcutaneously. Animals which died were autopsied and all neoplasms discovered were studied under the microscope. Student's t test and P criterion were used in the statistical analysis of the results [14]. Single wholebody irradiation of the rats in a dose of 4 Gr led in these experiments to the development of tumors in 74.1% of animals that survived until discovery of the first tumor. Administration of epithalamin had a distinct inhibitory effect on radiation carcinogensis: the frequency of appearance both of all tumors and of only malignant tumors was reduced (by 1.3 and 2.7 times respectively). The effect of the thymic factor was a little weaker than the effect of the pineal factor, and was expressed as a reduction in the frequency of malignant neoplams by 1.9 times, whereas the total frequency of tumor development showed no significant change compared with the control (Table 1; Fig. 1).

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TABLE 1. Frequency, Location, and Type of Tumors Developing in Irradiated Rats Receiving Injections of Thymic Factor (Thymarin) and Pineal

Experimental conditions	Number of rats	Number of rats with tumors	Number of rats with malignant tumors	Number of tumors		Mean length of survival of rats, days	Location and type of tumors													
							mammary gland			thyroid gland		ovary		uterus			hematopoietic system		
								fibroadenoma											
				total	malignant		adenocarcinoma	number of rats	number of tumors	adenocarcinoma	adenoma	thecoma	thecafolliculoma	polyp	adenocarcinoma	sarcoma	leukemia	lymphosarcoma	other
Irradiation + 0.9% NaCl solution	58	43 (74%)	21 (36%)	78	26	461±15	9	27	35	1	6	1	1	6	2	1	5	1	10 a
Irradiation + thymarin	36	25 (69%)	7* (19%)	42	7	456±20	1†	18	24	—	1	1	—	3	1	—	2	1	8 b
Irradiation + epithalamin	38	22 (57%)	5* (13%)	40	5	497±21	1†	16	23	—	1	—	—	8	—	—	1	—	6 c

Legend. $^{*}P < 0.05$, $^{\dagger}P$ 0.025. a) Adenoma of adrenal cortex, two pituitary adenomas, one carcinoma of male mammary gland, osteosarcoma, soft tissue sarcoma, angiosarcoma, two adenocarcinomas of intestine, one lung carcinoma; b) four pituitary adenomas, one fibroma of skin, one fibroma of soft tissues, osteosarcoma, and soft tissue sarcoma; c) three pituitary adenomas, one carcinoma of male mammary gland, two lung carcinomas.

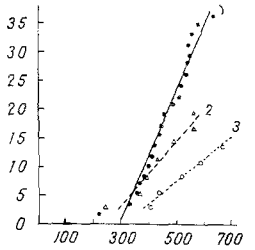

Fig. 1. Effect on thymic factor (thymarin) and pineal factor (epithalamin) on development of malignant tumors in irradiated female rats. Abscissa, days after irradiation; ordinate, number of rats with malignant tumors (in %). 1) Control; 2) thymarin; 3) epithalamin.

Both preparations significantly ($P \leqslant 0.025$) inhibited the development of mammary adenocarcinoma in the irradiated rats. An inhibitory effect of thymarin and epithalamin on the development of these neoplasms induced in female rats by administration of 7,12-dimethylbenz-(a)anthracene [3, 8] or developing spontaneously in C3H/Sn mice [5], was discovered previously. Although the frequency of appearance of fibroadenomas and fibromas of the mammary gland in animals of the control and experimental groups was the same, their mean latent period in the group of rats receiving epithalamin was 2 months longer than in the control (504 ± 23.4 and 440 ± 17.6 days, respectively, $P < 0.05$). After administration of thymarin the corresponding figure was 496 ± 28.8 days ($P > 0.05$). In irradiated rats treated with epithalamin, tumors of the thyroid gland ($P < 0.05$) and hematopoietic system ($0.05 < P < 0.08$) developed a little less frequently than in the control animals, and in no case were neoplasms of the ovaries or malignant tumors of the uterus observed (Table 1.) Thymarin had no effect on the frequency of appearance of these tumors.

In the modern view, the basis of the pathogenesis of neoplasms in an irradiated individual consists of two radiobiological effects: a change in the hereditary structure of somatic cells and the onset of irreversible changes, giving rise secondarily to continous proliferation [1]. Inhibition of cellular immunity induced by ionizing radiation makes it more likely that the transformed (malignant) cell is not eliminated, but is given the opportunity for unrestricted growth and progression. It can be tentatively suggested that disturbance of the function of the T system of immunity in the irradiated organism is connected with inhibition of thymic function and lowering of production of the endogenous thymic factor. The thymic preparation thymarin, when administered to animals, restores the immunocompetence of the T system of immunity [10], and it is evidently this which determines its inhibitory influence on carcinogenesis.

Single whole-body x-ray irradiation of female rats in doses of 3-6 Gy has been shown to lead to the development of a long-lasting syndrome of continuous estrus [9]. This state, in which the reproductive period in rats regularly culminates, can be induced by various methods in young animals also, and it is characterized by a number of hormonal shifts and disturbances of lipid and carbohydrate metabolism, and also by an increase in the frequency of development of neoplasms [6]. It can be postulated that the state of anovulation and the hormonal and metabolic shifts corresponding to it, induced in rats by irradiation, play an essential role in tumor development in them, by bringing about the realization of the stage of promotion of radiation carcinogensis. It is instructive in this connection that 85% of all neoplasms which developed in the present experiments were located in endocrine glands and reproductive organs. Administration of pineal factor, which normalizes many of the shifts and disturbances mentioned above and abolishes the phenomenon of metabolic immunodepression [4, 8], was found to have an inhibitory effect on spontaneous carcinogenesis in rats and mice [5, 7, 8], induced by chemical carcinogens [8] or by x-ray irradiation (as shown in the present investigation), and also inhibited growth of certain transplantable tumors [8]. The fact that thymic factor, which specifically stimulates T lymphocyte function, had a narrower spectrum of antitumor action than pineal factor, is evidence of the need to supplement traditional methods of immunotherapy with agents correcting the hormonal and metabolic disturbances that develop in the tumor carrier.

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EXPERIMENTAL BIOLOGY

ATYPICAL CELLS SYNTHESIZING α-FETOPROTEIN IN THE REGENERATING MOUSE LIVER

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The tumor and embryonic protein α-fetoprotein (AFP) is synthesized during normal development by yolk sac cells and by fetal hepatocytes. AFP synthesis is temporarily resumed in the regenerating liver of adult mice. The results of immunomorphologic studies at the light-optical level have led to the view that, depending on the character of the repair process, AFP can be synthesized in the adult liver by two types of cells: differentiated hepatocytes during regeneration of the liver after partial hepatectomy or a single poisoning with hepatotoxins, and by hepatite precursor cells (transitional cells and small hepatocytes) in the acute phase of chemical hepatocarcinogenesis [1]. However, an immunoelectron-microscopic study of the AFP localization in the regenerating liver of SWR mice [4] revealed synthesis of this protein not only in typical hepatocytes, but also in smaller cells similar in their ultrastructure to oval and transitional cells of the rat liver during chemical carcinogensis [11].

This paper describes a comparative electron-microscopic study of AFP containing cells in the regenerating liver of different lines of mice, using monospecific and monoclonal antibodies (AB) against AFP.

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