ONCOLOGY

Anticarcinogenic Effect of Beta Carotene on the Development of Renal Tumors in Rats Induced by 3-(αL-Arabinopyranosyl-1) Methyl-1-Nitrosourea (AMNU)

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The effect of beta carotene on AMNU-induced carcinogenesis was studied in rats. Administration of beta carotene reliably decreased both the total incidence of tumors and the incidence of renal tumors. The results are an experimental validation of the possibility of using beta carotene to lower the risk of second primary malignancies during the treatment of cancer patients with nitrosoalkylurea drugs.

Key Words: *beta carotene; tumor; kidney*

Alkylating agents, which include derivatives of embikhine, chlorobutane, cyclophosphamide, sarcolysine, thiophosphamide, and nitrosourea, are potent carcinogens that are characterized by organ-specific effects and induce numerous types of tumors, depending on the route of their administration and dose, as well as on the type and strain of laboratory animals [13].

Epidemiological studies of the carcinogenicity of these substances demonstrate an increased risk of a second primary cancer in patients after chemotherapy [1,5,6,8,9,14]. An appreciable proportion of second primary malignant tumors are leukemias, but the risk of solid tumors is also high. These data confirm the need for research devoted to the prevention of remote biological aftereffects of drugs used in cancer treatment. At present the possible anticarcinogenic role of carotenoids, specifically, beta carotene, towards squamous-cell carcinoma of the lungs [15] and skin [7,11,12] is being discussed. On the other hand, published data do not always confirm the prevalent view of carotenoids as universal anticancer agents; rather they indicate that the prophylactic value of a drug and its use in public health should be decided individually with due consideration for its role in a specific type of carcinogenesis.

MATERIALS AND METHODS

Beta carotene and AMNU synthesized at the Cancer Research Center, Russian Academy of Medical Sciences, were used in the study. Experiments were carried out with 95 outbred male albino rats weighing 180 to 200 g and on 65 females weighing 160-170 g.

The rats were kept in plastic cages, 5 animals in each, and fed a standard diet. In groups 1 and 2 (25 females and 25 males in each) AMNU was injected

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TABLE 1. Effect of Beta Carotene on Carcinogenesis in Rats Induced by AMNU

Number of rats	Group and type of exposure			
	1st: AMNU		2nd: AMNU+beta carotene	
	females (n=23)	males (n=23)	females (n=23)	males (n=20)
With tumors[1]	17 (74)	8 (35)	7 (30)*	4 (20)**
With several tumors[2]	3 (18)	-	1 (14)	1 (25)
With mesenchymal renal tumor	14 (61)	2 (9)	7 (30)*	-
With mammary fibroadenoma	1	-	-	-
With uterine sarcoma	1	-	-	-
With sarcoma of the skin and subcutaneous fat	2	3	-	3
With small-intestine sarcoma	-	-	-	1
With pelvic sarcoma	-	1	-	-
With lympholeukemia	2	2	1	1

Note. [1]In comparison with the number of rats surviving till detection of the first tumor. [2]In comparison with the number of rats with tumors. In parentheses: the percentage. *p<0.05 in comparison with group 1 (χ^2 test).

intravenously in a single dose of 250 mg/kg b.w. In groups 2 and 3 (5 females and 20 males) beta carotene in sunflower oil was introduced with the feed 3 times a week in a dose of 30 mg/kg. In group 4 (5 females and 10 males) feed was given only with sunflower oil. Group 5 (5 females and 10 males) were the intact control. Beta carotene was added to the ration of rats 1.5 months before AMNU and was given throughout the experiment. The animals were weighed every month. The experiment was completed in 14 months.

All the rats were subjected to autopsy. For histological study, fragments of the tumor were fixed in neutral formalin and embedded in paraffin. The slices were stained with hematoxylin-eosin. Results were statistically processed using Student—Fisher's reliability test and the method with the Yates correction for a small number of animals.

RESULTS

The changes in body weight of the experimental rats virtually did not differ from those in the control group over the entire course of the experiment. By the time the first tumor was detected, the survival for the females and males in group 1 were the same, 92%, while for group 2 these values were 92 and 80%, respectively. By the end of the experiment 80% of females and 80% of males had survived in group 1, 64% of females and 80% of males in group 2. The results indicate that beta carotene did not appreciably alter the survival of rats with cancer induced by AMNU. In 3 rats which died 1-3 weeks after AMNU injection (2 rats in group 1 and 1 in group 2) degenerative changes in the parenchymatous organs were revealed, presenting as numerous punctate hemorrhages.

The results confirm the known fact of carcinogenic activity of antitumor agents belonging to the nitrosoalkylurea class [1,2,13]. A single intravenous injection of AMNU in a dose of 250 mg/kg induced tumors of different localization in many cases (Table 1). Females proved to be more sensitive to aranose, the total incidence of tumor development in them being 74% *vs.* 35% in the males. The mean latency of tumor development in females was 177±63 days, in males 300 days. The tumors were localized mainly in the kidneys, very seldom in other organs and tissues. Renal tumors were found in 61% of females but in only 9% of males. The tumors were bilateral in the majority of cases and varied in size from very small to large, occupying the greater part of the abdominal cavity. Histologically they were classified as mesenchymal tumors with various degrees of tissue differentiation.

Beta carotene brought about a reduction of both the total incidence of tumors and the incidence of renal tumors in the rats induced with AMNU; in addition, it prolonged the latency of tumor development. The anticarcinogenic effect of beta carotene was most manifest in females. The total incidence of tumors fell from 74 to 30% in them, the incidence of renal tumors from 61 to 30% (p<0.05). The mean latency of tumor development was 259±97 days. In the males the inhibitory effect of beta carotene was weaker (the differences were statistically unreliable), but a tendency for the total incidence of tumors to drop and for the mean latency of their development to be prolonged was observed all the same. Beta carotene did not appreciably alter the

morphological picture of the tumors induced by AMNU. Histologically their structure was characteristic for the carcinogenic effect of the nitrosocompounds of this group [2].

Rats administered beta carotene alone (group 3), sunflower oil (group 4), and intact animals developed no tumors.

Hence, this study demonstrated the possibility of mitigating the carcinogenic effect of AMNU with beta carotene. The anticarcinogenic action of carotenoids is explained by several mechanisms, one of which is realized during their interaction with cell macromolecules, involving the cell membranes and nuclear structures, and the second is due to their immunostimulating and suppressive effects, preventing the growth and progress of tumor cells that have already formed [10]. These results experimentally validate the possibility of starting beta carotene therapy in order to lower the risk of second primary tumors during the treatment of cancer patients with nitrosoalkylurea agents.

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