EFFECT OF POTASSIUM IODIDE ON TUMOR GROWTH

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UDC 616.34-006.04-02:615.31:546.32]-07

KEY WORDS: potassium iodide, tumor growth.

In the course of preclinical trials of a technique of immunoscintigraphy of carcinoma of the colon [1, 11, 16] in nude mice with xenografts of human malignant tumors, we noted that in animals receiving potassium iodide perorally in order to block the thyroid gland against radioactive iodine, the tumors grew more slowly than in mice not receiving potassium iodide. This phenomenon attracted our attention, and we undertook special experiments to study the effect of potassium iodide on tumor growth. The results are described below.

EXPERIMENTAL METHOD

The research was conducted on mice with primary tumors obtained from the tumor bank of the All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR. The following animals were used: 20 nude male mice weighing 20-22 g with subcutaneous xenografts of carcinoma of the human rectum strain RPK-10, 156 BALB/c female mice weighing 21-23 g with subcutaneous syngeneic grafts of murine carcinoma of the colon strain AKATOL, and 23 male C57BL mice weighing 21-23 g, with intramuscular syngeneic grafts of murine epidermal lung carcinoma, strain Lewis LLC. The animals were divided into groups: mice of the experimental groups received 0.1% (0.006 M) potassium iodide solution instead of drinking water (in the experiments with nude mice, starting with the 8th day after inoculation of the tumor tissue, in the remaining experiments immediately after implantation); mice of the control groups drank water or an equimolar solution of sodium iodide, potassium chloride, or sodium chloride. Mice with the RPK-10 tumor were killed 12-19 days after implantation (on the 4th-12th day of receiving KI), mice with the LLC tumor were killed 8 days after implantation, and those with the AKATOL tumor after 15-17 days. The weight of the tumors was determined and the arithmetic means and standard error for the groups and also the significance of the difference between the means were calculated.

EXPERIMENTAL RESULTS

In the experiments aimed at developing a technique of immunoscintigraphic visualization of carcinomas of intestinal origin, ^{131}I-labeled rabbit antibodies to intestinal antigen β_1MA were injected intravenously into nude mice 10 days after transplantation of RPK-10 tumor tissue into them [12]. This diagnostic preparation contained 2% of antibodies not bound with ^{131}I as impurity. To protect the recipients' thyroid gland against radioactive iodine, the animals were given 0.1% KI solution to drink. The experimental animals also included a group of the same mice with RPK-10, and which also received the ^{131}I antibodies, and which differed only in the fact that their thyroid gland was not blocked, for they drank only water. The radioactively labeled antibodies injected into the animals accumulated specifically in the tumors, but the doses of iodized antibodies used (0.01 MBq/mouse) were sufficient for diagnostic purposes only and could not by themselves have any marked therapeutic action on tumors. The animals were killed at various times after injection of the labeled antibodies and their organs and tissues were studied, including tumors, for determination of their specific radioactivity. It was found that in 90% of cases in mice receiving KI were appreciably smaller in size and weight than those in mice not receiving potassium iodide (Table 1). This effect, which can

Research Institute of Viral Preparations, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR I. N. Blokhin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 111, No. 1, pp. 64-66, January, 1991. Original article submitted November 11, 1989.

0007-4888/91/0001-0087$12.50

TABLE 1. Comparison of Weight of RPK-10 Tumor Tissue in Nude Mice Receiving and not Receiving KI (mg)

Group of animals	Time after inoculation of tumor (days)				
	12	13	14	17	19
Receiving 0.1% KI solution from 8th day after inoculation	183	273	202	1006	715
	132	242	358	348	760
				205	
Not receiving KI	129	372	562	570	2608
	522	416	1258	1768	

Legend. All animals received intravenous injection of 0.05 μg of rabbit ^{131}I antibodies to β_1MA (0.01 MBq) 10 days after inoculation of tumors.

TABLE 2. Action of KI on Growth of Lewis Carcinoma

With KI		Without KI		Significance of difference
n	mass of tumor (g)	n	mass of tumor (g)	
12	1,87±0,17	11	2,50±0,32	$p \leqslant 0,25$

TABLE 3. Action of Iodides on Growth of AKATOL Tumor

Expt. No.	1			2			3			4			
Salt soln. received by mice	n	mass of tumors (g)	p	n	mass of tumors (g)	p	n	mass of tumors (g)	p	n	mass of tumors (g)	p
KI	10	1,24±0,08	⩽0,001	10	2,18±0,11	⩽0,01	10	1,43±0,18	⩽0,5	9	1,73±0,21	⩽0,05
NaI	9	1,55±0,13	⩽0,01	9	2,75±0,17	⩽0,05	9	1,16±0,16	⩽0,25	7	1,16±0,17	⩽0,01
KCl	10	2,01±0,23	n.s.	9	3,97±0,22	n.s.	8	2,12±0,25	n.s.	9	2,74±0,39	n.s.
NaCl	—	—	—	—	—	—	—		—	9	3,04±0,31	n.s.
—	10	2,35±0,12	—	10	3,76±0,27	—	9	2,00±0,32	—	9	3,12±0,27	—

Legend. n) Number of mice in group, p) significance of difference between means in particular group and in control, n.s.) not significant.

be regarded as an extraneous result obtained in experiments carried out for quite different purposes, attracted our attention. It was therefore next decided to undertake experiments to study the effect of KI on growth of malignant tumors.

Table 2 gives the results of an experiment to study the action of KI on growth of a Lewis LLC lung carcinoma transplanted into male C57BL mice. These results demonstrate that a therapeutic effect was obtained in this case also: in mice drinking KI solution the tumors were significantly smaller than in control mice not receiving KI.

The next experiments were carried out on female BALB/c mice with transplanted AKATOL tumors. The aim of these experiments was to discover not only whether this type of tumor is sensitive to potassium iodide, but also with which ion, namely K^+ or I^-, the observed effect is most closely linked. We found that KI significantly inhibits growth of the AKATOL (Table 3). Tumor growth was significantly inhibited by an equimolar solution of NaI. The Na^+ and K^+ cations in the composition of these chlorides had no effect on tumor growth. These results are evidence that inhibition of tumor growth was linked mainly with the effect of the iodine ion.

Thus experiments on mice with grafted malignant tumors of three different types, including murine and human, showed that peroral administration of potassium or sodium iodide leads to inhibition of tumor growth. We know that KI solution is given perorally for the treatment of diffuse mastopathies [3, 7]. The positive results obtained with a course of potassium iodide treatment has been linked with the effect of this compound on pituitary function, mediated through the thyroid gland: adminis-

tration of KI leads to a decrease in estrogen production in the body, due to inhibition of the follicle-stimulating function and stimulation of the luteinizing function of the pituitary [5, 14]. The action of iodides in our experiments on malignant growth may perhaps also have been effected through a change in hormonal action on the tumors. However, it would be difficult to explain the results purely on these grounds. Inhibition of tumor growth, moreover, was observed in the case of different types of tumors differing in their hormone dependence, and also in males (RPK-10, LLC) and females (AKATOL). Meanwhile, iodides are known to act as chaotropic agents, destabilizing the cell membrane [15]. Membranes of tumor cells are characterized by increased sensitivity to destabilizing influences [9, 17]. Destabilization of membranes as a result of the chaotropic action of the I^- anion stimulates or induces realization of phenomena associated with the sodium-potassium balance. Research which convincingly showed the effect of a change in the intracellular ratio between monovalent Na^+ and K^+ cations on the working of the tumor cell genome has been published [4, 6, 10, 18-20]. Maintenance of a state of equilibrium between the Na^+ and K^+ concentrations in the cell is also an energy-demanding process [8, 9], and it must be assumed that a sufficiently prolonged action of an excess of one of these cations may exhaust the energy reserves of the tumor cells, thereby delaying tumor growth.

In this connection also we must recall publications reporting the beneficial effect of preparations obtained from marine animals in cancer. For example, data on inhibition of growth of tumors induced by 3,4-benz(a)pyrene, sarcoma 37, and Erhlich's solid carcinoma by feeding the tumor-bearing mice with preserved Japanese sea-cucumber. Very probably in these cases also the observed effect may have been due, at least partly, to iodides, whose concentration in such preparations is undoubtedly high.

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