TRANSPLACENTAL CARCINOGENIC ACTION OF THE SEROTONIN DERIVATIVE 5-METHOXYINDOLYL-3-ACETIC ACID

N. V. Malakhova and M. O. Raushenbakh

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Among the factors predisposing to tumors in children (transplacental influences, genetic predetermination, disturbances of immunity) pediatric oncologists ascribe an important role to transplacental carcinogenic influences [2]. This view has largely been formed on account of experimental research into the principles governing the effects of carcinogens from the external environment on the fetus, which has developed rapidly in recent years [1, 10], and also on the basis of important arguments in support of the etiologic role of endogeneous carcinogens, obtained in the course of clinical-biochemical and experimental studies of the possible mechanisms of development of congenital tumors in children.

Combined studies have demonstrated disturbances of metabolism of the amino acid tyrosine in all children with leukemias, with the formation and excretion of p-hydroxyphenyllactic acid (PHPLA). Meanwhile high concentrations of this carcinogen have been found in all mothers, and also in many fathers of the affected children [6]. Among the offspring of female mice receiving PHPLA during pregnancy, the frequency of development of neoplasms was 50-64% higher than in the control; tumors of varied genesis appeared much earlier in the progeny and were more malignant in character [4].

The character of disturbances of tyrosine metabolism in children with leukemia and in their parents is evidence that two factors may play a role in the genesis of congenital leukemias: transplacental transmission of endogenous carcinogens and an inherited defect of tyrosine metabolism.

Increased formation and excretion of aromatic and indole derivatives of the amino acid tryptophan were established previously in patients with different kinds of hemoblastoses in the course of extensive studies carried out in the All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR [5]. The presence of familial disturbances of tryptophan metabolism was demonstrated in parents of children with leukemia, high concentrations of carcinogenic tryptophan metabolites were found in the mothers [7], and this also suggests a transplacental carcinogenic action.

In a study of indole derivatives of tryptophan carcinogenic properties were found not only in 3-indolylacrylic acid and indole itself, but also in methoxy derivatives of tryptophan along the pathway of synthesis and breakdown of serotonin, namely in melatonin, mexamine, and their terminal metabolite 5-methoxyindolyl-3-acetic acid (5-MIAA). These properties were most marked in the case of the last of these compounds [9].

The results of our investigations showed that melatonin, if injected into female C57BL mice during pregnancy, causes an increase in the frequency of neoplasms in their progeny by about 26% [8].

The aim of this investigation was to study the transplacental carcinogenic action of 5-MIAA as a compound responsible for the carcinogenic properties of the above-mentioned methoxyindoles.

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TABLE 1. Carcinogenic Action of 5-MIAA on C57BL/6 Mice after Transplacental Exposure and Injection into Adult Animals

Group of animals	Number of mice attaining age of 17 months	Number of animals with neoplasms		Type of neoplasm						
		absolute	%	hemoblastosis	adenoma of the lungs	adenoma of the intestine	carcinoma of the bladder	papilloma of the bladder	hepatoma	osteoma
Transplacental exposure	32	26	84	22	1	—	—	2	2	—
Control	25	9	32	8	—	—	—	—	1	—
Adult mice	45	25	56	21	1	1	1	3	—	—
Control	22	4	18	4	—	—	—	—	—	—
Mother mice	8	3	—	2	—	—	—	—	—	1

EXPERIMENTAL METHODS

5-MIAA was synthesized at the All-Union Pharmaceutical Chemical Scientific-Research Institute under the direction of Professor N. N. Suvorov. The substance is a white crystalline powder, readily soluble in water.

Experiments were carried out on C57BL/6 mice of both sexes from the Nursery of the Animal House of the All-Union Oncologic Research Center, Academy of Medical Sciences of the USSR. An aqueous solution of the compound was injected subcutaneously into the mothers from the 10th day of pregnancy until birth of the offspring, in a total dose of 50 mg per mouse. The animals were kept under observation until the age of 17-22 months, after which they were killed. The mice were not vaccinated against ectromelia on the grounds that vaccination itself leads to an increase in frequency of neoplasms along them [3]. Mice receiving injections of the solvent alone during pregnancy served as the control.

Unvaccinated adult C57BL mice (25 females and 25 males) also were subjected to the action of 5-MIAA. The compound was injected into these animals in a dose of 2.5 mg in 0.25 ml water subcutaneously 3 times a week for a long period of time, up to a total dose of 100 mg per mouse. The control for this group consisted of 22 adult intact unvaccinated mice of the same line.

Eight female mice which produced offspring during the experiment also were kept under observation. They each received 50 mg of 5-MIAA during pregnancy.

All animals which died and were killed in the experimental and control groups were autopsied and examined for presence of neoplasms. To make the diagnosis, morbid anatomical, hematologic, and cytologic data obtained during the study of organs and tumors were taken into account. Paraffin sections of the organs and squash preparations were stained with hematoxylin and eosin.

The experimental results were subjected to statistical analysis by Student's test. Indices of frequency of the neoplasms were calculated relative to the number of animals which reached the age of 17 months, because it was at this age that neoplasms first appeared in the mice.

RESULTS

Analysis of the experimental results showed that in the group of offspring from mice exposed to the action of 5-MIAA during pregnancy 26 of the 32 animals developed neoplasms (Table 1). The commonest neoplasms were hemoblastoses (22 cases), but an adenoma of the lung, papillomas of the urinary bladder, and hepatomas also were found. Meanwhile, the number of neoplasms found in the control animals was much smaller than in the experiment: 9 of 25 cases. They developed at the age of 21-22 months, i.e., later than in animals of the experimental group, in which the main number of tumors appeared at the age of 17-21 months. In the control group hemoblastoses were diagnosed in 8 mice and a hepatoma in 1 mouse. Differences in the frequency of development of neoplasms in the experimental and control groups were statistically highly significant ($P < 0.001$).

In both experimental and control groups the most frequent type of hemoblastosis was a lymphosarcoma of mixed type, and in a few cases lymphatic leukemia was observed. In mice with lymphosarcoma in the experimental group the thyroid gland, spleen, and intestine were affected more often than in the control animals, in which the disease most frequently involved the mesenteric lymph nodes.

In mice exposed for a long time to the action of 5-MIAA in the antenatal period, 25 of the 45 animals developed neoplasms, i.e., 56% of cases, which was statistically significantly more than the number of neoplasms observed in the corresponding control group (18%). The histogenesis of the neoplasms developing under the influence of 5-MIAA in adult mice differed from that observed in the group of offspring, and included the appearance of carcinoma of the bladder and adenoma of the intestine. Although in the case of transplacental exposure the dose of the carcinogen used was only half as large, the number of neoplasms which developed in the mice in the two experiments differed about equally from the control (by 38% in the case of injection of 5-MIAA into adult animals and by 52% in the case of transplacental exposure); this may be evidence that embryonic tissues are rather more sensitive to the action of this carcinogen.

In the group of mice which had already given birth, lymphosarcomas and an osteoma of the jaw were found; moreover, the mouse developed the osteoma before all the other neoplasms observed in this investigation, namely at the age of 13.5 months. Since neoplasms of the bones are extremely rare in mice, there is reason to suppose that the tumor was induced by 5-MIAA, further confirmation that this serotonin metabolite possesses carcinogenic properties.

Comparative analysis of the results of this investigation thus suggests that 5-MIAA, a methoxy indole derivative of tryptophan, has a transplacental carcinogenic action on C57BL/6 mice. Evidence that this is so is given, first, by the more than twofold increase in the frequency of development of neoplasms in offspring of mothers treated with this compound during pregnancy, and also the much earlier times of development of the neoplasms compared with the control.

The transplacental action of 5-MIAA is much stronger than that of melatonin. Under the influence of 5-MIAA the frequency of development of noeplasms in the progeny of the experimental females was increased by 52%, compared withonly 26% by melatonin.

The results of these investigations add to our information on transplacental carcinogenesis and may serve as a guide for the identification of groups of children at risk of developing neoplasms.

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