also were observed in the structure of the mucosa of the cecum. The proliferative zone in the crypts was widened, the number of wandering cells was increased, and atypical growths projecting into the lumen of the intestine appeared (Fig. 3).

Since according to data in the literature A/He mice do not develop spontaneous intestinal tumors, the tumors described in this paper were evidently induced by OAT. Consequently, this compound is carcinogenic for the intestine also. However, intestinal tumors develop under the influence of OAT in these experiments only in A/He mice. In mice of lines CC57BR, C57BL/6, C3H/He, and DD receiving the carcinogen in the same way as A/He mice, no tumors were found in this situation (up to 40-60 animals of each line were studied). It is not clear with what genetic peculiarities of mice of line A/He the sensitivity of the tissues of the cecum of these animals to the carcinogenic action of OAT is linked.

LITERATURE CITED

1. H. B. Andervont, H. G. Grady, and J. E. Edwards, J. Nat. Cancer Inst., 3, 13 (1942).
2. Y. Nishizuka, K. Ito, and K. Nakakuki, Gan (Tokyo), 56, 135 (1965).

PATTERN OF TRANSPLACENTAL PENETRATION OF 7,12-DIMETHYLBENZ(a)ANTHRACENE AND ITS DISTRIBUTION IN THE FETAL ORGANS IN MAN

L. N. Baranova and V. A. Aleksandrov

UDC 612.649:612.388-064:615.277.4

On the 21st day of pregnancy 7,12-dimethylbenz(a)anthracene (DMBA) was injected into female rats in a dose of 15 mg/kg and its concentration in the liver of the pregnant rats, the placenta, and the fetus was determined by a fluorescence-spectral method. The maximal concentration was rapidly reached (after 10-15 min) in the liver of the pregnant rats (45 mg/kg) and placenta (6.3 mg/kg), but more slowly (after 1 h) in the tissues of the fetus (2.4 μg/kg). Clearance of the carcinogen from all the tissues took place relatively slowly (in about 5 h). DMBA was shown to be irregularly distributed in the different organs of the fetus 1 h after its injection into the pregnant rats: maximally in the fetal liver, minimally in the carcass, compared with its concentration in other organs (kidneys, lungs, brain, intestine). The results do not correlate with data showing the development of tumors predominantly in the kidneys and nervous system of rats following transplacental exposure to DMBA.

KEY WORDS: 7,12-dimethylbenz(a)anthracene; placental barrier.

The study of the placental barrier in rats and mice has demonstrated its high permeability to carcinogenic polycyclic hydrocarbons and also certain general principles regarding their accumulation in the fetal tissues and their subsequent elimination. It is interesting to study the pattern of accumulation of carcinogens in the various organs of the fetus. This problem has a direct bearing on the mechanisms of transplacental carcinogenesis, i.e., the phenomenon of development of tumors in the progeny as a result of administration of chemical carcinogens to the mother during pregnancy. It was shown previously that following transplacental exposure (on the 21st day of pregnancy) to 7,12-dimethylbenz(a)anthracene (DMBA), injected intravenously in a dose of 15 mg/kg, tumors mainly of the nervous system and kidneys developed in the progeny of the rats [1]. After administration of the compound at the same period of pregnancy but in a larger dose (25 mg/kg) the penetration of DMBA through the placenta and the dynamics of its entry into the fetus were studied in detail in rats [2]. Under these circumstances, a fluorescence-spectral method was used to determine the concentration in the tissues.

Laboratory of Biophysics and Laboratory of Experimental Tumors, Professor N. N. Petrov Research Institute of Oncology, Ministry of Health of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR L. M. Shabad.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 10, pp. 477-479, October, 1978. Original article submitted December 22, 1977.

 0007-4888/78/8610-1376$07.50

The object of the present investigation was as follows: first, to study the dynamics of penetration of DMBA into the fetus following administration of the carcinogen at the same period to pregnant rats and in the same dose as in the experiments to study transplacental carcinogenesis; second, to determine the character of accumulation of DMBA in the various organs of the fetus within the time interval when the concentration of the carcinogen is maximal in the embryonic tissues after its administration to the mother; third, to compare the character of primary accumulation of the carcinogen in the various organs of the rat fetus with the frequency of origin of tumors in different situations, using the results of earlier experiments to study the transplacental carcinogenic effect of DMBA [1].

EXPERIMENTAL METHOD

Albino rats from the Rappolovo Nursery, Academy of Medical Sciences of the USSR, were used. On the 21st day of pregnancy the females were given a single intravenous injection of DMBA, in the form of a water-lipid emulsion, in a dose of 15 mg/kg.

In the experiments of series I the rats were killed 5, 15, 30, 60, 120, 180 and 300 min after injection of the compound. At least four pregnant animals were killed at each of the above times. The uterus with the fetuses was removed and washed free from blood in 0.9% NaCl solution. In the experiments of series II the rats were killed 1 h after injection of the compound, i.e., when the maximal DMBA concentration on the tissues of the fetus was recorded. The fetuses, taken from the uterus, were dissected and the liver, lungs, intestine, kidneys, brain, and "carcass," i.e., the rest of the body, were isolated. The DMBA concentration was determined in all the organs thus isolated. Fetuses from 42 pregnant rats were used in this series of experiments. The method of extraction of the carcinogen from the tissues was as follows: The tissues, carefully cut into small pieces with scissors, were frozen in liquid nitrogen, and then extracted three times with hot ethyl alcohol. The extracts were purified on alumina columns and chromatographs on plates with an unfixed layer of alumina. Quantitative determination of the carcinogen in the fractions was carried out by the standard method described previously [2]. Modifications of the method by comparison with the description given in [2] increased its sensitivity and enabled the quantity of material required for analysis to be reduced to 2 g tissue.

EXPERIMENTAL RESULTS

The dynamics of entry of DMBA into the liver of the pregnant rats and the tissues of the placenta and fetus following injection of the carcinogen is illustrated in Fig. 1. Clearly the DMBA concentration in the liver of the pregnant rats reached a maximum during the first 10-15 min after injection. This was followed by gradual removal of the carcinogen from the liver tissue. The concentration of the carcinogen in the placenta showed similar changes although its maximal concentration (6.3 μg/kg) was less than in the liver (45 μg/kg).

The DMBA concentration in the tissues of the fetus rose much more slowly. Its concentration reached a maximum 1 h after administration to the mother. By 5 h, only traces of the carcinogen were discovered in the fetal tissues. The much slower accumulation of the carcinogen in the fetal tissues and its slower elimination from them than in the case of the liver of the pregnant rats and the placenta will thus be noted. The results for a dose of 15 mg/kg were in good agreement with those for administration of DMBA in a dose of 25 mg/kg [2].

To study the character of distribution of the carcinogen in the different organs of the fetus, an interval of 1 h after injection of DMBA into the mother was chosen. In these experiments an irregular distribution of the carcinogen was found in the different organs of the fetus (Table 1). The highest DMBA concentration was observed in the fetal liver; the difference from all other organs studied was significant ($P < 0.001$). On the other hand, the lowest concentration of the carcinogen was found in the carcass, and this difference from the level in all other organs likewise was significant. The DMBA concentration in the kidneys, lungs, brain, and intestine was practically identical and lay at an intermediate level between the extremes: the maximum in the liver and the minimum in the carcass of the fetus.

According to Takahashi [3, 4], who studied the distribution of labeled benz(a)pyrene (BP) and 3-methylcholanthrene (MCh) in the organs of mouse fetuses by an autoradiographic method, the highest concentration of the label was found in the intestine, followed by the liver and kidneys. These observations, however, relate to a longer time interval (5 h) after intravenous injection of BP and MCh into the pregnant animals, for in the present experiments

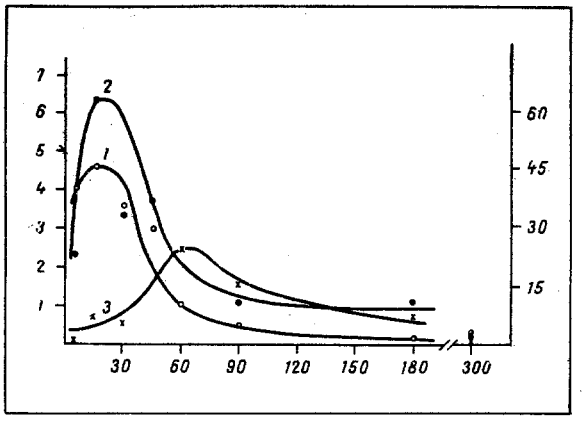

Fig. 1. DMBA concentration in liver of pregnant rats (1), placenta (2), and fetus (3), at different time intervals after intravenous injection of compound in dose of 15 mg/kg on 21st day of pregnancy. Abscissa, time of investigation (in min); ordinate, DMBA concentration (in μg/mg): on left — in fetuses and placenta, on right — in liver.

TABLE 1. DMBA Concentration in Organs of Fetus 60 Min after Injection of Carcinogen (15 mg/kg, intravenously) into Rats on 21st Day of Pregnancy

Organs	Number of analyses	Mean and limits of variation, μg/g (M ± m)
Liver	12	4,7±0,46 (3,0—8,55)
Kidneys	3	2,4±0,58 (1,3—3,1)
Lungs	8	2,2±0,21 (1,2—2,9)
Brain	6	1,5±0,16 (0,8—2,0)
Intestine	6	1,8±0,12 (1,4—2,1)
Carcass	12	1,1±0,14 (0,3—1,8)

the DMBA concentration was determined after 1 h. Furthermore, because of the method of fluorescence-spectral analysis used in the present investigation, the results reflect the accumulation of only the unchanged carcinogen, whereas in the investigation cited above metabolic products of the polycyclic hydrocarbons may also have been included.

The results of the study of the transplacental carcinogenic action of DMBA in experiments on rats [1] indicate that tumors develop in the body mainly in different parts of the central and peripheral nervous system (46.6%) and also in the kidneys (34.4%). The frequency of brain tumors (9.4%), incidentally, was not the highest for neoplasms of the nervous system. Comparison of the data for the frequency of neoplasms induced by transplacental exposure to DMBA in the various organs and the results of determination of the concentration of this carcinogen in them in this investigation show no correlation between them. In the kidneys, as target organs, the accumulation of DMBA was not greater than in the liver, lungs, or intestine of the fetus. Consequently, with respect to this particular model the primary maximal concentration of unchanged carcinogen determined by a fluorescence-spectral method does not determine the subsequent onset of tumors in a particular organ.

LITERATURE CITED

1. N. A. Aleksandrov and N. P. Napalkov, Vopr. Onkol., No. 8, 50 (1974).
2. V. A. Aleksandrov and I. A. Shendrikova, Vopr. Onkol., No. 10, 56 (1972).

3. G. Takahashi, Bull. Chest. Dis., 7, 155 (1974).
4. G. Takahashi, Cancer Res., 33, 23 (1975).