ADAPTATION TO THE ACTION OF SOME TERATOGENS FOLLOWING ADMINISTRATION OF PESTICIDES DURING PREGNANCY

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In experiments on female Wistar rats the effect of the pesticides DDT and γ-BHC, administered from the beginning of pregnancy, on the intensity of the teratogenic action of sodium salicylate (SS) and of benlate, a pesticide of the carbonate group, was studied. The compounds were given on the 10th and 12th days of pregnancy respectively. Preliminary administration of the pesticides was shown to weaken the teratogenic and embryotoxic action of benlate, given in a dose of 250 mg/kg, and of SS in a dose of 400 mg/kg. Under the influence of SS in a dose of 600 mg/kg preliminary injection of the pesticides reduced the postimplantation mortality of the embryos, but the number of fetuses with developmental anomalies was the same as after the isolated action of SS in the same dose.

KEY WORDS: *adaptation*; *teratogenic action*; *embryotoxic action*; *pesticides*.

Investigations have shown that the teratogenic action of some preparations when given as a single dose on one particular day of pregnancy is greater than in the case of prolonged exposure in the same doses throughout pregnancy [5, 6, 7]. Activation of enzymes of the microsomal fraction of the liver, metabolizing substances foreign to the body, is evidently, one of the mechanisms responsible for the adaptation of animals to the harmful action of these substances. On the other hand, the enzymes of the microsomal fraction of the liver are not strictly specific but determine the course of various types of chemical reactions [2]. It could accordingly be postulated that pregnant animals could become adapted to the teratogenic action of substances of one chemical structure as a result of their preliminary exposure to other chemical compounds.

This paper gives the results of a study of the effect of the pesticides DDT and γ-BHC on the intensity of the action of two teratogens: sodium salicylate (SS) and benlate, a pesticide of the carbonate group.

EXPERIMENTAL METHOD

Wistar rats were used and were fed on the ordinary animal house diet consisting of natural products. Females were mated with males kept in individual cages. The day of discovery of spermatozoa in the vaginal smear was regarded as the first day of pregnancy. On the 20th day of pregnancy the females were decapitated, the fetuses were removed and, the corpora lutea, implantation sites, and cases of resorption were counted, and the pre- and postimplantation mortality of the embryos was determined. The 20-day fetuses were investigated by the usual teratological methods [1]. Benlate and SS were used as teratogens. According to available data [4] SS is teratogenic for rats and causes craniorhachischisis, rachischisis, exencephalia, cleft plate, hare lip, and certain other developmental anomalies in their fetuses. This action was most marked after oral administration of SS in a dose of 400-600 mg/kg body weight on the 10th day of pregnancy. Benlate is also teratogenic for Wistar rats [3], causing hydrocephalus and encephalocele in fetuses if administered on the 12th day of pregnancy in doses of 125 mg/kg or more. With these data in mind, in the present investigation SS was given by mouth to the rats as an aqueous solution on the 10th day of pregnancy in doses of 400 and 600 mg/kg; benlate was given on the 12th day as a suspension in vegetable oil in a dose of 250 mg/kg. DDT and γ-BHC were given by mouth as a suspension in vegetable

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TABLE 1. Effect of DDT and γ-BHC on Intensity of Teratogenic Action of SS and Benlate

Substances	Dose, mg/kg	Number of pregnant females	Preimplantation mortality of embryos, % (mean for group)	Postimplantation mortality of embryos, % (mean for group)	Number of fetuses with developmental anomalies, % of total number of living fetuses
Control	—	18	9,0	8,8	1,8
SS	600	16	5,4	82,1	30,0
DDT + SS	600	15	6,2	47,7*	30,5
γ-BHC + SS	600	15	6,7	40,2*	28,2
SS	400	15	6,8	35,5	39,0
DDT + SS	400	17	6,9	11,1*	13,5*
Benlate	250	11	6,4	44,1	55,2
DDT + benlate					
Series I	250	10	5,0	7,2*	0,0*
Series II		12	5,8	17,2*	6,3*
γ-BHC + benlate	250	14	8,0	8,4*	0,0*

*Difference statistically significant ($P < 0.05$) between this group and group of animals exposed to isolated action of teratogen in same dose.

oil in doses of 20 and 10 mg/kg respectively, starting from the 1st and continuing until the 9th or 11th day of pregnancy. These doses were chosen on the basis of preliminary experiments as having neither teratogenic nor embryotoxic action on rats, yet at the same time considerably shortening the duration of hexobarbital sleep. The results were subjected to statistical analysis using the Kolmogorov–Smirnov criterion.

EXPERIMENTAL RESULTS

The results are given in Table 1. They show that preliminary administration of the pesticides caused a marked decrease in both the teratogenic and the embryotoxic (postimplantation mortality of the embryos) action of benlate and SS when the latter compound was given in a dose of 400 mg/kg. If SS was given in a dose of 600 mg/kg, preliminary administration of the pesticides caused a marked decrease in the postimplantation mortality of the fetuses; however, the number of fetuses with developmental anomalies was practically the same as when SS was given alone in the same dose. This difference in the effect due to preliminary administration of pesticides on the intensity of the teratogenic and embryotoxic action of different doses of SS was evidently the result of the fact that the ratio between the number of fetuses with developmental anomalies and the postimplantation mortality of the embryos differs for different doses of SS. Investigations showed that if SS was given in a dose of 300 mg/kg the number of fetuses with developmental anomalies was 14.7% and the postimplantation mortality of the embryos 19.9%, whereas if SS was given in a dose of 800 mg/kg the postimplantation mortality of the embryos was 100%. If these results are compared with those given in Table 1 for the action of SS in doses of 400 and 600 mg/kg, it will be clear that whereas the postimplantation mortality of the embryos decreased with a decrease in the dose from 800 to 300 mg/kg, the number of fetuses with developmental anomalies was practically the same after doses of 600 and 400 mg/kg and it fell only when the dose was reduced to 300 mg/kg. Since preliminary administration of the pesticides weakened the teratogenic action of SS by a definite amount but did not change the character of its harmful action on the embryos, the effect thus revealed (the number of dying embryos and fetuses with developmental anomalies) must be determined by the ratio between these indices which are characteristic of this particular preparation when given on this day of pregnancy in different doses.

It must also be noted that doses of pesticides which cause activation of the enzymes of the microsomal fraction of the maternal liver, metabolizing substances foreign to the body, were used in this investigation. However, it is known that both DDT and γ-BHC, when given in large doses, can inhibit the activity of these enzymes [8]. Since it can be postulated that the adaptation to the teratogenic action of SS and benlate observed in these

experiments was the result of activation of enzymes of the microsomal fraction of the liver by the pesticides and, consequently, of the more rapid detoxication of the teratogens given, it will be evidence that potentiation of the action of the teratogens may be observed as a result of the inhibitory action of DDT and γ-BHC on these enzymes.

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KINETICS OF BONE MARROW CELLS DURING FRACTIONATED X-RAY IRRADIATION

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The harmful action of fractionated x-ray irradiation (12 rad daily, total dose 250, 500, 750, 1000, or 1500 rad) on hematopoiesis was studied in guinea pigs. The dynamics of the changes in erythro- and myelopoiesis after irradiation was phasic in character. In the first phase activation of proliferative processes was manifested as an increase in the mitotic index, shortening of the mitotic cycle of cells of the erythroid and myeloid series, and their more rapid differentiation, so that as a result a sufficient number of cells entered the blood stream and maintained a near-normal number of erythrocytes and leukocytes in peripheral blood. In the second phase weakening of proliferative processes was observed in the bone marrow, the mitotic index was reduced, the duration of the mitotic cycle was increased, and differentiation of cells of the erythroid and myeloid series was slowed, with the development of anemia and leukopenia in the peripheral blood.

KEY WORDS: *x-ray irradiation*; *blood*; *bone marrow*; *mitotic cycle*.

A single irradiation of animals with x rays in large [2, 4, 7, 9] and small doses [1, 3, 5, 6] causes considerable disturbance of the life cycle of the proliferating bone marrow cells. However, data in the literature are contradictory, evidently because of the use of different sources, conditions, and doses of irradiation, and also with the use of different methods of calculating the duration of the mitotic cycle and of its individual periods.

EXPERIMENTAL METHOD

Guinea pigs were subjected to fractionated x-ray irradiation (tube voltage 180 kV, current 10 mA, filters 0.5 mm copper and 1.0 mm aluminum, focal length 40 cm, daily dose of irradiation 12 rad, total doses 250, 500, 750, 1000, and 1500 rad, total duration of irradiation

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