

EXPERIMENTAL BIOLOGY

STIMULATION OF MITOTIC ACTIVITY OF EMBRYONIC CELLS BY PENTOXYL

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A single dose of pentoxyl (100 and 500 mg/kg) was given by gastric tube to Wistar rats on the 10th and 13th days of pregnancy. On the 20th day of pregnancy the animals were sacrificed, the liver and kidneys of the mother and embryos were fixed, and the number of dividing cells was determined in histological sections. The mitotic index also was determined in the corneal epithelium of nonpregnant rats also receiving pentoxyl in doses of 100 or 500 mg/kg. In a dose of 100 mg/kg pentoxyl stimulates mitotic activity of hepatocytes and cells of the renal cortex in rat embryos and also in the corneal epithelium. An increase in the dose to 500 mg/kg considerably weakens the stimulant action of pentoxyl and leads to the appearance of toxic properties.

Pentoxyl (4-methyl-5-hydroxymethyluracil) is one of a group of therapeutic substances which stimulates hematopoiesis [8, 12] and reparative regeneration [7, 11]. Because of its wide spectrum of action, the compound is extensively used in clinical medicine.

The effect of pentoxyl on mitotic activity in the cells of rat embryos was investigated and compared with its action on cell division in adult rats.

EXPERIMENTAL METHOD

In the experiments of series I a single dose of 100 or 500 mg/kg of pentoxyl was given by gastric tube to female Wistar rats on the 10th and 13th days of pregnancy. On the 20th day of pregnancy the rats were sacrificed; the liver and kidneys of the mothers and the embryos were fixed in 10% formalin, after which the kidneys and liver were removed from some of the fetuses. The maternal and embryonic organs were examined histologically in sections stained with Mayer's hematoxylin and eosin.

In series II nonpregnant sexually mature rats were given pentoxyl at 7 a. m. The animals were sacrificed 4 h later; total preparations of the cornea stained with Yasvoin's iron-hematoxylin were studied.

The mitotic index (the number of dividing cells per thousand cells) was determined in the liver and kidneys of mother and fetus and also in the corneal epithelium. In each case from 5,000 to 10,000 cells were examined.

All the numerical results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

Pentoxyl had a marked stimulant action on mitotic activity of the hepatocytes and epithelial cells of the renal cortex of the rat embryos (Table 1).

The effect was particularly marked when the compound was given in a dose of 100 mg/kg, for the number of dividing hepatocytes was increased by almost eight times, and the number of dividing renal cortical epithelial cells by 2.7 times. With an increase in the dose of pentoxyl to 500 mg/kg its effect on mitotic

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TABLE 1. Effect of Pentoxyl on Mitotic Activity

Expt.	Conditions	Dose (in mg/kg)	Object	Organ	Period of pregnancy when compound given (in days)	Mitotic index (per 1000 cells; $M \pm m$)
1	Control	—	Mother	Liver	—	$0,6 \pm 0,2$
2	Pentoxyl	100	»	»	13	$1,0 \pm 0,2$
3	»	500	»	»	13	$0,8 \pm 0,1$
4	»	500	»	»	10	$0,7 \pm 0,1$
5	Control	—	Fetus	»	—	$13,0 \pm 0,7$
6	Pentoxyl	100	»	»	13	$102,6 \pm 5,1$
7	»	500	»	»	13	$25,8 \pm 3,4$
8	»	500	»	»	10	$23,4 \pm 1,5$
9	Control	—	Mother	Kidneys	—	$0,8 \pm 0,2$
10	Pentoxyl	100	»	»	13	$1,2 \pm 0,2$
11	»	500	»	»	13	$0,6 \pm 0,2$
12	»	500	»	»	10	$0,8 \pm 0,2$
13	Control	—	Fetus	»	—	$33,8 \pm 1,6$
14	Pentoxyl	100	»	»	13	$87,8 \pm 3,6$
15	»	500	»	»	13	$48,0 \pm 4,0$
16	»	500	»	»	10	$46,8 \pm 0,7$
17	Control	—	Mother	Cornea	—	$30,6 \pm 1,9$
18	Pentoxyl	100	»	»	—	$36,4 \pm 2,0$
19	»	500	»	»	—	$26,7 \pm 3,2$

activity of the embryonic cells was considerably reduced. Although in this dose the compound also stimulated mitotic division, the effect was much weaker than in a dose of 100 mg/kg.

Although it increased the mitotic index in the fetal liver and kidney tissues pentoxyl had no effect on the distribution of the number of dividing cells per phases of mitosis, i.e., it increased the number of embryonic cells in all the phases of cell division equally.

The number of dividing cells in the liver and kidneys of adult animals is very small [5, 13, 15, 16]. By contrast with embryonic cells the mitotic activity of hepatocytes and renal cortical cells of the adult rats remained unchanged after administration of pentoxyl.

The number of dividing cells in the corneal epithelium of adult rats is fairly high [1, 2, 9]. Well marked diurnal rhythms of mitotic activity are found in the corneal epithelium of the rats, with an increase in the number of mitoses in the early morning (6-8 a. m.) [5].

Pentoxyl stimulated mitotic activity only in a dose of 100 mg/kg. In a dose of 500 mg/kg it had no effect on the mitotic activity of the corneal epithelium.

The results of the experiments on rats thus show that pentoxyl stimulates mitotic activity of embryonic cells, and that this effect is inversely proportional to the dose used. In a smaller dose the compound stimulates mitotic division, while in a larger dose its toxic properties become predominant and lead to a marked disturbance of differentiation of the embryonic cells.

Stimulation of mitotic activity by pentoxyl is evidently connected with its interference with metabolism of nucleic acids and, in particular, of RNA [4], as is confirmed by the increased content of nucleic acids in various organs during the action of the compound [10].

The results of the present investigation suggest that in the induction of fetal damage by various altering (including chemical) agents not only depression of mitotic activity of the embryonic cells [3] but also stimulation of their reproduction may play an important role. Further experimental verification of this hypothesis is necessary.

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