

EXPERIMENTAL BIOLOGY

SUPEROVULATION AND THE DECIDUAL REACTION OF THE RAT'S UTERUS AFTER ADMINISTRATION OF MYLERAN AT VARIOUS TIMES BEFORE OVULATION

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The object of this investigation was to study superovulation and the changes in the decidual reaction of the uterus in rats receiving the anti-leukemic drug myleran.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats weighing 180-200 g. Myleran (1, 4-dimethanesulfonyloxybutane) was dissolved by heating in peach oil and injected intraperitoneally (once) in a dose of 10 mg/kg body weight. The interval between the injection of myleran and insemination of the female was 8-9, 12-14, or 36-48 h, or 3-3.5, 4-5, 8-9, 10-11, and 15-20 days. The results of the experiments were read on the 10th and 17th days of pregnancy. The corpora lutea in the ovaries and the living and resorbed embryos were counted. The deciduomas on the 10th day of pregnancy were fixed in Bouin's fluid, sections were cut, and were stained with iron-hematoxylin and eosin. The pituitary, thyroid, and adrenals of the experimental females were weighed. Altogether 232 pregnant rats (174 experimental and 58 control) were used.

EXPERIMENTAL RESULTS

On the 10th day of pregnancy thickenings of the uterine wall several times larger than the decidua in a normal pregnancy of the same period were found in the uterine cornua of the experimental rats. The number, size, and shape of these thickenings varied from one rat to another. Their arrangement along the length of the uterus also varied. Sometimes they alternated with normal decidual swellings, sometimes they lay in groups, and sometimes the whole uterus consisted of bead-like thickenings. Often there was no clear line of demarcation between the larger thickenings. Hypertrophied areas of the uterine wall could be found in both cornua, in one cornu, or in neither. The massive decidual swellings in the uterus were mainly observed in rats with an interval of 5 days between administration of myleran and insemination.

In the histological preparations the uterine thickenings consisted of proliferating decidual tissue with the same structure as at the sites of implantation of the embryos. The central part of the decidual swellings usually consisted of loose tissue with hemorrhages. Since these decidual swellings as a rule contained neither embryos nor remains of embryos, they were described as pseudodeciduae. By the 17th day of pregnancy the pseudodeciduae were completely or partly absorbed. In the latter case they looked like elongated or circular structures on the mesometrial wall of the uterus and outwardly they resembled the remains of the placenta after early death and absorption of the embryos.

Analysis of the experimental material obtained on the 10th day of pregnancy (see Table) showed that the total number of decidual swellings per experimental rat rose with an increase in the time interval between injection of myleran and insemination, reaching its maximum when the preparation was given 3 and 5 days before the expected ovulation. With a further increase in the interval between injection of the preparation and insemination, the number of decidual swellings in the experimental animals fell and by the 15th-20th day it was close to the control value.

Of the 96 rats of the experimental group 52 had between 13 and 25 decidual swellings, whereas in the control group (24 rats) their number did not exceed 12 per animal.

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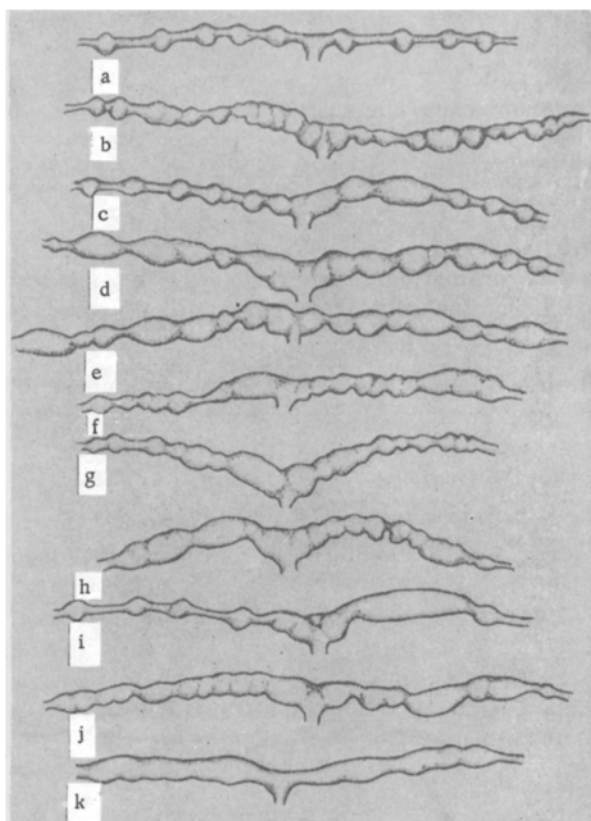


Fig. 1. Decidual reaction of the rat's uterus on the 10th day of pregnancy: a) control; b-k) after injection of myleran into rats before insemination.

In the experimental rats receiving myleran 2 days before copulation the number of corpora lutea in the ovaries was smaller than the number of decidual swellings. When the preparation was injected 12-14 h before the expected ovulation, for example, on the 10th day of pregnancy there were 2.5 ± 0.8 more decidual swellings per rat than corpora lutea. When myleran was injected 8-9 and 36-48 h before copulation the difference between the number of corpora lutea and decidual swellings in the experimental rats was not statistically significant. When myleran was injected 3-3.5 days before the expected ovulation the number of corpora lutea in the ovaries and of decidual swellings in the uterus of the experimental females showed a further increase, but there were more of the former than of the latter. When myleran was injected 10 days before ovulation the number of corpora lutea and decidual swellings was less than at the preceding times, and with an increase in the interval between injection of the preparation and copulation the relative numbers of corpora lutea and decidual swellings in the experimental animals returned to the control level (see Table).

Hypothyroidism caused by administration of 6-methylthiouracil is known to depress the decidual reaction to uterine trauma and to injection of histidine into the uterus of pseudopregnant rats; injection of progesterone prevents the depressant action of 6-methylthiouracil on development of the decidua [1]. Experiments with myleran were carried out in February and March, 1965. In all the rats obtained from the nursery the weight of the thyroid was considerably increased (26.9 mg/100 g). The suggestion has been made that the intensified decidual reaction of the uterus in the experimental animals was due to thyroid hyperfunction. However, when the experiments were repeated in May-June and in October, when the weight of the thyroid was close to normal for rats (about 10 mg/100 g), supernumerary and pseudodeciduae appeared in the experimental females receiving myleran. The reaction of the thyroid to myleran was determined by its functional state. When the thyroid of the rats was enlarged (February-March) administration of myleran doubled the weight of the gland, whereas in the rats with a thyroid of normal weight (May-June) it led to only a very slight increase in its weight.

Number of Corpora Lutea and Deciduae after Injection of Myleran at Various Times before Insemination (calculated per rat, $M \pm m$)

Date of pregnancy	Interval between injection of myleran and insemination of rats	No. of pregnant rats	Corpora lutea	Deciduae
10-th	8-9 h	7	12.0 ± 0.3	13.1 ± 1.0
	12-14 »	18	13.4 ± 0.5	15.9 ± 0.7
	36-48 »	8	13.8 ± 0.8	15.4 ± 1.5
	3-3.5 days	12	17.3 ± 1.2	16.5 ± 1.4
	4-5 days	16	18.9 ± 1.3	16.9 ± 1.1
	8-9 »	16	19.6 ± 1.2	14.1 ± 0.7
	10-11 »	13	18.2 ± 0.8	11.2 ± 1.4
	15-20 »	6	12.3 ± 0.5	10.8 ± 0.3
	Control	24	11.5 ± 0.3	9.5 ± 0.6
17-th	8-9 h	7	12.0 ± 0.5	13.9 ± 1.0
	12-14 »	8	14.9 ± 0.8	13.9 ± 1.1
	36-48 »	6	14.0 ± 1.3	15.7 ± 1.7
	3-3.5 days	12	15.1 ± 1.4	9.7 ± 1.0
	4-9 days	16	17.1 ± 0.7	14.7 ± 0.7
	10-20 »	7	15.1 ± 0.7	12.0 ± 1.0
	Control	15	11.5 ± 0.5	9.3 ± 0.4

Myleran was also found to produce superovulation, its degree depending on the time of injection of the preparation before the expected ovulation. The number of corpora lutea in the ovaries (ovulation) increased progressively with an increase in the interval between injection of myleran and insemination to about 10 days, in the animals investigated on both the 10th and the 17th days of pregnancy (see Table).

No demonstrable connection could therefore be found between the state of the thyroid and the formation of pseudodeciduae in the experimental rats after administration of myleran. Since the decidual reaction of the uterus is ultimately determined by interaction between many endocrine organs (the system: pituitary-thyroid-adrenals-ovaries), the adrenals and pituitary of the experimental rats were also weighted. However, no difference between the weight of these glands in the experimental and control animals was found in all the series of experiments.

Changes in the hormone balance in the female rats after administration of myleran were revealed by the presence of superovulation. This is also produced by x-ray irradiation of nonpregnant mice [4, 5] and rats [2, 3], but its mechanism is unknown. Superovulation is a manifestation of the radiomimetism of myleran, belong to the class of the alkylating compounds.

Further investigations are needed to provide the solution to the problem of the causes and mechanism of the abnormal decidual reaction of the uterine mucosa produced by administration of myleran in the stages preceding ovulation.

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