EFFECT OF LYSERGIC ACID DIETHYLAMIDE ON OESTRUS CYCLE AND OFFSPRING IN RATS

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Summary: Lysergic acid diethylamide (LSD-25) was studied for its effect on oestrus cycle and offspring in rats. The drug in a single dose of 5 μg/kg sc did not produce by any alteration in the normal four day oestrus cycle of rats. Though an oral dose of 200 μg/*kg* given in early pregnancy did not produce any change in either litter size or foetal mortality rate, 100 and 200 μg/*kg* sc given at a similar period of pregnancy decreased litter size, produced stunted foetuses, increased foetal mortality rate and the number of resorptions as evidenced by increase in vascularity and beading in the uteri of drug treated females. No unusual specific deformities were noticed in either live or dead foetuses.

Key words: lysergic acid diethylamide foetal mortality rate litter size

INTRODUCTION

Cases of malformation in infants born of lysergic acid diethylamide (LSD-25) users have been reported (3, 9, 12, 13, 21). The drug is reported to produce teratogenicity in mice (4) rats (1, 2) and hamsters (11, 14). Other workers did not observe any teratogenic effect either in rats (20) hamsters (7) or rabbits (10). The drug is also reported to cross the placental barrier (14).

It is, therefore, apparent that the influence of LSD-25 on offspring and genetics is a much controversial subject and offers a wide field for further study in the light of the agent being unduly misused. The present study reports the effect of LSD-25 on oestrus cycle, conception and offspring in rats.

MATERIALS AND METHODS

Laboratory bred albino rats of proven fertility weighing 130-150 *g* were used. Each treatment group consisted of ten rats and a corresponding number of saline controls. They were housed in single cages except at the time of mating and were allowed food and water *ad libitum*.

Drugs: LSD-25 was obtained from Sandoz Ltd. as a pale yellow amorphous readily soluble powder. Stock solution of 1 *mg/ml* was made in pyrogen free distilled water and was stored for not more than four days at a time. Solution for injection was made daily from the stock and was given in the volume 0.5 *ml*/100 *g* body weight.

Effect of LSD-25 on oestrus cycle: The oestrus cycle of femle rats were studied by taking daily vaginal smears and staining with haematoxylin. Only animals having two normal four day

cycles were used for the subsequent studies. After a single subcutaneous injection of 5 $\mu g/kg$ of the drug, daily vaginal smears were studied for two weeks.

Effect of LSD-25 on offspring when administered prior to mating: Male and female rats were injected 5 $\mu g/kg$ of the drug subcutaneously for three days prior to mating with untreated females and males respectively. The presence of the vaginal plug indicated successful mating. The pregnant animals were separated, kept in individual cages and weighed daily until littering. The litters were examined as to litter size, any foetal abnormality gross or otherwise, number of stillborn and foetal deaths within one week.

Effect of LSD-25 on offspring when administered early in pregnancy: Adult male and female rats were mated for two days in the ratio 1:1. The pregnant rats were separated and housed in single cages. Each group was treated on the 4th day of pregnancy with: LSD-25: 5, 100, or 200 $\mu g/kg$ sc. In addition, 5 animals were treated orally with 200 $\mu g/kg$.

Daily weights were recorded and the animals were allowed to proceed to term. Litters were examined as mentioned earlier. Animals which failed to deliver on the expected date were autopsied a few days later, and their uteri and ovaries examined.

RESULTS

LSD-25 in the dose of 5 $\mu g/kg$ sc did not produce any change in the normal four day oestrus cycle of rats. No significant change either in average litter size or foetal mortality rate was seen when either males or females were treated with 5 $\mu g/kg$ sc of LSD-25 prior to mating. All foetuses of the male treated group were normal whereas in the female treated group one was shunted weighing only 2.5 g (average normal weight 10.0 g) and one was macerated.

TABLE I: Effect of LSD-25 on the offspring of rats. LSD-25 was given to either parent prior to mating and to females on the 4th day of pregnancy.

Group and treatment	*No. of rats used*	*No. that literated*	*Mean litter size ± S.E.*	*Percentage foetal mortality*
1. Males prior to mating				
saline control	10	10	8.0±0.59	8.45
LSD-25 5 $\mu g/kg$ sc	10	10	7.7±0.93	9.87
2. Females prior to mating				
saline control	10	10	6.5±0.65	12.95
LSD-25 5 $\mu g/kg$ sc	10	10	6.2±1.45	19.20
3. 4th day of pregnancy				
saline control sc				
LSD-25 5 $\mu g/kg$ sc	10	10	7.2±0.47	15.27
LSD-25 100 $\mu g/kg$ sc	10	10	6.7±1.13	19.42
LSD-25 200 $\mu g/kg$ sc	10	5	6.4±0.97	*34.36
Saline control orally	10	3	5.3±0.27*	*37.50
LDS-25 200 $\mu g/kg$ orally	5	5	7.0±0.71	11.40
*P<.01	5	5	8.2±1.59	9.75

When LSD-25 was given to females on the 4th day of pregnancy the observations were as follows: The 200 $\mu g/kg$ sc dose significantly ($P \ll .01$) reduced the mean litter size. A dose-related increase in the foetal mortality rate was also observed. The increase with 100 $\mu g/kg$ sc were statistically significant (Table I). 8.7% of born foetuses were stunted with a

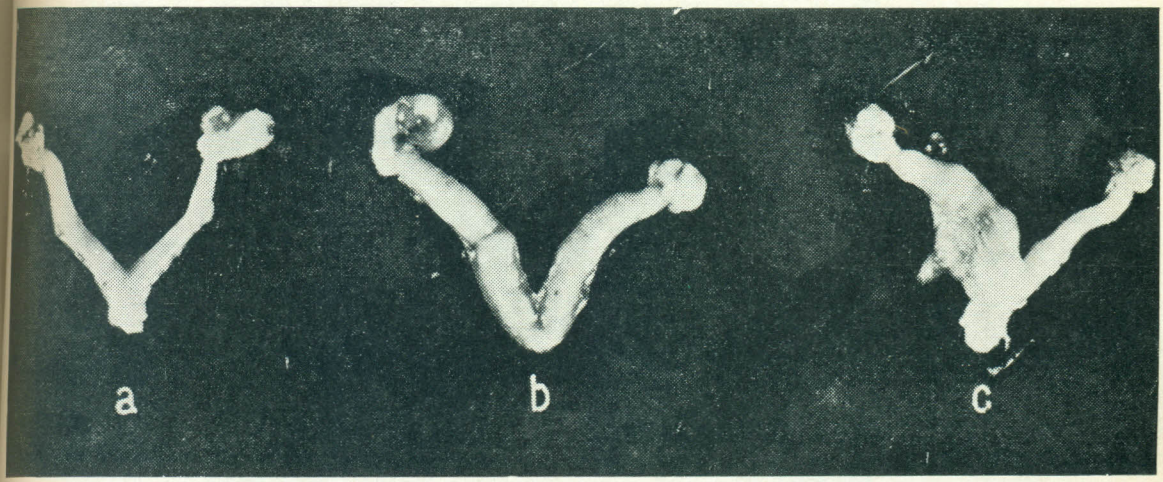

Fig. 1: Foetuses of normal and (200 $\mu g/kg$ sec) treated rats;
a. normal b. stunted offspring of LSD treated rat.

weight range from 2.0—3.5 g (Fig. 1); otherwise they did not show any gross pathology. An interesting finding was that, with the higher doses of LSD-25 given sc 40% of the animals failed to litter, though they did become pregnant as evident from the autopsy findings. The uteri of all these rats showed increased vascularity and thickened endometrium. In some, the uterine horn showed beaded appearance (Fig. 2); obviously the growth of the embryo must have been arrested. In the group receiving 200 $\mu g/kg$ sc, one mother died four days after littering and another one three days after injection of the drug. In the latter, bleeding from the vagina was noted. Postmortem examination sh owed thickened and haemorrhagic uterus.

Oral administration of the drug (200 $\mu g/kg$) did not produce any significant change in the litter size, or foetal mortality and only one out of the 41 foetus born was stunted (Table I).

DISCUSSION

Our data suggest that 5 $\mu g/kg$ of LSD-25 sc did not affect the normal four days oestrus cycle in rats, 5 $\mu g/kg$ (sc) dose given to either parent prior to mating also did not affect the foetus. The linear increase in foetal mortality rate seen with 5, 100 and 200 $\mu g/kg$ doses of drug sc could have been due to the drug producing chromosomal damage. Chromosome damage in human leucocytes *in vitro* and *vivo* has been reported (6, 8, 15, 21) but these effects *in vivo* could not be reproduced by others (5, 16, 18, 19). Meiotic chromosome damage in mice treated with high doses of LSD-25 has also been observed (17).

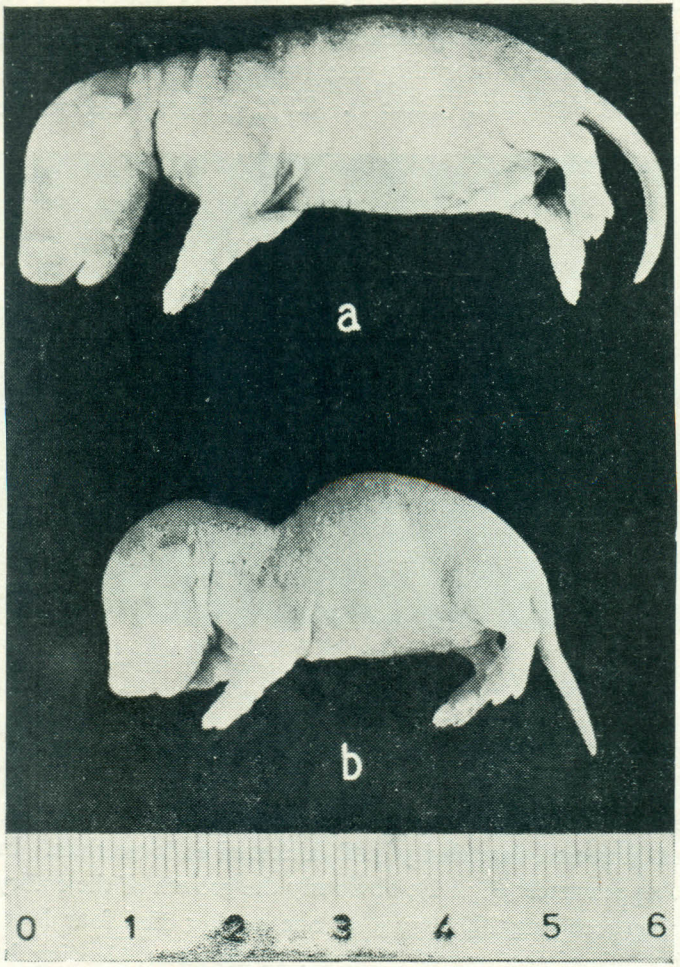

Fig 2: Uteri of normal non-pregnant rat (a) and of rats treated with LSD-25 (200 $\mu g/kg$ sc) on the 4th day of pregnancy. Note the thickened endometrium in b and beaded appearance in C.

Alexander, *et al.* (1, 2) reported an increase in the proportion of deaths during gestation, abortions, resorptions, runting, still births and offspring mortality even with a single dose of 5 $\mu g/kg$ of LSD-25. In our study, though this dose did not produce any effect on offspring, higher doses of 100 and 200 $\mu g/kg$ (sc) significantly increased the foetal mortality. Autopsy of non-littering females showed increased vascularity of uteri, thickened endometrium, and arrest of foetal growth. These are in accord with those of Alexander *et al.* (1,2). We did not interrupt pregnancy after treatment but the animals were permitted to come to term. Auerbach and Rugowski (4) who interrupted pregnancy on the 7th day in mice observed a

six-fold increase in the number of deformities in the CNS of embryos. Our studies did not indicate any specific pattern of damage to organs except that some animals were stunted. However, detailed pathological work may reveal changes which we were unable to detect.

No conclusion on the teratogenic potential of LSD-25 can be drawn from our study. 5 $\mu g/kg$ of LSD-25 orally would be the dose comparable to human consumption. In the present study even 200 $\mu g/kg$ orally did not produce any offspring damage. Only subcutaneous administration of 100 and 200 $\mu g/kg$ doses produced increase in off-spring mortality, decrease in litter size, and increase in the number of resorptions. These doses are far in excess of the comparably human doses customarily employed for self medication. Moreover, toxic activity of a drug in one species need not imply toxic activity in other species. Detailed studies in humans being LSD-25 chronically and the effects of the drug on pregnancy and human foetuses are essential. However, caution is indicated in the indiscriminate use of the drug.

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