EFFICACY OF PROGESTERONE ON THE MAINTENANCE OF PREGNANCY IN PHENOBARBITAL OR BARBITAL SODIUM-TREATED RATS

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ABSTRACT

Effect of barbiturates in the blockade of proestrous LH surge and their inhibition in the release of pituitary gonadotrophins and prolactin are well established. Besides, these drugs inhibit overian compensatory hypertrophy in hemispayed rats and cause abortion in pregnant rats. Administration of human chrionic gonadotrophin has failed to maintain the pregnancy in barbiturate-treated pregnant rats as resorption of foetuses is observed at autopsy. In the present experiment phenobarbital or barbital sodium, is administered to the pregnant rats. Simultaneously progesterone in olive oil is administered subcutaneously. Foetal survival of 77.4 % to 93.9 % is observed in these progesterone treated groups on day 20 at autopsy. The results also indicate that these drugs act directly on overian progesterone synthesis besides their prime action on hypothalamo-hypophysial axis in the inhibition of gonadotrophin release.

INTRODUCTION

BARBITURATES are known to inhibit pituitary LH surge and tonic release of gonadotrophins in rats and hamsters[1-5]. Besides, these drugs also interfere with the pituitary prolactin release when administered on proestrus[6,7]. Karavolas and coworkers observed lowered progesterone synthesis in the ovaries and adrenals of phenobarbital treated rats both *in vivo* and *in vitro*[8-10]. In our earlier studies barbiturates have been found to inhibit the ovarian compensatory hypertrophy in hemispayed rats and cause abortion or foetal resorption in pregnant rats[11-12]. As pituitary gonadotrophins are essential during the first 12 days of pregnancy for successful maintenance of gestation, the failure of maintenance of pregnancy in barbiturate-treated rats is likely to be due to inadequate supply of pituitary gonadotrophins[13-15]. Therefore an attempt is made to maintain pregnancy in barbiturate-treated rats by administering HCG, but under these conditions poor foetal survival was observed indicating the failure of maintenance of pregnancy[16]. In the present investigation, progesterone has been administered to these barbiturates-treated rats to test the efficacy of this hormone to maintain pregnancy.

MATERIALS AND METHODS

Nulliparous rats of Holtzman's strain, weighing 140–180 g (80–90 days old) at proestrus or early estrus were kept in the cage with "proven" males. The rats showing sperms in the vaginal smear on the subsequent day were selected for experimentation and the day was designated as day 1 of pregnancy. All the pregnant rats were laparotomized on day 8, to note the number of implantations and the treatment was started from the same day.

EXPERIMENT-I

A dose of phenobarbital (7.5 mg/100 g body wt) found effective[12] was administered in 0.5 ml saline, twice a day from day 8–11 of pregnancy. Progesterone at a dose of 5 mg/100 g body weight in 0.2 ml olive oil was administered subcutaneously to the phenobarbital treated rats from day 8–19 or 8–12 of pregnancy.

EXPERIMENT-II

Barbital sodium (20 mg/100 gm body wt)[12] was administered in 0.5 ml saline, twice a day from day 8–11 of pregnancy. Progesterone 5 mg in 0.2 ml olive oil was administered subcutaneously to the barbital sodium-treated rats from day 8–19 or 8–12 of pregnancy.

All the rats were housed in individual cages during the period of experimentation, at a room temperature of 27 ± 1°C with Hindustan Lever rat pellets and water *ad libitum* with a lighting schedule of 12 hr light/12 hr darkness. All the rats were autopsied on day 20 of pregnancy. Ovaries, placeatae and foetuses were weighed. The number of implantations, live foetuses,

placentomas and placental scars was counted and the per cent foetal survival was calculated.

RESULTS

Pregnancy maintenance

In saline-treated control group 5/5 rats maintain pregnancy to full term. But phenobarbital and barbital sodium treatment caused loss of pregnancy completely in 8/8 or 8/9 rats respectively, as observed by profuse vaginal bleeding on day 12–13 of pregnancy. Administration of progesterone from day 8–19 of gestation to phenobarbital-treated rats maintained gestation completely in 2/6 rats and the other 4 rats maintained partial pregnancy. Likewise in barbital sodium-treated rats 3/5 rats maintained complete pregnancy and in the other two rats partial maintenance was seen. The pregnancy loss was indicated by the placentomas and placental scars in progesterone-treated rats at autopsy are negligible. Progesterone treatment from day 8–12, concurrently with phenobarbital or barbital sodium was also successful in counteracting the adverse effect of these sedatives on pregnancy, as respectively 4/6 or 4/7 rats maintained complete pregnancy in both the groups. In all these experimental groups, no rat exhibited complete abortion or foetal resorption indicating the effectiveness of progesterone in the maintenance of pregnancy in barbiturate-treated rats.

Foetal survival

In saline-treated control group 97% foetal survival is observed. 37 foetuses/38 implantation sites were observed at autopsy. But with phenobarbital treatment all the implantations were lost with no foetal survival. When progesterone was administered from day 8–19 or from day 8–12, along with phenobarbital 43 foetuses/48 implantations or 46 foetuses/48 implantations survived respectively. The progesterone treatment from day 8–19 or from day 8–12 to barbital sodium-treated rats also maintained pregnancy successfully as 35 foetuses/39 implantations or 41 foetuses/53 implantations are seen respectively.

Changes in the weights of the ovaries

The ovaries of saline-treated controls weigh 40 $\pm$ 4 mg. Significant reduction in the ovarian weight is observed after phenobarbital or barbital sodium treatment as the ovarian weight is 31 $\pm$ 1 mg ($P < 0.05$) or 26 $\pm$ 1 mg ($P < 0.01$) respectively. Progesterone administration to barbiturate-treated rats showed no change in the ovarian weight when compared to saline-treated controls.

DISCUSSION

Several investigations showed that pregnancy is dependent on pituitary luteotrophins during the first 12 days and thereafter placental luteotrophins take over the function of pituitary gonadotrophins in rats[17–19]. But the ovaries in pregnant rat remain in functional status throughout the pregnancy as the regression of corpora lutea is observed only after day 18 of pregnancy[20–21]. As barbiturates block the pituitary LH surge and tonic release of LH, FSH and prolactin, the interruption of pregnancy by barbiturates may be due to the continued blockade of pituitary gonadotrophins during early part of gestation[12]. In our earlier experiments the failure of pregnancy by the administration of gonadotrophin in barbiturates-treated rats may be due to improper steroid production from the ovary[16, 22]. In the present experiment concomitant administration of 5 mg progesterone from day 8–19 to the barbiturates-treated rats results in 89.7% foetal survival. The failure of pregnancy maintenance by gonadotrophins and its maintenance by the progesterone in barbiturates-treated rats suggests that barbiturates may act on ovaries, directly affecting the progesterone synthesis as observed by Karavolas and co-workers. Survival of the foetuses with the concomitant cessation of barbiturate and progesterone treatment after day 12, indicates that the barbiturate action on the ovarian steroidogenesis is not prolonged.

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ANNOUNCEMENT

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