A local signal from the gravid horn to the ovary for the onset of parturition in rats

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Summary. Rats were unilaterally ovariectomized on Day 17 of pregnancy and the times of onset of parturition were recorded. Unilateral ovariectomy did not delay the onset of parturition in bilaterally pregnant rats. In rats which were unilaterally pregnant (spontaneously or after ligation of one uterine horn), removal of the ovary on the side of the gravid horn led to delayed or partial parturitions. When fetuses and placentas were removed from one uterine horn on Day 13 and the ovary from the opposite side on Day 17, or when the uterine artery and/or vein were ligated on one side and the ovary removed from the other, about half of the parturitions were abnormal. It is suggested that a substance produced by the gravid uterine horn is transmitted to the ovary, primarily by a local circulatory system, and thus initiates the onset of parturition.

Introduction

In rats, the maintenance of pregnancy depends upon the ovarian secretions and, after Day 12 of pregnancy these secretions are maintained by a placental lactogen factor (Astwood & Greep, 1938; Ray, Averill, Lyons & Johnson, 1955; Wiest, Kidwell & Balogh, 1968; Sin, Eto, Hashimoto & Suzuki, 1971). At the end of pregnancy, the ovarian production of progesterone falls, particularly after Day 18 (Hashimoto, Henricks, Anderson, & Melampy, 1968; Csapo & Wiest, 1969; Uchida, Kadowaki, Nomura, Miyata & Miyake, 1970; Wiest, 1970; Morishige, Pepe & Rothchild, 1973; Fuchs, 1974), while that of oestrogens rises sharply on Days 21 and 22 (Yoshinaga, Hawkins & Stocker, 1969; Shaikh, 1971; Waynforth, Pope & Hosking, 1972). In rats, hypophysectomy does not delay parturition (Rodway & Kuhn, 1975). It has been suggested that prostaglandin (PG) F-2 α , which is able to induce luteolysis in late pregnancy (Fuchs & Mock, 1973; Dukes, Chester & Atkinson, 1974; Fuchs, Mock & Sundaram 1974; Strauss *et al.*, 1975), might be the initiator of parturition in rats.

The aim of the present investigation was to demonstrate that the signal which initiates parturition in rats comes from the gravid uterine horn and is transmitted to the ipsilateral ovary by a local systemic mechanism, in the same way as the signal for luteolysis at the end of the ovarian cycle is transmitted in sheep (Goding, 1974) and cows (Hansel, Concannon & Lukaszewa, 1973).

Materials and Methods

Animals

Primiparous Sherman or Wistar rats (CNRS, Orléans) were used. They were fed with commercial laboratory food (UAR 103) and kept in groups of 6/cage in a constant temperature (23°C) and photoperiod (14 h light/24 h, lights on 06:00–20:00 h). A proven fertile male was placed into each cage for 1 night. The day of mating was considered to be Day 1 of pregnancy and fertilization was assumed to occur at 02:00 h on that day. After 14 days the rats were palpated to confirm pregnancy.

Each female was isolated after operation on Day 17 so that the time of parturition could be determined. All the rats were killed 1 day after they had given birth.

Treatments

The rats were anaesthetized with ether for all operations and the ovariectomies on Day 17 were performed after handling of the uterine horns while the fetuses were counted.

Group 1 consisted of control rats which were bilaterally pregnant and were unilaterally ovariectomized on Day 17.

Groups 2, 3, 4 and 5 contained unilaterally pregnant animals. Those in *Group 2* were rats which were found to have fetuses in only one horn although corpora lutea were present in both ovaries. In *Group 3* one uterine horn had been ligated at the ovarian extremity 2 weeks before mating so that implantations were possible in only one horn. In *Groups 4 and 5* the fetuses and placentas were removed from one uterine horn at Day 13 of pregnancy. On Day 17 of pregnancy, the ovary on the contralateral side (i.e. that of the empty horn) was removed (*Groups 2, 3 and 4*). The presence of corpora lutea in the excised ovary was confirmed macroscopically and histologically. In *Group 5* the rats were subjected to sham ovariectomy in that they were laparotomized and the uterine horns handled.

Groups 6, 7 and 8. These contained bilaterally pregnant rats and on Day 17 a ligature was placed round the uterine vein (*Group 6*) or the uterine vein and uterine artery (*Groups 7 and 8*). The ligature was on the right or left side and was just before the junction of the utero-ovarian vessels with the uterine vessels (Text-fig. 1). No venule draining the uterine horn flows into the uterine vein above this ligature. The ovary on the side contralateral to the ligatures was then removed from rats in *Groups 6 and 7* and left *in situ* in *Group 8* (controls).

Text-fig. 1. Diagram of the vasculature of a gravid uterine horn in the rat showing the direction of blood flow (solid arrows) and the position of the ligatures in *Groups 6, 7 and 8* (open arrow).

Results

In our rat colony parturition occurs between 12:00 h on Day 20 and 12:00 h on Day 21 in 90% of the animals (Maltier & Cavaillé, 1975). Therefore parturitions occurring during this period were considered as 'normal' and those after 12:00 h on Day 21 as 'delayed'. The delay of parturition was variable, usually from a few hours to 1 day, rarely more because death of the rat tended to supervene before parturition. When fetuses were still present in the uterus at autopsy, parturition was designated as 'partial', whether delayed or normal, but if the rats died before parturition began they were classified as 'no parturition'.

Table 1. The types of parturition obtained (see text) in rats after unilateral ovariectomy on Day 17 of pregnancy

Group	Type of rat	No. of rats	Parturition					Significance*
			Normal	Complete but delayed	Partial but at normal time	Partial and delayed	No parturition	
1	Bilaterally pregnant	18	16	—	2	—	—	—
2	Unilaterally pregnant (spontaneous)	9	1	4	2	1	1	$P < 0.05$
3	Unilaterally pregnant (1 horn ligated)	12	1	3	2	4	2	$P < 0.05$
4	Unilaterally pregnant (fetuses and placentas removed)	15	8	—	4	2	1	$P < 0.05$
5	As for Group 4 but not ovariectomized	9	7	1	—	—	1	N.S.
6	Bilaterally pregnant ligation of uterine vein	20	7	3	6	1	3	$P < 0.95$
7	Bilaterally pregnant ligation of uterine vein + artery	19	10	1	3	2	2	$P < 0.05$
8	As for Group 7 but not ovariectomized	10	10	—	—	—	—	—

* χ^2 test of the ratio of normal parturition : all forms of abnormal parturition compared with that in Group 1.

The results of the experiments are shown in Table 1.

Group 1. Nearly all the parturitions of these rats were normal; one fetus was found *in utero* on the ovariectomized side in each of the two 'abnormal' parturitions.

Groups 2, 3, 4 and 5. Most (90%) of the parturitions in Groups 2 and 3 were abnormal: 12/21 parturitions were delayed (mean delay 26 h) and 3 rats died before parturition. In Group 4 about half the rats had a normal parturition: of the abnormal parturitions, 2 were delayed (occurring at 17:00 h on Day 21 and 08:00 h on Day 22), 4 were partial and 1 rat died on Day 22 without giving birth. In Group 5 only 2 parturitions were abnormal, 1 being delayed (Day 22, 17:00 h) and 1 rat dying.

Groups 6, 7 and 8. In Groups 6 and 7 about half of the parturitions were complete, and most of these were normal rather than delayed. In the 'partial' parturitions the fetuses remaining *in utero* were found in the ligated or ovariectomized sides with equal frequency. All the parturitions in Group 8 were normal.

Discussion

The results show that in all the treated rats, after unilateral ovariectomy on Day 17, the remaining ovary is able to maintain the pregnancy: none of the rats gave birth prematurely.

Maltier & Cavaillé (1975) have previously shown that laparotomy and handling of the uterine horns to inject saline solution into the uterine lumen do not disturb parturition if the injections are performed before Day 18 of pregnancy. In the present study, therefore, the unilateral ovariectomies after laparotomy and handling of the uterus were performed on Day 17 of pregnancy so that any handling effect on the uterus is not implicated in the disturbance of parturition. Removal of the fetuses and placentas from one uterine horn on Day 13, followed by sham ovariectomy on Day 17 (Group 5), or unilateral ovariectomy of bilaterally pregnant animals (Group 1), does not result in significant disturbance of parturition. However, the abnormalities of parturition after unilateral ovariectomy in animals with unilateral pregnancy (Groups 2 and 3) suggest that the gravid horn may have to be near the ovary for normal initiation and performance of parturition.

Ligation of the uterine blood vessels on one side but leaving both ovaries *in situ* (Group 8) results in normal parturition: there was no mortality or resorption of fetuses and the newborn young

appeared normal. However, unilateral ligation of the blood vessels and contralateral ovariectomy (Groups 6 and 7) leads to many abnormal parturitions and indicates that the signal for the initiation of parturition may be transmitted from the uterine horn to the ipsilateral ovary through the local circulatory system, as is the signal for luteolysis in sheep and cows (Goding, 1974; Hansel *et al.*, 1973).

In the rat, the ability of the uterus to limit the life-span of the corpora lutea during pseudopregnancy depends upon the proximity of the uterus to the ovary (Barley, Butcher & Inskeep, 1966); the utero-ovarian vein and artery also adhere very closely to one another (Del Campo & Ginther, 1972). The possibility of a transfer of substances from the venous uterine blood to arterial ovarian blood is suppressed after ligation of the uterine vein or uterine vein and artery simultaneously and in such rats half the parturitions are abnormal although most of them occur in the normal period (partial or complete). It therefore seems that the signal for parturition can be transferred to the contralateral ovary in bilaterally pregnant rats and in those in which the unilateral pregnancy is achieved by excision of the fetuses and placentas, but not in the rats in Groups 2 and 3 with other types of unilateral pregnancy (spontaneous or after ligation of one uterine horn). This difference is perhaps due to the hypertrophy of the vascularization which occurs in the two uterine horns in rats with bilateral pregnancy. Another explanation is that the production of the substance giving the signal for parturition is greater (perhaps linked to the number of fetuses) in rats with bilateral pregnancy or in rats in Group 4 (in which the decidua exists in both uterine horns), and therefore its transfer to the contralateral ovary would be easier.

There is much evidence to indicate that the substance produced by the gravid horn would be a prostaglandin: the ability of the rat uterus to produce PGF-2 α in late pregnancy has been shown (Harney, Sneddon & Williams, 1974; Williams, Sneddon & Harney, 1974) and Labhsetwar & Watson (1974) have found PGF-2 α in the uterine venous blood. Moreover, Parnham, Sneddon & Williams (1974) have shown that the fetuses control the uterine output of prostaglandins.

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