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UTERINE REACTIVITY AND ACTIVITY IN THE MOUSE AT VARIOUS STAGES OF THE SEX CYCLE.

By J. M. ROBSON,

Beit Memorial Research Fellow.

(*From the Institute of Animal Genetics, University of Edinburgh.*)

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That the corpus luteum plays a part in determining the reactivity of the uterine muscle at various stages of the sex cycle in certain animals seems to be definitely established. In the rabbit this has been shown by the direct injection of extracts, while in the human subject the lack of reactivity to oxytocin during the later stages of the intermenstruum and during the early stages of gestation are, according to Knaus [1931], also referable to the luteal function. On the other hand, such a mechanism does not appear to exist in the lower rodents, for in these animals the administration of a potent luteal extract does not abolish the uterine reactivity to oxytocin [Siegmund, 1930 *a*], and, moreover, the uterus apparently responds to the posterior lobe hormone during the whole course of gestation [Siegmund, 1930 *b*].

Now previous studies in the rabbit and on the human subject have shown [Robson, 1933 *a*, *b*] that, in as far as the reactivity of the uterus to oxytocin is concerned, pregnancy can in both these species be divided into two stages, namely:

(1) a period during which the uterus shows no reaction whatsoever even to large doses of oxytocin, and

(2) a subsequent period during which the reactivity to oxytocin returns and gradually increases up to parturition at which it attains a maximum.

The development of reactivity during the second part of pregnancy does not appear to be dependent merely upon the withdrawal of the luteal secretion [Robson, 1934] and may to some extent at least be due to the action of œstrin [Robson, 1933 *c*].

The present experiments were undertaken with the object of determining whether in the lower rodents too the later stages of gestation are accompanied by an increasing sensitivity of the uterine muscle to oxytocin. At the same time the physiological state of the uterine muscle during the puerperium and during the œstrous cycle was also investigated.

Technique.

The experiments were performed on mature mice; the animals were mated, and vaginal plugs looked for once a day; pregnancy was dated from the first finding of the plug.

The uterine strips removed at various stages of the sex cycle were suspended in Ringer-Locke solution and maintained at a temperature of 37·5° C. with constant oxygen bubbling. When the strips were removed during the earlier stages of gestation the whole horn was used, while later on in pregnancy and during the earlier stages of the puerperium an attempt was made to use strips of a constant length. During the later stages of the puerperium and in non-pregnant animals the whole horn was used. All experiments were performed in duplicate, either both horns or strips from both horns being employed.

In all cases the minimum dose of oxytocin capable of causing a motor effect was determined. A purified preparation of the posterior lobe hormone, "pitocin," kindly supplied by Parke, Davis and Co., was used in this investigation.

Results.

The reactivity of the uterine strips at the various stages of pregnancy and of the puerperium is shown in Table I. It will be seen that during the earliest stages of gestation comparatively high doses of oxytocin are necessary to cause a motor effect. Nevertheless, the response to the hormone is not consistently absent, for in one case (M 29) investigated on the seventh day of gestation 0·2 unit of oxytocin in 100 c.c. of solution brought about a contraction, while in another case (M 3) investigated at the same stage of pregnancy 1 unit of oxytocin caused a contraction.

In those cases investigated later on during gestation from the twelfth day up to full term the uterine muscle showed a higher reactivity and gave a response to doses of the posterior lobe hormone ranging from 0·02 to 0·05 unit, with the exception of animals M 6 and M 7 where the reactivity was considerably lower.

In four animals uterine strips were removed within 1 hour following

parturition, and their reactivity to oxytocin was found to be extremely high, as they gave a reaction to a concentration of the hormone of 0·002–0·003 unit in 100 c.c. of Ringer-Locke.

TABLE I. Showing the reactivity to oxytocin (in units per 100 c.c.) and the spontaneous rhythmic activity of uterine strips removed at various stages of pregnancy and of the puerperium.

Animal No.	Days after mating	Reactivity to oxytocin, units	Spontaneous activity (i)	Spontaneous activity (ii)	Remarks
M 29	7	0·2	1·3	2·0	
M 3	7	1·0	2·0	2·0	
M 4	8	>1·0	—	0·7	
M 5	10	>0·5	0·5	2·4	
M 19	12	0·05	3·5	8·0	Showing placental sign
M 17	12	0·03	6·5	>11·0	
M 6	14	>1·0	6·0	6·0	
M 21	15	0·05	5·5	12·0	
M 18	16	0·05	10·0	>12·0	
M 7	16	0·6	5·0	11·0	
M 13	17	0·03	4·5	>11·0	
M 8	18	0·03	5·0	10·0	
M 1	18	0·02	4·0	3·0	
M 2	18	0·003	8·0	11·0	Within few hours following parturition
M 9	18	0·002	11·0	13·0	1 hour after parturition
M 10	18	0·002	6·0	7·0	Less than 1 hour after parturition
M 31	—	0·003	6·0	9·5	Do.
M 25	—	0·005	4·5	20·0	Morning after parturition
M 16	—	0·1	2·5	2·5	2 days after parturition. Suckling
M 14	22	0·3	1·0	1·0	3 days after parturition. Suckling
M 22	—	0·05	4·5	5·5	4 days after parturition. Not suckling
M 24	—	0·05	1·5	2·0	4 days after parturition. Not suckling
M 11	25	0·1	—	—	6 days after parturition. Suckling
M 20	—	0·05	2·0	2·5	6 days after parturition. Not suckling
M 36	—	0·02	1·5	2·5	10 days after parturition. Not suckling
M 15	31	>0·6	0·7	1·0	11 days after parturition. Not suckling
M 26	—	0·5	—	—	11 days after parturition. Suckling
M 30	32	>0·5	3·5	3·5	13 days after parturition. Not suckling

Eleven animals were investigated at various stages during the puerperium. In one animal (M 25) the experiment was performed on the morning following parturition and the uterus responded to a dose of oxytocin of 0·005 unit. In all other cases the uterine reactivity was lower. An attempt was also made to determine whether suckling had any effect on the reactivity during the puerperium and the relevant data are presented in Table II, from which it would appear that during the earlier stages following parturition the uterine reactivity is higher in the non-suckling than in the suckling animals, while later on there is little or no difference.

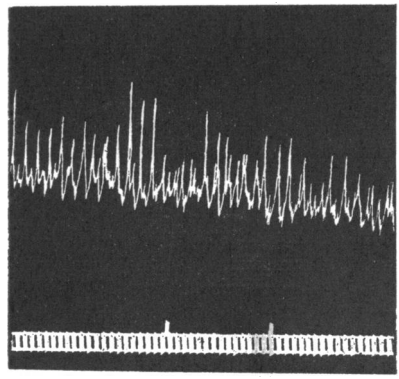

Fig. 1. Showing absence of reactivity to oxytocin of uterine strip removed at the 14th day of pregnancy (M 6). First signal: 0·5 unit oxytocin added to bath. Second signal: 0·5 unit oxytocin added to bath. Time intervals = 1 min.

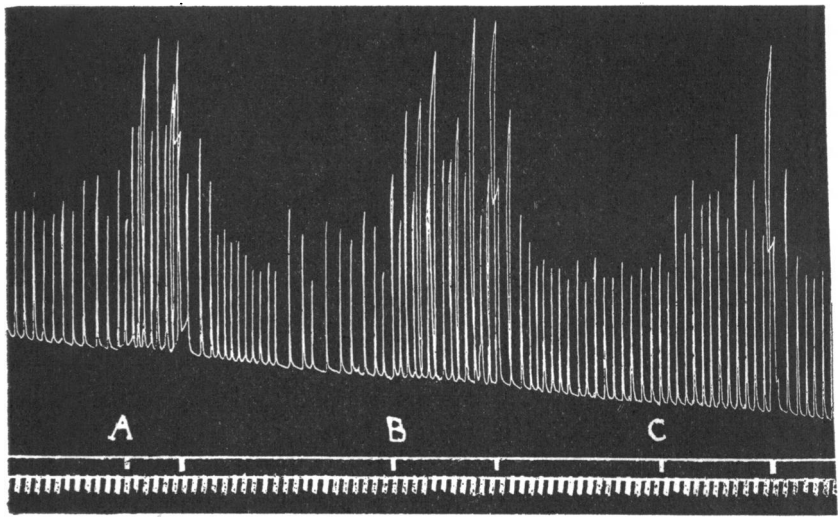

Fig. 2. Showing reactivity to oxytocin of uterine strip removed from the uterus 1 hour after parturition (M 9). *A*, 0·01 unit of oxytocin added to bath; *B*, 0·005 unit of oxytocin added to bath; *C*, 0·002 unit of oxytocin added to bath. Solution changed after every addition of drug. Time intervals = 1 min.

Four animals were mated with vasectomized males and the uterine reactivity investigated from the fourth to the ninth day of pseudo-pregnancy. The minimum effective dose of oxytocin varied from 0·1 to 0·25 unit.

TABLE II. Showing the reactivity to oxytocin and spontaneous rhythmic activity of uterine strips removed at various stages of the puerperium.

R. = reactivity to oxytocin in units per 100 c.c.
S.A. = spontaneous rhythmic activity.
O. = œstrus.
D. = diœstrus.

Suckling				Non-suckling				
Animal No.	Day of puerperium	R.	S.A.	Animal No.	Day of puerperium	R.	S.A.	Vaginal smear
M 16	2	0·1	2·5					
M 14	3	0·3	1·0					
				M 22	4	0·05	4·5–5·5	O.
				M 24	4	0·05	1·5–2·0	D.
M 11	6	0·1	—	M 20	6	0·05	2·0–2·5	O.
M 26	11	0·5	—	M 36	10	0·02	1·5–2·5	O.
				M 15	11	>0·6	0·7–1·0	D.
				M 30	13	>0·5	3·5	D.

Spontaneous activity.

The spontaneous rhythmic activity exhibited by the strips *in vitro* was also determined and is given in Table I. The results have been expressed in quite arbitrary units, the figures given actually representing the height in centimetres of the maximum contractions given in each experiment by the two strips, and measured on the tracings. It is not suggested that the figures represent exactly the spontaneous contractility of the muscle as, though the length of the strips has been kept constant as far as possible, the actual mass of the muscle has varied very considerably. There can be little doubt that the marked differences in spontaneous activity exhibited between the strips removed during the earlier and later stages of gestation is to some extent due to differences in the muscle mass. On the other hand the strips removed during the later stages of pregnancy and during parturition were of fairly uniform size, and the results obtained with them suggest that the spontaneous rhythmic contractility (obtained *in vitro*) during parturition is not appreciably greater than during the days immediately preceding parturition. During the puerperium the rhythmic contractions rapidly decrease, but it is difficult to determine to what extent this is due to involution of the uterus.

Alterations during the œstrous cycle.

The reactivity to oxytocin and spontaneous rhythmic activity were determined in seven animals at various stages of the œstrous cycle. Smears were taken daily and only those animals used which showed

regular cycles for several weeks. The results (cf. Table III) appear to show that the reactivity is rather higher during œstrus than during dicestrus, and that at both these stages it is less than at parturition.

TABLE III. Showing the reactivity to oxytocin and spontaneous rhythmic activity of uterine strips removed at various stages of the œstrous cycle.

R. = reactivity to oxytocin in units per 100 c.c.
S.A. = spontaneous rhythmic activity.

Animal No.	Stage of Œstrous Cycle. Pro-œstrus R.	Pro-œstrus S.A.	Œstrus, 1st day R.	Œstrus, 1st day S.A.	Œstrus, 3rd day R.	Œstrus, 3rd day S.A.	Dicestrus R.	Dicestrus S.A.
M 41	0·02	0·7–0·9	—	—	—	—	—	—
M 36	—	—	0·02	1·5–2·5	—	—	—	—
M 32	—	—	0·005	2·0–4·0	—	—	—	—
M 35	—	—	—	—	0·02	1·4–3·0	—	—
M 34	—	—	—	—	—	—	0·05	0·8–2·0
M 37	—	—	—	—	—	—	0·05	0·2–0·4
M 38	—	—	—	—	—	—	0·05	0·7

DISCUSSION.

The experiments described in this paper indicate that in the mouse the reactivity of the uterus shows definite alterations during the various stages of the sex cycle, of which the essential features are:

(1) It is comparatively low during the early stages of gestation, increases later and reaches a maximum at parturition, to fall again during the ensuing puerperium.

(2) It is comparatively low during pseudo-pregnancy.

(3) It is, on the whole, slightly higher during œstrus than during dicestrus.

It is to be noted that at no stage was a complete absence of reactivity consistently found, and in this respect the observations are in agreement with those of Siegmund [1930 *b*].

The data obtained during pregnancy resemble, in some important respects, those previously described for the rabbit and for the human subject. The complete absence of reactivity to oxytocin which characterizes the first half of gestation in the rabbit, and the early stages of pregnancy in the human subject is not observed in the mouse, but on the other hand the uterine reactivity at the later stages of gestation are very similar in all three species. Moreover, not only does parturition mark the apex of the uterine sensitivity to oxytocin in these animals, but the actual concentrations of the posterior lobe hormone necessary to bring about contraction of the uterus are remarkably similar, being all within the range of from 0·01 to 0·001 unit of oxytocin in 100 c.c. of

solution. It is worthy of emphasis that this obtains, even though the actual mass of muscular tissue was considerably less in the experiments on the mouse than in those performed on the rabbit and human subject. Further, the reactivity in the mouse during the puerperium rapidly falls and in this respect the findings are again very similar to those reported for the rabbit. Moreover, the recent work of Moir [1934] tends to show that in the human subject too the post-parturient period is marked by a very rapid fall in the uterine reactivity to oxytocin.

As regards the control of the alterations in the uterine muscle, it appears likely that in the mouse an inhibitory hormone of the corpus luteum is not the main factor concerned in the determination of the reactivity to oxytocin, since at no stage of gestation is there a complete absence of such reactivity. This is in harmony with the finding of Siegmund [1930 *a*], who was unable to produce inhibition of the reactivity to oxytocin by the injection of a potent luteal extract. At the same time further work is necessary before it can be asserted that the luteal hormone plays no part whatever in determining the comparatively low reactivity observed during the early stages of pregnancy and during pseudo-pregnancy in the mouse.

The spontaneous rhythmic activity of the uterine strips appears to be substantially higher during the second half of gestation and during parturition than before and after these two periods respectively; there is, however, no evidence that the rhythmic contractions at parturition are appreciably greater than during the latter part of gestation, and in this respect the results are similar to those previously described for uterine strips removed from the pregnant and parturient human uterus [Robson, 1933 *b*].

SUMMARY.

The reactivity to oxytocin and spontaneous rhythmic activity exhibited by isolated uterine strips removed from the mouse at various stages of the œstrous cycle, of pregnancy and parturition and of the puerperium have been determined. As has previously been observed in the rabbit and in the human subject parturition marks the apex in the reactivity curve of the uterine muscle to oxytocin. The spontaneous rhythmic activity increases markedly during the later stages of gestation, but does not show any further increase at parturition. The hormonic control of the alterations in the uterine muscle is discussed.

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