BIOLOGY OF REPRODUCTION 19, 552–557 (1978)

Effects of Oxytocin Antiserum and of Indomethacin on hCG-Induced Ovulation in the Rabbit

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ABSTRACT

The main purpose of this investigation was to determine whether oxytocin participates in the process of ovulation in the rabbit. Part of the study was directed to investigate the possibility of a relationship between oxytocin and prostaglandins in connection with ovulation.

Ovulation was induced by the administration of human chorionic gonadotropin (hCG). A group of rabbits was treated with two different concentrations (1/5 dilution and undiluted) of a specific antiserum to oxytocin injected immediately before the administration of hCG. The number of ruptured follicles was determined 12 h after administration of hCG. The number of ovulation points in control rabbits was 7.7 ± 0.8, while the group treated with the highest concentration of antiserum showed a mean of 3.8 ± 1.1. The difference was statistically significant ($P < 0.02$). Other groups of animals were treated with indomethacin or with the combined administration of indomethacin and oxytocin antiserum. The number of ovulation points observed in the animals treated with indomethacin and antiserum was not significantly different from that of the group of animals in which those agents were administered separately.

It is concluded that oxytocin may play a role in ovulation. The possible mechanisms of action are discussed.

INTRODUCTION

The mechanisms which cause follicular rupture and extrusion of the ovum have still not been completely elucidated. The enzymatic digestion of the follicular wall as well as local vascular changes have been postulated as possible mechanisms of ovulation. In the last few years, substantial evidence has been accumulated to implicate the contractility of ovarian smooth muscle in the ovulatory process (Rocereto et al., 1969; Palti and Freund, 1972; Virutamasen et al., 1976; Wright et al., 1976). The effect of several agents including catecholamines and prostaglandins, among others, on ovarian contractility has been widely studied (Virutamasen et al., 1972; Walles et al., 1974). It has been demonstrated that the blockade of prostaglandin synthesis brought about by indomethacin prevents ovulation and also inhibits ovarian contractility in several animal species (Armstrong and Grinwich, 1972; Grinwich et al., 1972; O'Grady et al., 1972; Armstrong et al., 1974; Wallach, De la Cruz et al., 1975). These effects can be reversed by the administration of prostaglandin $F_{2\alpha}$ (Diaz-Infante, Wright et al., 1974; Saksena et al., 1974; Wallach, Bronson et al., 1975).

The effect of oxytocin on ovarian contractility has been studied in animals and in the human (Virtamasen et al., 1973; Díaz Infante, Virutamasen et al., 1974; Sterin-Borda et al., 1976; Roca et al., 1976). It has been shown that this hormone stimulates the smooth muscle fibers of the ovary and that its effect is greater near ovulation (Gimeno et al., 1974; Roca et al., 1977; Garófalo et al., 1977). However, to our knowledge, the participation of oxytocin in ovulation itself has not yet been studied.

On the other hand, the interaction observed between oxytocin and prostaglandins on the uterus (Brummer, 1972; Flint et al., 1975; Roberts et al., 1976) along with the well known participation of prostaglandins on ovulation, raise the possibility of an interaction of these hormones in connection with the ovulatory process.

Accepted March 28, 1978

Received January 20, 1978

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The purpose of the present study is: first, to determine whether the *in vivo* inactivation of oxytocin by a specific antiserum can prevent gonadotropin-induced ovulation in the rabbit; second, to establish whether there is a relationship between oxytocin and prostaglandins in connection with ovulation.

MATERIAL AND METHODS

Female, sexually mature New Zealand white rabbits, weighing 3.5-4.5 kg. were used. The animals were kept in individual cages under controlled temperature and lighting for at least 2 weeks prior to study. In all the rabbits, ovulation was induced with 100 IU human chorionic gonadotropin (hCG, Serono, Italy) in 1 ml of saline given into the marginal ear vein. Ovulation induced by hCG was studied under the effect of 3 different treatments: oxytocin antiserum; indomethacin and oxytocin antiserum plus indomethacin. In all the experiments, 12 h after the injection of hCG, the animals were killed by an i.v. injection of sodium pentobarbital (60 mg/kg bw). Both ovaries were removed and examined under a stereo microscope. The number of ruptured and nonruptured follicles (hemorrhagic, vascularized and bulging, clear, preovulatory follicles) was recorded. Ovaries and uterus were weighed in all experiments.

The experimental groups were the following:

Oxytocin Antiserum Treatment

Oxytocin antiserum (1 ml) was given into the marginal ear vein immediately before hCG.

Group 1—Oxytocin antiserum undiluted

Group 2—Oxytocin antiserum diluted to 1/5.

Indomethacin Treatment

Indomethacin was injected i.m. at different doses immediately before hCG.

Group 3—5 mg/kg bw.

Group 4—7.5 mg/kg bw.

Group 5—10 mg/kg bw.

Indomethacin was dissolved in distilled water containing Tween 80 (10%) and propyleneglycol (1%).

Combined Treatment with Oxytocin Antiserum and Indomethacin

Intramuscular indomethacin and i.v. antiserum were given immediately before hCG.

Group 6—Indomethacin 5 mg/kg bw and 1 ml of oxytocin antiserum diluted to 1/5.

Group 7—Indomethacin 7.5 mg/kg bw and 1 ml of undiluted oxytocin antiserum.

Control Experiments

Group 8—The animals received only hCG.

Group 9—Rabbit antibovine-gammaglobulin serum (1 ml) injected i.v., immediately before hCG.

Group 10—Vehicle of indomethacin injected i.m., immediately before hCG.

Production of Antisera

Oxytocin antisera were obtained by immunizing rabbits with an oxytocin-bovine gammaglobulin complex. The coupling of oxytocin to bovine gammaglobulin (Schwarz-Mann, USA) was carried out with ethyl-carbodiimide, following the technique of Goodfriend et al., 1964. The immunization was performed injecting 2 mg of the complex dissolved in 1 ml of saline and 1 ml of complete Freund's adjuvant (Difco Laboratories, Detroit, MI) in the foot pads, then 6 more i.m. injections of 1 mg of the complex plus adjuvant were given every 2 weeks. The binding capacity and specificity was assessed by radioimmunoassay (Chard et al., 1970; Roca et al., 1972; Garofalo et al., 1972); the antiserum used in this study exhibited a cross reactivity of 1% with lysine vasopressin. The ability of this antiserum to inhibit the biologic activity of oxytocin was assayed on a strip of lactating mouse mammary gland (Fielitz et al., 1970; Roca et al., 1972). The antiserum completely inhibited the biologic activity of 1.0 ng/ml of oxytocin even at a dilution of 1/200. Antibovine gammaglobulin serum was obtained in rabbits; bovine gammaglobulin was administered following the same schedule used for the complex (see above). The antiserum contained a similar titer of bovine gammaglobulin antibodies as the oxytocin antiserum (tested by immunodiffusion techniques). This antibovine gammaglobulin serum was used in our experimental design to minimize any possible effect of bovine gammaglobulin antibodies on ovulation.

The data were statistically analyzed by the Student's t test for independent samples.

RESULTS

Oxytocin Antiserum Treatment

Administration of oxytocin antiserum resulted in an inhibition of exogenously induced ovulation. As shown in Table 1, the inhibition was obtained in the rabbits treated with undiluted antiserum (group 1), which had a significantly lower number of ovulation points than the corresponding controls (groups 8 and 9), $P < 0.02$ and $P < 0.05$, respectively. Oxytocin antiserum

TABLE 1. Number of ovulation points in rabbits under different treatments.

	hCG	Anti-bovine gammaglobulin	Oxytocin antiserum dilution 1/1	Oxytocin antiserum dilution 1/5	Vehicle	Indomethacin (mg/kg bw) 5	Indomethacin (mg/kg bw) 7.5	Indomethacin (mg/kg bw) 10	Combined treatment low level	Combined treatment high level
No. of rabbits	10	6	10	9	8	10	10	10	9	9
	9	11	1	5	6	8	7	7	5	0
	11	7	4	10	5	5	0	6	5	0
	10	7	1	9	5	8	1	4	10	7
	10	11	8	7	11	7	6	1	6	5
	2	7	5	7	9	7	3	0	2	4
	6	5	10	9	7	8	9	8	9	0
	8		1	7	8	10	1	0	1	0
	6		0	9	9	10	8	0	4	4
	8		1	9		1	0	0	7	5
	7		7			3	0	0		
Mean ±	7.7	8.0[a]	3.8[a]	8.0	7.5[b]	6.7	3.5[b]	2.6[b]	5.4	2.7
SEM	0.83	1.0	1.12	0.53	0.75	0.92	1.15	1.04	0.98	0.92

[a]Oxytocin antiserum 1/1 vs anti-bovine gammaglobulin ($P<0.05$)
[b]Indomethacin 7.5 and 10 mg/kg bw vs vehicle of indomethacin ($P<0.02$ and $P<0.01$, respectively).
The other groups did not show significant differences with their corresponding controls.

diluted to 1/5 proved to be insufficient to inhibit the ovulatory response. Animals treated with anti-bovine gammaglobulin did not differ in the number of ovulations from the rabbits treated with hCG only. Regarding the number of nonruptured, mature follicles, no significant differences were observed among the mentioned groups (see Table 2).

Indomethacin Treatment

Blockade of ovulation by indomethacin showed a dose response relationship (Fig. 1); the correlation coefficient was significant ($P < 0.01$). As may be observed in Table 1, the dose of 5 mg/kg bw did not affect ovulation at all, while 7.5 and 10 mg/kg bw of indomethacin produced an inhibition of ovulation that was proportional to the dose. The vehicle used for the injections of indomethacin had no detectable effect on ovulation. No significant differences were found among the number of nonruptured mature follicles (Table 2).

Combined Treatment with Oxytocin Antiserum and Indomethacin

The combined treatment, which was performed at 2 levels, i.e., a high dose of antiserum plus a high dose of indomethacin (group 7) and a low dose of antiserum plus a low dose of indomethacin (group

TABLE 2. Number of mature nonruptured follicles in rabbits under different treatments.

	hCG	Anti-bovine gammaglobulin	Oxytocin antiserum dilution 1/1	Oxytocin antiserum dilution 1/5	Vehicle	Indomethacin (mg/kg bw) 5	Indomethacin (mg/kg bw) 7.5	Indomethacin (mg/kg bw) 10	Combined treatment low level	Combined treatment high level
No. of rabbits	10	6	10	9	8	10	10	10	9	9
	2	2	10	12	13	8	9	7	6	18
	10	8	5	10	8	7	12	5	6	13
	2	5	13	2	1	0	9	7	1	9
	8	0	9	4	4	5	7	10	3	12
	12	7	9	4	7	5	7	13	11	7
	10	7	4	19	4	6	1	4	8	15
	5		12	4	7	0	15	16	14	21
	14		8	7	2	8	4	12	10	7
	5		15	2		25	21	14	8	5
	17		3			12	14	21		
Mean	8.5	4.8	8.8	7.1	5.7	7.6	9.9	10.9	7.4	11.9
±SEM	1.59	1.3	1.24	1.88	1.35	2.24	1.83	1.68	1.33	1.8

No significant differences were found between the treated animals and their corresponding controls.

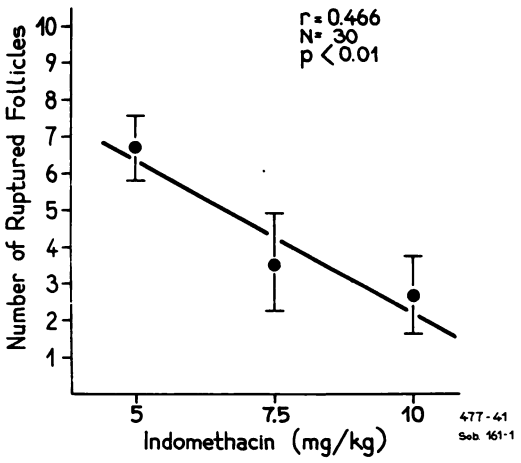

FIG. 1. Inhibition of ovulation by increasing doses of indomethacin. Vertical lines indicate ± SEM.

6), were compared against the corresponding noncombined treatments. As can be seen in Table 1, the inhibitory effect on ovulation produced by oxytocin antiserum plus indomethacin tends to be greater than that of any of those inhibitors when given alone. However, the statistical analysis showed no significant differences.

Uterine and Ovarian Weights

In all the experiments, the weight of uterus and ovaries was the expected one for the estrogenic effect induced by hCG. No significant differences were found among the experimental groups studied (Table 3).

DISCUSSION

Our results show that biological inhibition of oxytocin by the administration of a specific antiserum determined a blockade or, at least a delay, in ovulation. The possibility that ovulation is only delayed should not be discarded because the ovaries were not observed for more than 12 h after hCG. Since follicle maturation was not significantly altered in our experiments, the inhibition of ovulation, which is partial at the antiserum doses used, probably takes place at the last stages of the process. On the other hand, no significant modifications of the uterine and ovarian weights were observed. This may be an indirect index showing that ovarian steroidogenesis was not substantially altered. Since present data suggest that oxytocin is involved in the ovulatory process, its possible mode of action will be discussed. It has been reported that oxytocin is capable of stimulating ovarian contractility (Virutamasen et al., 1973; Díaz-Infante, Virutamasen et al., 1974; Sterin-Borda et al., 1976; Roca et al., 1976) and this effect was found increased near ovulation in some animal species (Gimeno et al., 1974; Roca et al., 1977; Garófalo et al., 1977). These findings, along with present observations, lead us to postulate that the lack of oxytocin determines the absence of ovarian smooth muscle stimulation and ultimately impedes follicular rupture.

Does oxytocin act directly on the ovary and more specifically on the ovarian smooth muscle or could it trigger other mechanisms? It is widely accepted that prostaglandins play an important role in ovulation (Tsafriri et al., 1972; Grinwich et al., 1972; Wallach, Bronson et al., 1975). Some authors suggested that prostaglandins exert their action through the stimulation of ovarian contractility (Díaz-Infante, Wright et al., 1974; Armstrong et al., 1974). On the other hand, in the last few years, many papers have been published about the interrelationship between oxytocin and prostaglandins. Brummer (1971, 1972) and Gillespie (1972) showed that the effect of oxytocin

TABLE 3. Uterine and ovarian weights in the different groups of rabbits.

Group	Treatments	Uterine weight Mean ± SEM	Ovarian weight Mean ± SEM
1	Undiluted oxytocin antiserum	3.33 0.44	0.38 0.02
2	Oxytocin antiserum diluted to 1/5	4.96 0.26	0.52 0.11
3	Indomethacin 5 mg/kg bw	4.44 0.50	0.56 0.08
4	Indomethacin 7.5 mg/kg bw	6.0 0.59	0.54 0.04
5	Indomethacin 10 mg/kg bw	4.48 0.50	0.51 0.05
6	Oxytocin antiserum (1/5) plus Indomethacin 5 mg/kg bw	5.61 0.35	0.67 0.08
7	Oxytocin antiserum (1/1) plus Indomethacin 7.5 mg/kg bw	4.57 0.39	0.60 0.06
8	hCG only	3.63 0.36	0.46 0.02
9	Bovine-gammaglobulin antiserum	3.93 0.41	0.44 0.03
10	Vehicle of Indomethacin	4.55 0.71	0.58 0.07

No significant differences were found between the treated animals and their corresponding controls.

on the human uterine muscle *in vitro* and *in vivo* is enhanced or potentiated by prostaglandins. Furthermore, there is enough evidence showing that the release of prostaglandins F by the uterus is stimulated by oxytocin and this stimulation would depend also on the ovarian steroids levels (Vane and Williams, 1973; Sharma and Fitzpatrick, 1974; Mitchell et al., 1975; Flint et al., 1975; Roberts et al., 1976; Roberts and McCracken, 1976; Newcomb et al., 1977). On this basis, the second objective of our study was to determine whether or not a relationship between oxytocin and prostaglandins takes place at the ovulatory process. The combined treatment with oxytocin antiserum and indomethacin did not give a significant difference, in terms of ovulation inhibition, with the antiserum or indomethacin given separately. However, the combined treatment seems to have a greater inhibitory effect than each individual treatment. Evidently these results are not conclusive. Probably, the experimental design carried out was not the most adequate to investigate if there is any interaction between oxytocin and prostaglandins. Further studies must be performed to give a more definitive answer to this point.

We may conclude that a new approach on the physiological role of oxytocin results from these preliminary studies, that is, its participation in the process of ovulation.

ACKNOWLEDGMENTS

This investigation received financial support from the World Health Organization.

We are grateful to Prof. Dr. Roberto Caldeyro-Barcia and Prof. J. A. Coch for their encouragement and advice. We are grateful to Dr. F. Nieto for his advice in the statistical treatment of data.

We acknowledge with thanks the cooperation of Mrs. Doris S. de Palumbo and Mrs. Sheila Coronel de Feria in the preparation of the manuscript.

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