Effects of prostaglandins on ovarian blood flow in the bitch

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Summary. Oestrous and anoestrous mongrel dogs were anaesthetized with chloralose-urethane. In one group, the ovaries were isolated *in situ* and the effects of a 15-min infusion of PGF-2 α or PGE-2 on perfusion pressure were measured. In the other group, heated thermocouples were introduced into the stroma of each ovary to measure the changes of local blood flow in response to PGF-2 α and PGE-2 infused into the ovarian bursa for 15 min. Intra-arterial infusion of 25, 50, 100 or 200 ng PGF-2 α /kg/min did not affect perfusion pressure; PGE-2 doses of 3.1, 6.2, 12.5 or 25 ng/kg/min caused reductions in proportion to the dose. All doses of PGF-2 α (50.0, 100 or 200 ng/kg/min) or PGE-2 (25, 50 or 100 ng/kg/min) increased blood flow in the ovarian stroma in proportion to the dose when administered by infusion into the ovarian bursa. There were no differences in the results from oestrous and anoestrous dogs.

It is concluded that PGF-2 α changes intraovarian blood distribution without interfering with the total blood flow while PGE-2 increases both the total and local ovarian blood flow.

Introduction

The uterine luteolytic factor is assumed to be prostaglandin (PG) F-2 α (Pharriss, 1971; McCracken, 1971; McCracken *et al.*, 1972; Horton & Poyser, 1973) and its effect depends on an intact utero-ovarian vascular system (Baird & Land, 1973) for the veno-arterial transfer of the luteolytic factor to the ovaries (Hixon & Hansel, 1974). The inhibitory effect of PGF-2 α on the progesterone secretion of the corpus luteum may be connected with the constriction of the ovarian blood vessels, thereby decreasing ovarian blood flow (Pharriss, 1971; McCracken, 1971). However, Baird (1974) reports that PGF-2 α reduces progesterone secretion in sheep but does not reduce ovarian blood flow. In pseudopregnant rabbits, PGF-2 α increased local blood flow in the stroma while that to the corpus luteum was reduced (Novy & Cook, 1973; Janson, Albrecht & Ahrén, 1975). In the bitch, PGF-2 α is known to reduce ovarian progesterone secretion (Jöchle, Tomlinson & Anderson, 1973), but ovarian blood flow has not been determined.

We therefore studied the effects of PGF-2 α and PGE-2 on the vascular resistance and local blood flow of canine ovaries.

Materials and Methods

The 39 dogs used were mongrels weighing 10-20 kg and of unknown reproductive history. They were classed as being oestrous or anoestrous from examination of the external genitalia and the ovary. Anaesthesia was induced by chloralose and urethane (0.075 and 0.75 g/kg, respectively).

Measurement of vascular resistance. In 19 animals (2 oestrous) the ovaries were isolated *in situ* from the surrounding fat tissues and uterine horn. The arteries and veins were cannulated on both sides and both arteries were perfused with a constant volume of blood by means of a two-channel peristaltic pump from the left femoral artery. Each ovary was perfused with 3-5 ml blood/min at a perfusion pressure to reach 100-120 mmHg. In the arterial cannula there were two side-arms. In one of these perfusion pressure was measured by a Statham's pressure transducer and recorded. Through the other, various doses of PGF-2 α and/or PGE-2 (Upjohn) were administered to the left or right ovary, by an infusion pump, in a random sequence in volumes of ≤ 0.1 ml/min for 15 min. When the

perfusion pressure had returned to the basal value, another PG dose was infused. Blood from the two ovarian veins was led into the right jugular vein, but during infusions this connection was interrupted to prevent the applied agents from getting into the systemic circulation. Blood coagulation was inhibited by heparin (200 i.u./kg: Richter). When necessary, blood loss was counteracted by blood from intact dogs.

Measurement of local blood flow. Flexible, heated thermocouples (Hensel & Ruef, 1954) were introduced parallel to the longitudinal axis into the stroma of both ovaries in another 20 dogs (3 oestrous) so that the changes in local blood flow could be determined by application of heat-clearance principles (McCaffrey & McCook, 1975). The changes were expressed as a percentage of the resting value (100%). Blood pressure was measured in the femoral artery by a Statham's pressure transducer. Because PGs are known to be effective in the systemic circulation, they had to be applied locally. Direct administration into the ovarian artery was not feasible because of the resulting damage of the vascular wall. The introduction of a cannula into the blood vessel, however, necessitates pretreatment with heparin, which, in turn, might lead to the development of a haematoma around the thermocouple. Therefore, PGF-2 α and PGE-2 were administered through a thin cannula built into the ovarian bursa in volumes of 0.1 ml/min over 15 min. PGs were administered into the left or right ovarian bursa once only. Preliminary experiments, in which the effects of administration of PGE-2 by intra-arterial injection and by way of the bursa were compared, showed that absorption by the latter route was satisfactory.

Statistical analysis. Changes occurring in a definite time were calculated and compared to the control level by analysis of variance and Student's *t* test.

Results

The application of PGE-2 into one isolated ovary caused a reduction in the perfusion pressure and thus induced vasodilatation while PGF-2 α had no effect on the contralateral ovary (Text-fig. 1). Overall, none of the PGF-2 α doses had an effect on perfusion pressure but the response to PGE-2 was proportional to the dose given (Table 1).

Text-fig. 1. A typical result to show the effect of prostaglandins on perfusion pressure for bitch ovaries isolated *in situ*. (a) Left ovary, 12.5 ng PGE-2/kg/min, (b) right ovary, 200 ng PGF-2 α /kg/min (arrows).

Table 1. The effects of various doses of PGF-2 α and PGE-2 on the changes of mean $\pm$ S.E.M. perfusion pressure (AmmHg) of isolated in-situ bitch ovaries

PG and dose (ng/kg/min)	No. of exps	Minutes of infusion							Sum of changes during 15 min	
		2	4	6	8	10	12	14		
PGF-2 α										
25	9	1.1 $\pm$ 2.7	2.2 $\pm$ 3.3	2.8 $\pm$ 3.6	2.2 $\pm$ 3.2	2.9 $\pm$ 3.5	2.9 $\pm$ 3.5	5.0 $\pm$ 4.5	33.3 $\pm$ 46.4	
50	6	-2.5 $\pm$ 1.7	-4.2 $\pm$ 2.4	-9.2 $\pm$ 2.4*	-14.2 $\pm$ 2.7**	-14.2 $\pm$ 3.5**	-12.5 $\pm$ 5.6	-14.1 $\pm$ 6.8	-141.7 $\pm$ 41.2*	
100	10	2.5 $\pm$ 3.6	2.5 $\pm$ 3.4	4.0 $\pm$ 5.4	4.0 $\pm$ 5.2	2.5 $\pm$ 6.7	2.0 $\pm$ 8.0	1.0 $\pm$ 8.2	37.0 $\pm$ 77.7	
200	6	0.0 $\pm$ 2.5	-3.2 $\pm$ 2.5	-3.8 $\pm$ 4.2	-4.4 $\pm$ 4.2	-6.9 $\pm$ 3.9	-10.0 $\pm$ 4.2	-8.5 $\pm$ 5.0	-68.8 $\pm$ 44.9	
PGE-2										
3.1	6	-2.5 $\pm$ 2.5	-7.5 $\pm$ 3.4	-14.2 $\pm$ 5.1*	-16.7 $\pm$ 4.8*	-20.0 $\pm$ 4.9**	-20.8 $\pm$ 4.9**	-20.8 $\pm$ 4.9**	-184.2 $\pm$ 44.8**	
6.2	16	-14.4 $\pm$ 2.3**	-18.8 $\pm$ 2.6**	-20.6 $\pm$ 2.3**	-23.4 $\pm$ 3.2**	-24.7 $\pm$ 3.2**	-25.9 $\pm$ 3.3**	-26.3 $\pm$ 3.4**	-281.9 $\pm$ 31.2**	
12.5	8	-18.8 $\pm$ 2.6**	-20.6 $\pm$ 2.6**	-22.5 $\pm$ 2.7**	-23.8 $\pm$ 2.5**	-23.8 $\pm$ 2.5**	-23.1 $\pm$ 2.3**	-21.3 $\pm$ 1.8**	-286.3 $\pm$ 30.8**	
25.0	8	-25.6 $\pm$ 5.6**	-28.8 $\pm$ 5.7**	-30.0 $\pm$ 5.8**	-28.8 $\pm$ 6.1**	-28.8 $\pm$ 5.9**	-28.8 $\pm$ 5.9**	-28.8 $\pm$ 5.7**	-370.0 $\pm$ 74.4**	

Values significantly different from those before infusion, * $P < 0.05$; ** $P < 0.01$.Table 2. The effects of various doses of PGF-2 α and PGE-2 administered by infusion into the ovarian bursa for 15 min on the changes of mean $\pm$ S.E.M. local blood flow (expressed as a % of the flow before infusion) in bitch ovaries

PG and dose (ng/kg/min)	No. of exps	Minutes after infusion								Sum of changes during 15 min
		5	10	15	20	25	35	55	75	
PGF-2 α										
50	5	5.0 $\pm$ 2.7	9.0 $\pm$ 5.6	8.0 $\pm$ 1.2**	10.0 $\pm$ 4.5	7.0 $\pm$ 2.6*	8.0 $\pm$ 3.0*	10.0 $\pm$ 4.2	11.0 $\pm$ 5.1	642.5 $\pm$ 195*
100	5	4.0 $\pm$ 2.4	13.0 $\pm$ 3.7*	21.0 $\pm$ 6.6*	24.0 $\pm$ 9.7	26.0 $\pm$ 11.7	27.0 $\pm$ 10.9	20.0 $\pm$ 7.1*	12.0 $\pm$ 3.4*	1430.0 $\pm$ 462*
200	6	5.8 $\pm$ 4.2	15.0 $\pm$ 5.2*	23.3 $\pm$ 5.4**	27.5 $\pm$ 5.5**	26.7 $\pm$ 4.8**	24.3 $\pm$ 4.0**	31.7 $\pm$ 10.7	22.5 $\pm$ 11.5	1777.2 $\pm$ 330**
PGE-2										
25	5	10.0 $\pm$ 3.5*	18.0 $\pm$ 5.1*	24.0 $\pm$ 4.0**	26.0 $\pm$ 5.1**	25.0 $\pm$ 6.3	24.0 $\pm$ 8.9	17.0 $\pm$ 10.1	14.0 $\pm$ 6.2	1417.5 $\pm$ 452*
50	7	24.3 $\pm$ 12.7	49.3 $\pm$ 20.7	62.0 $\pm$ 22.6*	58.6 $\pm$ 22.0	62.1 $\pm$ 21.9*	61.4 $\pm$ 21.8	45.7 $\pm$ 23.5	32.1 $\pm$ 16.3	3594.6 $\pm$ 1404*
100	5	49.0 $\pm$ 16.3*	70.0 $\pm$ 21.6*	84.0 $\pm$ 28.4*	87.0 $\pm$ 29.8*	91.0 $\pm$ 30.8*	96.0 $\pm$ 35.5*	91.0 $\pm$ 33.0*	82.0 $\pm$ 28.1*	6212.5 $\pm$ 2160*

Values significantly different from those before infusion, * $P < 0.05$; ** $P < 0.01$.

Text-fig. 2. A typical result to show the effect of prostaglandins administered by infusion into the ovarian bursa on the stromal blood flow of the bitch ovary. (a) Left ovary, 0.9% NaCl at a rate of 0.05 ml/min followed by 0.1 μ g PGE-2/kg/min; (b) right ovary, 0.9% NaCl at a rate of 0.05 ml/min followed by 0.2 μ g PGF-2 α /kg/min; (c) blood pressure. The vertical divisions in (a) and (b) represent 2-min periods; time in (c) is synchronous.

The administration of the PGs via the ovarian bursa caused an appreciable augmentation of blood flow in the ovarian stroma (Text-fig. 2) which was related to the dose given (Table 2). PGE-2 was more effective than PGF-2 α . No differences were found between the oestrous and anoestrous dogs in either of the experimental groups.

Discussion

Our results suggest that PGF-2 α increases blood flow in the ovarian stroma in the dog while the vascular resistance (total ovarian blood flow) of the organ remains unchanged. In dogs arterio-venous anastomoses can be observed in the hilum and in the stroma (B. Varga & G. Ungváry, unpublished) and the changes in blood flow are probably due to differential closing and opening of the shunts.

The canine utero-ovarian vascular arrangements would permit the existence of a countercurrent mechanism for transfer of the luteolytic factor (McCracken, 1971) and PGF-2 α could be the luteolytic factor in the dog as it is in the sheep (McCracken *et al.*, 1972) and guinea-pig (Horton & Poyser, 1973), but it does not elicit vasoconstriction.

PGE-2 is synthesized in rabbit and rat ovaries after gonadotrophin stimulation (LeMaire, Yang, Behram & Marsh, 1973; Bauminger & Lindner, 1975). In the dog, ACTH increases ovarian blood flow (Stark, Varga & Ács, 1967; Stark & Varga, 1968). This effect can be blocked by indomethacin, a specific PG-inhibitor, and PGE-2 appears to be the mediator in the blood flow stimulatory effect

of ACTH (Stark & Varga, 1975). Our results suggest that PGE-2 may play a role in the regulation of total and local blood flow of the ovaries, while PGF-2 α , whether originating from the uterus or formed in the ovary, may influence the redistribution of intraovarian blood flow.

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