The direct influence of the embryo on uterine $\text{PGF}_{2\alpha}$ and PGE_2 production in sheep

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In unilateral pregnant ewes, obtained by surgically transecting one uterine horn to isolate it from the rest of the pregnant uterus, the isolated horn develops endometrial oxytocin receptors by day 16 despite being in a hormonal environment equivalent of that of a pregnant ewe. This study examines uterine prostaglandin production in these animals. On day 16 of pregnancy, ewes were anaesthetized and a uterine vein draining each horn and the jugular vein cannulated. Venous blood samples were taken at 10 min intervals for 1 h before and 1 h after an i.v. injection of oxytocin (1 μg). Uterine vein samples were assayed for $\text{PGF}_{2\alpha}$ and PGE_2 and jugular blood samples assayed for 13,14-dihydro,15-keto- $\text{PGF}_{2\alpha}$. All ewes showed high plasma concentrations of 13,14-dihydro,15-keto- $\text{PGF}_{2\alpha}$ after the oxytocin injection. $\text{PGF}_{2\alpha}$ increased in the uterine vein draining the nonpregnant transected horn of a unilaterally pregnant ewe following oxytocin treatment, whereas there was no increase in concentration in plasma draining the pregnant horn. Basal plasma $\text{PGF}_{2\alpha}$ concentrations from the uterine vein draining the pregnant horn were significantly higher than concentrations obtained from the uterine vein of the transected horn while PGE_2 concentrations did not vary between the two horns. After oxytocin injection, there was a significant increase in plasma PGE_2 concentration in venous blood collected from both sides. These results indicate that (1) oxytocin receptors present in the isolated nonpregnant horn can be stimulated by oxytocin to produce $\text{PGF}_{2\alpha}$, despite the steroid environment being that of a pregnant ewe; (2) the presence of the conceptus locally inhibits the endometrial $\text{PGF}_{2\alpha}$ production following the challenge but enhances baseline production; (3) PGE_2 production does not differ between the pregnant and nonpregnant uterine horns of ewes with transected uteri and (4) oxytocin causes a bilateral increase in venous PGE_2 concentrations draining pregnant and nonpregnant uterine horns.

Introduction

Luteolysis in sheep occurs following the pulsatile release of prostaglandin $\text{F}_{2\alpha}$ ($\text{PGF}_{2\alpha}$) (Goding, 1974). Luteal oxytocin, acting at newly developed endometrial oxytocin receptors, is a prerequisite for the release of luteolytic pulses of $\text{PGF}_{2\alpha}$ (Sheldrick and Flint, 1985). The time course of the development of these receptors during the oestrous cycle is determined by ovarian steroid hormones (Vallet *et al.*, 1990). In early pregnancy, luteolysis is inhibited by trophoblast type I interferon (tIFN), an antiluteolytic protein produced by the conceptus between days 10 and 22 of pregnancy (Godkin *et al.*, 1984). tIFN acts by inhibiting the production of endometrial oxytocin receptors, thereby preventing the pulsatile release of $\text{PGF}_{2\alpha}$ by oxytocin (Flint *et al.*, 1991).

After surgical intervention in the cyclic ewe, where one uterine horn is isolated from the rest of the uterus, a unilateral pregnancy can be established following mating, providing an isolated uterine horn without a pregnancy, but subject to the same systemic hormone concentrations as the pregnant animal.

In these ewes, on day 16 of pregnancy, the isolated horn has a low tIFN concentration (as indicated by low antiviral potency) and a high concentration of endometrial oxytocin receptors, similar to that of the nonpregnant animal at luteolysis, whereas the pregnant horn has high antiviral activity and low endometrial receptor concentration (Lamming *et al.*, 1991; Stewart *et al.*, 1992). Endometrial oxytocin receptors occur either as binding sites that are coupled to the prostaglandin-releasing pathways, and can be stimulated by oxytocin to release $\text{PGF}_{2\alpha}$, or as binding sites that cannot be stimulated to release prostaglandin (Vallet *et al.*, 1990). Steroid hormones are implicated in the control of the binding site and the process of coupling the binding site to the prostaglandin pathway; however, the situation is not yet fully understood.

The purpose of this study was to enhance the understanding of the control of oxytocin receptors and their ability to release prostaglandins following oxytocin stimulation by determining whether the differences in oxytocin receptors between transected nonpregnant and intact, pregnant uterine horns are reflected in differences in basal and oxytocin-stimulated prostaglandin production.

Materials and Methods

Animals and surgery

Cyclic Finn-Dorset ewes ($n = 9$) between days 6 and 9 of the oestrous cycle (oestrus = day 0) were anaesthetized with 2.5% thiopentone administered i.v. (1 ml kg^{-1} body mass); an endotracheal tube was introduced and anaesthesia was maintained using halothane in O_2 and N_2O at a ratio of 2:1. The uterus was exposed via a midline laparotomy incision and one of the uterine horns (ipsilateral to an active corpus luteum) was sectioned, the endometrium was cauterized and the two ends sutured resulting in the uterine body and attached uterine horn being totally isolated from the transected uterine horn. On recovery, ewes were checked daily using a vasectomized ram and at oestrus were mated three times using a fertile ram (Stewart *et al.*, 1992).

On day 16 after mating, ewes were again anaesthetized and a uterine vein of each horn cannulated. Veins were chosen that drained a limited area of the appropriate uterine horn so that there was no risk of overlap of the pregnant and the non-pregnant venous drainage. Cannulae were inserted downstream, so that the tip of the cannula rested in close apposition to an appropriate branch of the uterine vein. This method ensured that the cannula could be securely ligated without disturbing the collection of venous blood draining the area. The ends of the cannulae were exteriorized through the sublumbar fossa and secured using a body net. One jugular vein of each ewe was also cannulated. Sodium citrate was used as the anticoagulant during anaesthesia. At the end of the experiment, ewes were killed and the uteri collected and flushed to confirm pregnancy status. Three animals were not pregnant as they had ovulated only on the transected side. These were used as additional nonpregnant controls.

Treatment and sampling regimens

While under anaesthesia, 5 ml blood samples from the jugular vein were obtained at 10 min intervals for 1 h before and 1 h after administration of an i.v. injection of oxytocin ($1 \mu\text{g}$; Hoescht, Frankfurt), placed in a heparinized blood tube and centrifuged at $3000 g$ for 10 min to separate the plasma. The plasma was then frozen at -20°C until analysis for 13,14-dihydro 15-ketoprostaglandin $\text{F}_{2\alpha}$ (PGFM) by radioimmunoassay.

Under a similar sampling regimen, blood samples taken from the uterine veins were placed in ice-cold tubes containing 12.5 mmol methyl salicylate l^{-1} in 6% sodium citrate for $\text{PGF}_{2\alpha}$ and PGE_2 determination. Plasma was immediately separated by centrifugation at $3000 g$ for 10 min at 4°C and approximately 1 ml frozen at -20°C until assayed for $\text{PGF}_{2\alpha}$. Some plasma (0.5 ml) was then added to 0.5 ml of oximating reagent (0.125 mol methoxylamine hydrochloride l^{-1} , 1.0 mol sodium acetate l^{-1} in 10% v/v ethanol, pH 5.6–5.8) to convert ketonic prostaglandins such as PGE_2 into their methyl-oximated derivatives (see Kelly *et al.*, 1986). These samples were left at room temperature overnight so that the oximating reaction could proceed to completion and were then frozen at -20°C .

Assay methods

Plasma PGFM concentrations were determined in samples extracted with diethyl ether using the radioimmunoassay described by Kaker *et al.* (1984). The extraction efficiency was $87.1 \pm 1.1\%$. The antiserum crossreactivity (relative to PGFM) was 8% with 15-keto $\text{PGF}_{2\alpha}$, 0.7% with 13,14-dihydro $\text{PGF}_{2\alpha}$, 0.5% with $\text{PGF}_{1\alpha}$, PGE_1 and PGE_2 and 0.1% with $\text{PGF}_{2\alpha}$. Sensitivity (calculated from $2 \times \text{SD}$ below the zero binding point) was 40 pg ml^{-1} plasma. Intra- and interassay coefficients of variation were 11.1% and 9.8%, respectively. All samples from each animal were analysed within one assay.

Plasma $\text{PGF}_{2\alpha}$ was measured using the direct tritiated radioimmunoassay described by Kelly *et al.* (1986). The limit of sensitivity of the assay was 61 pg ml^{-1} . Intra- and interassay coefficients of variation were 8.6% and 15.8%, respectively. The main crossreactions of the antiserum (relative to $\text{PGF}_{2\alpha}$) were with $\text{PGF}_{1\alpha}$ (7.2%), $\text{PGF}_{2\beta}$ (3.5%), $\text{PGE}_{3\alpha}$ (1.1%), 6-keto $\text{PGF}_{1\alpha}$ (1.05%) and PGFM (1.0%).

Plasma PGE_2 was determined as the methyl-oxime derivative ($\text{PGE}_2\text{-MOX}$), using the radioimmunoassay described by Kelly *et al.* (1986). Briefly, $200 \mu\text{l}$ plasma:oximating reagent mixture samples were used in the assay. Standards ranged from 1 to 1000 pg PGE_2 per tube made up in the assay buffer ($0.05 \text{ mol Tris l}^{-1}$, containing 0.5% w/v bovine gamma globulin (Sigma, Poole, Dorset) pH 7.4). Radiolabelled tracer and antiserum were used at 5000 c.p.m. per tube and 1:40 000, respectively. After overnight incubation at 4°C , bound radioactivity was precipitated by the addition of $750 \mu\text{l}$ 25% (w/v) polyethylene glycol (6000 grade; Fisons plc, Loughborough) in 10 mmol sodium phosphate buffer l^{-1} (pH 7.4). After centrifugation at $2000 g$ for 15 min, the supernatant was discarded by tipping the tubes over a mesh and allowing them to drain on to absorbent paper. The crossreactions of the $\text{PGE}_2\text{-MOX}$ antiserum (relative to $\text{PGF}_{2\alpha}$) were with methyl oximes of PGE_1 (53%), PGE_3 and 20-methyl PGE_2 (both 31%), 19-hydroxy PGE_1 (17.8%), but the antiserum had negligible crossreactions with the non-oximated prostaglandins tested.

The assay was validated for use in ovine plasma by demonstrating identical lines for standard curves containing 0, 10, 100 and $200 \mu\text{l}$ plasma:oximating reagent mixture, in a constant assay volume. In addition, serial dilutions of pooled plasma showed parallel displacement of radiolabelled $\text{PGE}_2\text{-MOX}$ to that exhibited by a series of $\text{PGE}_2\text{-MOX}$ diluted with assay buffer.

The limit of sensitivity of the $\text{PGE}_2\text{-MOX}$ assay was 20 pg ml^{-1} . The intra- and interassay coefficients of variation were 14.3 and 7.0%, respectively.

Statistical analyses

The responses to the i.v. oxytocin injection within groups were assessed by analysing data using analysis of variance and the time response subjected to Duncan's multiple range test to obtain a level of significance for the time points following oxytocin administration. The magnitude of the prostaglandin response to oxytocin was defined as the area under the curve for the hour following the oxytocin injection minus the area

Fig. 1. Mean ($\pm$ SEM) concentrations of 13,14-dihydro 5-ketoprostaglandin $F_{2\alpha}$ (PGFM) in plasma of blood taken from the jugular vein during the hour before and the hour after oxytocin administration. (●) Pregnant ewes ($n = 6$); (○) nonpregnant ewes ($n = 3$).

under the points for the hour preceding the injection. In this way, an estimate of total prostaglandin release in response to oxytocin could be obtained. Prostaglandin responses were compared between groups using Student's *t* test on log-transformed data. Paired and unpaired Student's *t* tests were used to compare baseline values. All values are expressed as mean $\pm$ SEM.

Results

Both transected ewes that were unilaterally pregnant ($n = 6$) and those that were not pregnant ($n = 3$) showed increased plasma concentrations of PGFM in jugular venous effluent following the oxytocin injection ($P < 0.05$ and $P < 0.01$, respectively). In pregnant ewes, the response varied between individual animals. The mean basal PGFM concentration was 128 pg ml^{-1} which increased to 197 pg ml^{-1} after the oxytocin injection. In nonpregnant ewes, the mean baseline concentration was 124 pg ml^{-1} , which rose to a peak concentration of 207 pg ml^{-1} after the oxytocin injection. The rise in plasma PGFM following oxytocin injection in the nonpregnant group was more protracted than that in pregnant ewes; however, there was no significant difference between the groups (Fig. 1).

Prostaglandin concentrations in plasma from a uterine vein draining the pregnant, intact uterine horn were compared with those from the nonpregnant transected horn of the same uterus (Fig. 2). In plasma from the nonpregnant horn, the mean $\text{PGF}_{2\alpha}$ concentrations before oxytocin administration were different from that of the pregnant horn ($1.1 \pm 0.1 \text{ ng ml}^{-1}$ versus $3.0 \pm 0.4 \text{ ng ml}^{-1}$, $P < 0.01$; Fig. 2a, Table 1). There was a 13.7-fold increase in $\text{PGF}_{2\alpha}$ concentration ($P < 0.01$) following the oxytocin injection in uterine venous plasma draining the

Fig. 2. Mean $\pm$ SEM plasma concentrations of (a) $\text{PGF}_{2\alpha}$ (ng ml^{-1}) and (b) PGE_2 (pg ml^{-1}) taken from the uterine veins of intact, pregnant and transected, nonpregnant uterine horns of sheep during the hour before and the hour after oxytocin administration. (●) Pregnant horn ($n = 6$); (○) nonpregnant horn, ($n = 6$).

nonpregnant transected horn, the mean peak concentration being $15.1 \pm 10.1 \text{ ng ml}^{-1}$. The increase in plasma $\text{PGF}_{2\alpha}$ concentration from the pregnant horn following oxytocin treatment was not significant (mean peak concentration, $11.1 \pm 8.6 \text{ ng ml}^{-1}$). Total $\text{PGF}_{2\alpha}$ released over the 2 h sampling period did not differ between the uterine horns (Table 1).

There was no difference in PGE_2 concentrations measured in venous plasma draining the pregnant and the nonpregnant uterine horns. Basal concentrations were $580 \pm 20 \text{ pg ml}^{-1}$ in the pregnant uterine vein and $472 \pm 25 \text{ pg ml}^{-1}$ in the nonpregnant uterine vein (Fig. 2b, Table 1).

There was an increase in plasma PGE_2 following oxytocin administration ($P < 0.05$; Fig. 2b) in both horns. In plasma from the pregnant uterine horn, total PGE_2 concentrations reached peak values of $1100 \pm 205 \text{ pg ml}^{-1}$. This was an increase of 90% above the mean baseline concentrations. Peak concentrations reached in the nonpregnant uterine vein were $940 \pm 160 \text{ pg ml}^{-1}$, an increase of 100% (Table 1).

There were no differences between plasma uterine vein concentrations of PGE_2 and $\text{PGF}_{2\alpha}$ from the two uterine horns of surgically transected bilaterally nonpregnant ewes and from the nonpregnant transected horn of unilaterally pregnant ewes.

Table 1. Peak (ng ml⁻¹) and total (ng ml⁻¹ h⁻¹) prostaglandin concentrations in plasma taken from the uterine veins draining nonpregnant, transected uterine horns and pregnant, intact uterine horns (*n* = 6) of sheep, before and after oxytocin administration

Prostaglandin	Nonpregnant transected horn		Pregnant, intact horn	
	Before oxytocin	After oxytocin	Before oxytocin	After oxytocin
PGF _{2α} : peak	1.1 ± 0.1	15.1 ± 10.1**	3.0 ± 0.4*	11.1 ± 8.6*
: total	65 ± 36	470 ± 200**	200 ± 122*	308 ± 131*
PGE ₂ : peak	0.5 ± 0.0	0.9 ± 0.2*	0.6 ± 0.0	1.1 ± 0.2*
: total	5.6 ± 1.1	9.3 ± 1.3*	7.0 ± 1.7	13.6 ± 3.8*

Values are means ± SEM.

Values significantly different from values for nonpregnant horn before oxytocin administration (**P* < 0.05; ***P* < 0.01).

Discussion

The results of this experiment showed that the transected nonpregnant uterine horn, in ewes that were pregnant in the intact horn, behaved similarly to the uterus of a nonpregnant ewe, in terms of prostaglandin release in response to acute oxytocin administration (McCracken *et al.*, 1984). The increase in endometrial oxytocin receptors in the transected nonpregnant horn (Stewart *et al.*, 1992) presumably allowed the uterus to release PGF_{2α} in response to oxytocin administration. These results showed that this increase in PGF_{2α} was reflected by increased concentrations of prostaglandin metabolites in the systemic circulation. However, luteolysis could not occur because the release of PGF_{2α} was contralateral to the active corpus luteum: PGF_{2α} could not reach the corpus luteum via countercurrent transfer and on entering the general circulation was rapidly metabolized to PGFM. This result confirms that the reappearance of endometrial oxytocin receptors is not dependent on a changing steroid environment, for example the fall in progesterone or the rise in oestradiol normally associated with luteolysis in cyclic ewes.

The release of PGF_{2α} from the nonpregnant transected horn can be monitored in the peripheral circulation by measuring PGFM. Pregnant ewes with transected uteri showed a significant increase in the concentration of PGFM in jugular plasma following the oxytocin challenge. Unexpectedly, basal concentrations of PGFM did not differ significantly between unilaterally pregnant ewes and nonpregnant ewes. However, administration of oxytocin and the resultant increase in PGF_{2α} had no adverse effects on the maintenance of pregnancy. The experiment was not designed to investigate nonpregnant transected ewes as a single group, since these ewes resulted from ewes that had ovulated from the ovary ipsilateral to the isolated, cut uterine horn and were, therefore, unable to be fertilized.

It is well documented that the presence of a conceptus inhibits the increase in oxytocin receptors at the time of expected luteolysis (Roberts *et al.*, 1976; Sheldrick and Flint, 1985). This inhibition is clearly a local effect since the presence of the conceptus in the intact horn inhibits the appearance of endometrial oxytocin receptors in the transected nonpregnant horn (Lamming *et al.*, 1991; Stewart *et al.*, 1992). tIFN, a protein secreted by the trophoblast between day 10 and day 22 of pregnancy, is known to inhibit formation of oxytocin receptors

(Flint *et al.*, 1991). Results from the present study indicate that there was a significant increase in PGF_{2α} in the uterine vein draining the nonpregnant uterine horn following oxytocin administration, indicating that the receptors were active and coupled to the prostaglandin-releasing pathway. The intact, pregnant horn failed to respond to oxytocin administration, confirming that the presence of the conceptus inhibits the prostaglandin response to oxytocin administration, presumably because of the lack of oxytocin receptors (Lamming *et al.*, 1991; Stewart *et al.*, 1992). The present data do not rule out the possibility that other components of the postreceptor signal transduction pathway are also inhibited in the pregnant horn.

Concentrations of PGF_{2α} before the oxytocin challenge were higher in plasma from pregnant horns than from plasma of nonpregnant horns in ewes with transected uteri; these findings are similar to those reported for pregnant ewes (Wilson *et al.*, 1972; Hooper *et al.*, 1986; Burgess *et al.*, 1990). There are two possible reasons for this increase in basal prostaglandin production in early pregnancy in ewes. The conceptus is known to produce large quantities of PGF_{2α} and PGE₂ between day 13 and day 15 of pregnancy (Hyland *et al.*, 1982). However, it is not known whether these products are confined to the uterine lumen or can escape into the venous drainage. However, if this occurs, increased concentrations of PGE₂, in addition to PGF_{2α}, would be expected in the uterine vein draining the pregnant horn. Alternatively, the increase in basal production of PGF_{2α} could simply reflect the metabolism of an unchanged total amount of the prostaglandin precursor arachidonic acid, solely through pathways responsible for basal endometrial PGF_{2α} production, since the pathway normally stimulated by oxytocin is not functioning. This would result in an increased, but more even, release of PGF_{2α}. In the study reported here, total PGF_{2α} production from the two horns was not different, although the pattern of release was altered. After oxytocin treatment, the release of PGF_{2α} was initially lower for the nonpregnant than for the pregnant uterine horn. However, the increase in PGF_{2α} production was sustained for longer in the nonpregnant horn. Phospholipase A₂ is activated by α-interferons (Hannigan and Williams, 1991); this pathway may therefore be responsible for basal PGF_{2α} production and stimulation of phospholipase A₂ may contribute to the redirection of arachidonic acid for increased basal PGF_{2α} release in early pregnancy.

The concentrations of PGE₂ measured in this study are comparable to those recorded by Nett and Niswender (1981) in

the early pregnant ewe. This study shows that PGE_2 production was not altered by the presence of a conceptus. This is in agreement with the *in vitro* findings of Thatcher *et al.* (1992). However, oxytocin administration increased PGE_2 production from both the transected, nonpregnant and the intact, pregnant uterine horns. Assuming that blood flow changes to the uterus are negligible on day 16 of pregnancy compared with that in nonpregnant ewes (Fleet and Heap, 1982), and visual examination and the relative ease of taking the blood samples support this, the results from the study reported here indicate that there was no difference in basal PGE_2 release during early pregnancy compared with that in cyclic ewes and that pregnant and nonpregnant ewes can respond in the same manner to oxytocin administration with increased plasma concentrations of PGE_2 . Since concentrations of endometrial oxytocin receptors are low in pregnant and high in nonpregnant ewes on day 16, the increase in PGE_2 concentrations is unlikely to be associated with endometrial receptors, instead this increase could be a direct effect on the uterine cardiovascular supply. This might also explain the small but nonsignificant increase in $\text{PGF}_{2\alpha}$ seen from the intact, pregnant horn.

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