Inhibition of luteal function by oxytocin antagonist in goats (*Capra hircus*)

A. M. Homeida and M. M. Al-EknaH

College of Veterinary Medicine and Animal Resources, King Faisal University, PO Box 1757,
Al-Ahsa 31982, Saudi Arabia

Summary. Early corpus luteum development in nonpregnant and pregnant goats was characterized by a steady increase in peripheral plasma concentrations of progesterone and a high release of prostacyclin (PGI-2) but low release of prostaglandin F-2 α (PGF-2 α). Jugular administration of oxytocin antagonist (OXA) (0.2 μ g/kg/day) on the day of oestrus and for 3 days thereafter to cyclic and mated goats, significantly ($P < 0.001$) inhibited progesterone and prostaglandin secretion and reduced conception rate. Co-administration of PGI-2 (200 μ g/day) with OXA resulted in a steady increase of progesterone and establishment of pregnancy, but co-administration of PGF-2 α (175 μ g/day) with OXA had no effect. It is suggested that oxytocin is required for early development of the corpus luteum and such effects may be mediated via PGI-2 production.

Keywords: oxytocin; oestrous cycle; prostaglandins; goat

Introduction

Recent investigations have shown that oxytocin is secreted in substantial amounts by the corpus luteum (CL) in several species (Flint & Sheldrick, 1982; Wathes & Swann, 1982; Fields *et al.*, 1983; Kahn-Dawood & Dawood, 1983; Wathes *et al.*, 1983; Kahn-Dawood *et al.*, 1984; Homeida, 1986a). Oxytocin could be involved in regulating luteal regression either directly by a local action on the corpus luteum as in monkeys (Auletta *et al.*, 1984) or indirectly by inducing the release of prostaglandin F-2 α (PGF-2 α), the uterine luteolysin (Horton & Poyser, 1976) in animals such as goat (Cooke & Knifton, 1981; Cooke & Homeida, 1982, 1983) and sheep (Fairclough *et al.*, 1984).

Several other prostanoids are produced by the uterus in response to oxytocin stimulation (Hansel & Dowd, 1986). For example, the myometrium synthesizes prostacyclin (PGI-2) in a greater amount than PGF-2 α (Alwachi *et al.*, 1980). PGI-2 is a luteotrophic agent (Hansel & Dowd, 1986) and is maximally produced by bovine luteal cells early in the oestrous cycle (Milvae & Hansel, 1983), the only time at which high doses of oxytocin are effective in inhibiting luteal function (Armstrong & Hansel, 1959; Cooke & Knifton, 1981; Cooke & Homeida, 1982). However, oxytocin at low doses can stimulate progesterone production by human and bovine luteal cells *in vitro* (Tan *et al.*, 1982a, b). In this study, an oxytocin antagonist (OXA), which inhibited luteal regression in goats (Homeida & Khalafalla, 1987, 1990), was administered at the beginning of the oestrous cycle in goats, to investigate the role of oxytocin on early development of the corpus luteum and on prostaglandin (PG) production.

Materials and Methods

Animals. Thirty-two mature Awassi goats (2–4 years old and with normal oestrous cycle of 19–20 days) were housed in pens under natural daylength and temperature. Animals were synchronized with two 5 mg injections of a

PGF-2 α analogue (Lutalyse: Upjohn Ltd, Crawley, UK) given 11 days apart. When the goats exhibited oestrus (determined by a fertile buck), they were randomly divided into eight groups.

Treatments. In group A, four goats were injected (i.v.) daily with saline (0.9% w/v NaCl) on the day of oestrus (Day 0) and for 3 days thereafter. In group B, four goats were mated to a fertile buck and treated with saline as for group A. In group C, six goats were treated as for group A, but with oxytocin antagonist (OXA) (1-(B-mercapto-B, B-diethylpropionic acid), 2-0-ethyltyrosine, 8-ornithino) vasotocin (dEt₂ Tyr (Et)-OVT, Code KB-IV-24) (a gift from Professor M. Manning) dissolved in saline and given i.v. at 0.2 μ g/kg body weight (Homeida & Khalafalla, 1990). In group D, six goats were mated to a fertile buck and treated as for group C. In group E, three goats were treated with OXA, but, in addition, 200 μ g PGI-2 sodium salt (Upjohn Co., Kalamazoo, MI, USA) in 1 ml saline was injected i.v. This dose produced ~2 ng 6 keto-PGF-1 α /ml in plasma and reduced spontaneous uterine activity (Cooke & Homeida, 1989). In group F, three goats were treated with OXA, but, in addition, 175 μ g PGF-2 α analogue (Cloprostenol, Estrumate, ICI, Pharma, MI, USA) was given intramuscularly; this dose is luteolytic in goats (Stubbings *et al.*, 1986). In groups G (three goats) and H (three goats), animals were mated and treated as for groups E and F, respectively.

All animals were observed for oestrus at least twice a day with the help of a buck. Intensive jugular vein blood (5 ml) was collected hourly between 07:00 and 15:00 h daily on the day of oestrus or mating and for 4 days thereafter by venepuncture using 23-gauge needles. Blood was collected into chilled heparinized tubes, centrifuged at 2000 g for 10 min and plasma was stored at -20°C until analysed. Progesterone and 13, 14 dihydro-15-keto-PGF-2 α (PGFM) and 6 keto PGF-1 α , the stable metabolites of PGF-2 α and PGI-2, respectively, were determined in each plasma sample. To compare the total production pattern of PGs during 8 h, PGs were estimated in pooled samples collected during that period.

Radioimmunoassay of hormones. Plasma progesterone was measured by the radioimmunoassay (RIA) method described by Homeida (1986b), Homeida *et al.* (1988) and Homeida & Khalafalla (1990). Progesterone antibody (provided by Dr H. Dobson) was raised in rabbits against progesterone-11-succinyl-bovine serum albumin, and used at a final dilution of 1:7000; cross-reactions were 100% with progesterone and <0.1% with corticosterone, desoxycorticosterone and ketocorticosterone.

The intra- and interassay coefficients of variation (CV) for progesterone were 4.1 ($n=25$) and 11.1% ($n=20$), respectively, for a plasma sample of low progesterone concentration (0.8 ng) and 4.2 ($n=25$) and 11.6% ($n=20$), respectively, for a plasma of high concentration (5 ng). The sensitivity of the assay was 48 pg/tube. Extraction efficiency was 85.4 ± 5.2 (s.d.)% and the results were corrected for extraction losses.

PGFM was extracted from plasma with diethyl ether and assayed as described by Cooke & Homeida (1985). The antibody (Upjohn, Kalamazoo, MI, USA) was used at a final dilution of 1:1000 and cross-reactions (relative to PGFM = 100%) were: 15-keto-PGF-2 α , 7.5%; 13,14-dihydro-PGF-2 α , 0.7% PGE-2, 0.5%, and PGF-2 α <0.01%. The sensitivity of the assay was 45 pg/ml. The intra- and interassay coefficients of variation were 8.0% ($n=11$) and 11.5% ($n=11$), respectively, for a sample with a low concentration of PGFM (100 pg/ml) and 8.1 ($n=11$) and 11.1% ($n=10$), respectively, for a sample with a high concentration (800 pg/ml). Extraction efficiency was 84.3 ± 7.2 (s.d.)% and results were corrected for extraction losses.

A specific RIA for 6-keto-PGF-1 α in homogenates of sheep uterus was used as described by Liggins *et al.* (1980) and validated by Cooke & Homeida (1989) using an antiserum (4V-208) at a dilution of 1:10 000. Standard curves were constructed using pure 6-keto-PGF-1 α (Upjohn). The recovery of added tracer was $71.0 \pm 5\%$ (mean $\pm$ s.e.m., $n=9$) and results were corrected for extraction losses; the recovery of standards (20, 50, 500, 1000 pg) added to goat plasma was 19.4 ± 1.6 , 51.6 ± 6.8 , 489.0 ± 14.1 and 893.0 ± 17.1 pg (mean $\pm$ s.e.m., $n=6$). The non-specific binding was 8%, the sensitivity of the assay 10 pg/tube, and the intra- and interassay coefficients of variation were 6.1 and 12.1%, respectively ($n=12$). Antiserum specificity has been reported previously (Liggins *et al.*, 1980).

Statistical analysis. Comparisons of hormone concentrations over time were made by ANOVA, taking account of repeated measures from the same animal. Conception rates were compared by χ^2 analysis.

Results

All animals in groups A and B developed corpora lutea (CL) as reflected in their peripheral plasma concentration of progesterone (Table 1). Animals in group A returned to oestrus 19–21 days later, whereas animals in group B did not ($P < 0.001$), and pregnancy was confirmed by steady progesterone concentrations; these animals gave birth to kids after 146–151 days.

All animals in groups C and D except one (OXA-treated) failed to develop CL; progesterone values were significantly ($P < 0.001$) lower than in groups A and B, respectively (Table 1). The mean ($\pm$ s.e.m.) length of oestrous cycle in goats treated with OXA (groups C and D) was 7.3 ± 1.1 ($n=11$) and this was significantly ($P < 0.001$) shorter than that of 19–20 days in animals treated with saline (group A). Post-treatment oestrous cycles were of 20–21 days. One doe in group D had a

Table 1. Mean ($\pm$ s.d.) plasma concentrations of progesterone (ng/ml) during the oestrous cycle in goats treated with saline (groups A and B), oxytocin antagonist (OXA) (groups C and D), OXA + prostacyclin (groups E and G) and OXA + prostaglandin F-2 α (groups F and H)

Day of normal oestrous cycle	n...	Group							
		A	B	C	D	E	F	G	H
		4	4	6	6	3	3	3	3
0*		0.45 $\pm$ 0.1	0.35 $\pm$ 0.1	0.4 $\pm$ 0.1	0.25 $\pm$ 0.1	0.30 $\pm$ 0.1	0.8 $\pm$ 0.1	0.4 $\pm$ 0.1	0.7 $\pm$ 0.1
1		0.7 $\pm$ 0.1	0.6 $\pm$ 0.1	0.8 $\pm$ 0.1	0.6 $\pm$ 0.1	0.7 $\pm$ 0.1	0.7 $\pm$ 0.1	0.8 $\pm$ 0.1	0.7 $\pm$ 0.1
2		1.1 $\pm$ 3.1	1.2 $\pm$ 3.1	0.7 $\pm$ 0.1	0.65 $\pm$ 0.1 ^b	0.6 $\pm$ 0.1	0.5 $\pm$ 0.1 ^a	0.7 $\pm$ 0.1	0.8 $\pm$ 0.1
3		1.8 $\pm$ 3.1	1.6 $\pm$ 0.4	0.51 $\pm$ 0.1 ^a	0.5 $\pm$ 0.1 ^b	1.1 $\pm$ 3.1	0.6 $\pm$ 0.1 ^a	1.3 $\pm$ 0.3	0.6 $\pm$ 0.1 ^b
4		2.1 $\pm$ 0.4	2.3 $\pm$ 0.4	0.35 $\pm$ 0.1 ^a	0.35 $\pm$ 0.1 ^b	2.1 $\pm$ 0.3	0.5 $\pm$ 0.1 ^a	1.8 $\pm$ 0.3	0.5 $\pm$ 0.1 ^b
6		3.3 $\pm$ 0.4	3.4 $\pm$ 0.4	0.45 $\pm$ 0.1 ^{a*}	0.5 $\pm$ 0.1 ^b	3.4 $\pm$ 0.4	0.5 $\pm$ 0.1 ^{a*}	3.1 $\pm$ 0.3	0.6 $\pm$ 0.1 ^b
8		4.1 $\pm$ 0.4	4.6 $\pm$ 0.4	0.50 $\pm$ 0.1 ^a	0.6 $\pm$ 0.1 ^{a*}	3.8 $\pm$ 0.4	1.3 $\pm$ 0.3 ^a	3.6 $\pm$ 0.3	0.7 $\pm$ 0.1 ^b
10		4.4 $\pm$ 0.4	4.6 $\pm$ 0.4	1.1 $\pm$ 0.3 ^a	1.4 $\pm$ 0.3 ^b	4.6 $\pm$ 0.4	1.8 $\pm$ 0.3 ^a	3.8 $\pm$ 0.4	1.3 $\pm$ 0.2 ^b
15		3.1 $\pm$ 0.4	4.5 $\pm$ 0.4	3.5 $\pm$ 0.4	3.1 $\pm$ 0.4	4.2 $\pm$ 0.4	2.1 $\pm$ 0.3 ^a	4.1 $\pm$ 0.4	3.1 $\pm$ 0.3
20		0.35 $\pm$ 0.1*	4.9 $\pm$ 0.4 ^a	3.1 $\pm$ 0.4	3.3 $\pm$ 0.4	0.85 $\pm$ 0.1	2.3 $\pm$ 0.3 ^a	5.1 $\pm$ 0.4	3.6 $\pm$ 0.3
21		0.35 $\pm$ 0.1	4.6 $\pm$ 0.4 ^a	3.4 $\pm$ 0.4	3.5 $\pm$ 0.4	0.5 $\pm$ 0.1*	3.1 $\pm$ 0.4	4.9 $\pm$ 0.4	4.0 $\pm$ 0.3

*Day of oestrus.

^aSignificantly ($P < 0.001$) different from saline-treated unmated goats (group A).^bSignificantly ($P < 0.001$) different from saline-treated mated goats (group B).

full pregnancy and kidded after 147 days. Oxytocin antagonist significantly ($P < 0.01$) reduced the conception rate from 100% to 16% (group B vs. group D).

Goats in groups E and G (PGI-2 administered with OXA) behaved similarly to those in groups A and B, respectively (Table 1). Animals in groups F and H (PGF-2 α with OXA) behaved similarly to animals in groups C and D, respectively.

Increasing concentrations of progesterone, high concentrations of 6-keto-PGF-1 α and low concentrations of PGFM were observed in animals of groups A and B (Fig. 1). OXA significantly ($P < 0.001$) inhibited the increase in progesterone and PG metabolite secretion in groups C and D during the treatment period.

Fig. 1. Mean ($\pm$ s.d.) peripheral plasma concentration of progesterone (■), 6-keto-prostaglandin F-1 α (●) and 13,14-dihydro-15-keto-prostaglandin F-2 α (○) in goats treated with either saline (groups A (a) and B (b)) or oxytocin antagonist (OXA) (groups C (c) and D (d)) daily for 3 days after oestrus.

The concentrations of PGs (during an 8 h period) were estimated in pooled samples collected daily in animals of groups A and B and compared during the early development of the CL. Concentrations of 6-keto-PGF-1 α were significantly ($P < 0.001$) higher than those of PGFM (Fig. 2). The

Fig. 2. Mean ($\pm$ s.d.) concentration of 6-keto-prostaglandin F-1 α (□) and 13,14-dihydro-15-keto-prostaglandin F-2 α (■) in pooled samples collected daily during early corpus luteum development in (a) cyclic (group A) and (b) mated (group B) goats.

ratios of 6-keto-PGF-1 α :PGFM on Days 0, 1, 2, 3 and 4 were, respectively, 2.5, 5, 6, 5 and 6 after oestrus and 3, 6, 7, 6 and 7 after mating.

Discussion

The development of a functional CL in both cyclic (group A) and pregnant (group B, mated, later confirmed to be pregnant) goats was evident on Day 2 after oestrus; plasma progesterone concentration being > 1 ng/ml (Homeida & Cooke, 1982). The administration of OXA to these animals completely inhibited progesterone secretion, shortened the oestrous cycle and reduced the conception rate. Similar effects on the CL of the cycle and pregnancy have been produced by indomethacin treatment in cattle (Milvae & Hansel, 1985) and active immunization against oxytocin in sheep (Wathes *et al.*, 1989), respectively. These observations suggest that agonistic actions of oxytocin may be required for early development of the CL, since such actions were blocked by OXA. OXA has been shown to be a potent antagonist to oxytocin in a rat uterus bioassay and a study of milk ejection response (Bankowski *et al.*, 1980) and PGF-2 α and testosterone secretion in rats and goats (Chan *et al.*, 1982; Homeida & Khalafalla, 1987, 1990). The origin of this oxytocin could be the follicle, the young CL (Wathes, 1984) or the pituitary gland (Mitchell *et al.*, 1982). Furthermore, high oestrogen production or mating at oestrus would provoke the release of oxytocin (Ferguson, 1941; Blank & Debias, 1977; Wathes, 1984).

The results also show that development of the CL was accompanied by release of PGs, mainly PGI-2, suggesting a luteotrophic effect of this PG around oestrus in the goat (Milvae & Hansel, 1980, 1983; Hansel & Convey, 1983; Hansel & Dowd, 1986). Differential release of the PGs (PGI-2 and PGF-2 α) may be explained by the fact that a substance may alter enzymic conversion of intermediates in prostaglandin biosynthesis (Alwachi *et al.*, 1980; Silvia *et al.*, 1984), that PGF-2 α and PGI-2 are derived from a common endoperoxide intermediate (Hamberg & Samuelsson, 1973; Alwachi *et al.*, 1980) and that driving synthesis towards one product therefore reduces concentrations of the other. The origin of PGI-2 may be the uterus or corpus luteum (Milvae & Hansel, 1983). It was demonstrated that the rat uterus and sheep endometrium can produce PGI-2 at 10 times the rate of PGF-2 α (Fenwick *et al.*, 1977; Alwachi *et al.*, 1980) and that an increase in the ratio of concentration of luteotrophic to luteolytic PGs during the critical stages of CL development, rather than the concentration of individual PGs, may be significant in luteotrophic events (Balmaceda *et al.*, 1979; Patwardhan & Lanthier, 1980). However, unlike the present study, these authors estimated the ratio of the amounts of different PGs produced by homogenates, which may not reflect the output of the PGs by the intact tissue (Poyser, 1985).

OXA was very effective in inhibiting both PGF-2 α (Homeida & Khalafalla, 1987) and PGI-2 production, thus removing the luteotrophic effects of PGI-2 on the CL. Furthermore, the finding that treatment with indomethacin, the PG-synthesizing inhibitor, during the early bovine oestrous

cycle inhibited development of the CL and lowered plasma progesterone (Milvae & Hansel, 1985) confirms that a prostaglandin of uterine origin is important as a luteotrophin.

To investigate further the luteotrophic effects of PGI-2, the drug was administered with OXA. A functional CL developed, suggesting that the effect of oxytocin on CL development is likely to be produced via PGI-2 production. However, other PGs, such as prostaglandin E-1 can produce similar effects to PGI-2, possibly because they act through the same receptors in some tissues (Abramowitz & Brinbaumer, 1979). It is proposed that uterine production of PGs in ewes is regulated by progesterone and oestrogens (Vallet *et al.*, 1990) which induce uterine oxytocin receptors and that oxytocin binding to these receptors stimulates phospholipase A₂, the arachidonic acid cascade and production of PGs (McCracken *et al.*, 1984; Bazer *et al.*, 1986). The administration of PGF-2 α with OXA had no effect.

It has been demonstrated that active immunization against oxytocin reduces the conception rate in ewes (Wathes *et al.*, 1989), suggesting that the effect may be mediated via interference with gamete or embryo transport. Our results confirm these findings using OXA and suggest that oxytocin may be implicated in gonadotrophin secretion (Homeida & Cooke, 1989), ovulation (Mitchell *et al.*, 1980), conception (Wathes *et al.*, 1989) and early development of a functional CL.

We thank the Director of the Experimental Station, King Faisal University, for providing the goats and feed; Professor M. Manning, Medical College, Ohio, Professor G. L. Liggins, Auckland, NZ and H. Dobson, University of Liverpool for the gift of antisera; M. A. Mastour for technical help and A. E. Elbashir and A. Osman for care of animals.

References

- Abramowitz, J. & Brinbaumer, L. (1979) Prostacyclin activation of adenylyl cyclase in rabbit corpus luteum membrane: comparisons with 6-keto-PGF_{1 α} and prostaglandin E₁. *Biol. Reprod.* **21**, 609–616.
- Alwachi, S.N., Bland, K.P. & Poyser, N.L. (1980) Production of 6-OXO-prostaglandin F_{1 α} and PGE₂ by sheep uterine tissue. *Prostaglandins & Med.* **4**, 329–332.
- Armstrong, D.T. & Hansel, W. (1959) Alteration of the bovine estrous cycle with oxytocin. *J. Dairy Sci.* **42**, 533–542.
- Auletta, F.J., Paradis, D.K., Wesley, M. & Duby, T.R. (1984) Oxytocin is luteolytic in the rhesus monkey (*Macaca mulatta*). *J. Reprod. Fert.* **72**, 401–406.
- Balmaceda, J., Asch, R.H., Fernandez, E.O., Valenzuela, G., Eddy, C.A. & Pauerstein, C.J. (1979) Prostaglandin production by rhesus monkey corpora lutea *in vitro*. *Fert. Steril.* **31**, 214–216.
- Bankowski, K., Manning, M., Seto, J., Haldar, J. & Sawyer, H.W. (1980) Design and synthesis *in vivo* of antagonists of oxytocin. *Int. J. Peptide Protein Res.* **16**, 382–391.
- Bazer, F.W., Vallet, J.L., Roberts, R.M., Sharp, D.C. & Thatcher, W.W. (1986) Role of conceptus secretory products in establishment of pregnancy. *J. Reprod. Fert.* **76**, 841–850.
- Blank, M.S. & Debias, D.A. (1977) Oxytocin release during vaginal distension in the goat. *Biol. Reprod.* **17**, 218–223.
- Chan, W.Y., Powell, A.M. & Hurby, V.J. (1982) Anti-oxytocic and antiprostaglandin-releasing effects of oxytocin antagonists in pregnant rats and pregnant human myometrium strips. *Endocrinology* **111**, 48–52.
- Cook, R.G. & Homeida, A.M. (1982) Plasma concentrations of 13,14-dihydro 15-keto-prostaglandin F_{2 α} and progesterone during oxytocin-induced oestrus in the goat. *Theriogenology* **18**, 453–460.
- Cooke, R.G. & Homeida, A.M. (1983) Prevention of the luteolytic action of oxytocin in the goat by inhibition of prostaglandin synthesis. *Theriogenology* **20**, 363–365.
- Cooke, R.G. & Homeida, A.M. (1985) Suppression of prostaglandin F_{2 α} release and delay of luteolysis after active immunization against oxytocin in the goat. *J. Reprod. Fert.* **75**, 63–68.
- Cooke, R.G. & Homeida, A.M. (1989) Effect of PGI₂ on uterine activity *in vivo* in non-pregnant ovariectomized goats (*Capra hircus*). *J. Reprod. Fert.* **87**, 175–178.
- Cooke, R.G. & Knifton, A. (1981) Oxytocin-induced oestrus in the goat. *Theriogenology* **16**, 95–97.
- Fairclough, R.J., Moore, L.G., Peterson, A.J. & Watkins, W.B. (1984) Effect of oxytocin on plasma concentrations of 13, 14-dihydro 15-keto-prostaglandin F and the oxytocin-associated neurophysin during the oestrous cycle and early pregnancy in the ewe. *Biol. Reprod.* **31**, 36–43.
- Fenwick, L., Jones, R.L., Naylor, E., Poyser, N.L. & Wilson, N.H. (1977) Production of prostaglandins by the pseudopregnant rat uterus, *in vitro* and the effect of tamoxifen with the identification of 6-keto-prostaglandin F_{1 α} as a major product. *Br. J. Pharmac.* **59**, 191–199.
- Ferguson, J.K.W. (1941) A study of the motility of the intact uterus at term. *Surg. Gynec. Obstet.* **73**, 359–366.
- Fields, P.A., Eldridge, R.K., Fuchs, A.R., Roberts, R.F. & Felds, M.J. (1983) Human placental and

- bovine corpora lutea oxytocin. *Endocrinology* **112**, 1544-1546.
- Flint, A.P.F. & Sheldrick, E.L. (1982) Ovarian secretion of oxytocin is stimulated by prostaglandin. *Nature, Lond.* **297**, 587-588.
- Hamberg, M. & Samuelsson, B. (1973) Detection and isolation of an endoperoxide intermediate in prostaglandin biosynthesis. *Proc. Natl Acad. Sci., USA* **70**, 899-903.
- Hansel, W. & Convey, E.M. (1983) Physiology of the estrous cycle. *J. Anim. Sci.* **57**: Suppl. **2**, 404-423.
- Hansel, W. & Dowd, J.P. (1986) New concepts of the control of corpus luteum function. *J. Reprod. Fert.* **78**, 755-768.
- Homeida, A.M. (1986a) Evidence for the presence of oxytocin in the corpus luteum of the goat. *Br. J. Pharmac.* **87**, 373-376.
- Homeida, A.M. (1986b) Use of spironolactone to investigate the role of testosterone secretion during luteolysis in the goat. *J. Reprod. Fert.* **76**, 153-157.
- Homeida, A.M. & Cooke, R.G. (1982) Peripheral plasma concentration of 13, 14-dihydro-15-keto prostaglandin $F_{2\alpha}$ and progesterone around luteolysis and during early pregnancy in the goat. *Prostaglandins* **24**, 313-321.
- Homeida, A.M. & Khalafalla, A.E. (1987) Effects of oxytocin-antagonist injections on luteal regression in the goat. *Br. J. Pharmac.* **90**, 281-284.
- Homeida, A.M. & Khalafalla, A.E. (1990) Effects of oxytocin and oxytocin antagonist on testosterone secretion during the oestrous cycle of the goat (*Capra hircus*). *J. Reprod. Fert.* **89**, 347-350.
- Homeida, A.M., Khalil, M.G.R. & Taha, A.A.M. (1988) Plasma concentrations of oestrogens, testosterone and LH-like activity during the oestrous cycle of the camel (*Camelus dromedarius*). *J. Reprod. Fert.* **83**, 593-598.
- Horton, E.W. & Poyser, L.N. (1976) Uterine luteolytic hormone: a physiological role for prostaglandin $F_{2\alpha}$. *Physiol. Rev.* **56**, 595-651.
- Khan-Dawood, F.S. & Dawood, M.Y. (1983) Human ovaries contain immunoreactive oxytocin. *J. clin. Endocr. Metab.* **57**, 1129-1132.
- Khan-Dawood, F.S., Marut, E.L. & Dawood, M.Y. (1984) Oxytocin in the corpus luteum of the monkey. *Endocrinology* **115**, 570-574.
- Liggins, G.C., Campos, G.A., Roberts, C.M. & Skinner, S.J. (1980) Production rates of prostaglandin F_2 , 6-keto-PGF $_{1\alpha}$ and thromboxane B_2 by perfused human endometrium. *Prostaglandins* **19**, 461-477.
- McCracken, J.A., Schramm, W. & Okulliez, W.C. (1984) Hormone receptor control of pulsatile secretion of PGF $_{2\alpha}$ from the ovine uterus during luteolysis and its abrogation in early pregnancy. *Anim. Prod. Sci.* **7**, 31-55.
- Milvae, R.A. & Hansel, W. (1980) The effects of prostacyclin (PGI $_2$) on bovine plasma progesterone and LH concentration. *Prostaglandins* **20**, 641-647.
- Milvae, R.A. & Hansel, W. (1983) Prostacyclin, prostaglandin $F_{2\alpha}$ and progesterone production by bovine luteal cells during the estrous cycle. *Biol. Reprod.* **29**, 1063-1068.
- Milvae, R.A. & Hansel, W. (1985) Inhibition of bovine luteal function by indomethacin. *J. Anim. Sci.* **60**, 528-531.
- Mitchell, M.D., Hayness, P.J., Anderson, A.B.M. & Turnbull, A.C. (1980) Oxytocin in human ovulation. *The Lancet* **i**, 704.
- Mitchell, M.D., Kraemer, D.L., Brennecke, S.P. & Webb, R. (1982) Pulsatile release of oxytocin during estrous cycle, pregnancy and parturition in sheep. *Biol. Reprod.* **27**, 1169-1173.
- Patwardhan, V.V. & Lanthier, A. (1980) Concentration of prostaglandins PGE and PGF, estrone, estradiol and progesterone in human corpora lutea. *Prostaglandins* **20**, 963-969.
- Poyser, N.L. (1985) Effects of TMB-8, an intercellular calcium antagonist, and W-7, a calmodulin antagonist, on prostaglandin output from the guinea-pig uterus. *J. Reprod. Fert.* **75**, 223-230.
- Silvia, W.J., Fitz, T.A., Mayan, M.H. & Niswender, G.D. (1984) Cellular and molecular mechanisms involved in luteolysis and maternal recognition of pregnancy in the ewe. *Anim. Reprod. Sci.* **7**, 57-74.
- Stubbings, R.B., Bosu, W.T.K., Bakker, C.A.V. & King, G.J. (1986) Serum progesterone concentrations associated with superovulation and premature corpus luteum failure in dairy goats. *Can. J. Vet. Res.* **50**, 369-370.
- Tan, G.J.S., Tweedale, R. & Biggs, J.S.G. (1982a) Effects of oxytocin on the bovine corpus luteum of early pregnancy. *J. Reprod. Fert.* **66**, 75-78.
- Tan, G.J.S., Tweedale, R. & Biggs, J.S.G. (1982b) Oxytocin may play a role in the control of the corpus luteum. *J. Endocr.* **95**, 65-70.
- Vallet, J.L., Lamming, G.E. & Batten, M. (1990) Control of endometrial oxytocin receptor and uterine response to oxytocin by progesterone and oestradiol in the ewe. *J. Reprod. Fert.* **90**, 625-634.
- Wathes, D.C. (1984) Possible action of gonadal oxytocin and vasopressin. *J. Reprod. Fert.* **71**, 315-345.
- Wathes, D.D. & Swann, R.W. (1982) Is oxytocin an ovarian hormone? *Nature, Lond.* **297**, 225-227.
- Wathes, D.C., Swann, R.H., Hull, M.G.R., Drife, J.O., Proter, D.G. & Pickering, B.T. (1983) Gonadal sources of the posterior pituitary hormones. *Progr. Brain Res.* **60**, 513-520.
- Wathes, D.C., Ayad, V.J., McGoff, S.A. & Morgan, K.L. (1989) Effect of active immunization against oxytocin on gonadotrophin secretion and establishment of pregnancy in the ewe. *J. Reprod. Fert.* **86**, 653-664.

Received 21 January 1991