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Control of luteolysis in the one-humped camel (*Camelus dromedarius*)

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Blood plasma concentrations of 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM) were measured in groups of mature non-pregnant and pregnant camels to study $PGF_{2\alpha}$ release patterns around the time of luteolysis and the timing of the signal for pregnancy recognition. Injection of each of four camels with 10 and 50 mg of $PGF_{2\alpha}$ showed clearly that five times the dose of exogenous hormone produced five times the amount of PGFM in peripheral plasma, thereby indicating that, as in other animal species, PGFM is the principal metabolite of $PGF_{2\alpha}$ in the camel. Serial sampling of three non-pregnant camels on each of days 8, 10 and 12, and three pregnant camels on day 10, after ovulation for 8 h showed a significant ($P < 0.05$) rise in mean plasma PGFM concentrations only on day 10 in the non-pregnant, but not the pregnant, animals. A single intravenous injection of 20, 50 or 100 iu oxytocin given to three groups of three non-pregnant camels on day 10 after ovulation did not increase their basal serum PGFM concentrations. However, daily treatment of six non-pregnant camels between days 6 and 15 ($n = 3$) or 20 ($n = 3$) after ovulation with 1–2 g of the prostaglandin synthetase inhibitor, meclofenamic acid, inhibited $PGF_{2\alpha}$ release and thereby resulted in continued progesterone secretion throughout the period of meclofenamic acid administration. These results showed that, as in other large domestic animal species, release of $PGF_{2\alpha}$ from, presumably, the endometrium controls luteolysis in the dromedary camel. Furthermore, reduction in the amount of $PGF_{2\alpha}$ released is associated with luteal maintenance and the embryonic signal for maternal recognition of pregnancy must be transmitted before day 10 after ovulation if luteostasis is to be achieved. However, the results also indicate that, in contrast to ruminants, the release of endometrial $PGF_{2\alpha}$ in the non-pregnant camel may not be controlled by the release of oxytocin.

Introduction

Luteolysis in ruminants, pigs, horses and many other large mammals is brought about by the pulsatile release of $PGF_{2\alpha}$ from the endometrium in late dioestrus. However, the precise mechanism that regulates the initiation of these $PGF_{2\alpha}$ pulses, and the significance of their frequency and amplitude, remains controversial (see Flint *et al.*, 1990, 1992; Silvia *et al.*, 1991). Current evidence from sheep and cattle suggests that progesterone from the corpus luteum and oestradiol from developing follicles act in tandem to control the development and sensitivity of receptors for oxytocin in the endometrium (Lamming and Mann, 1995; Wathes and Lamming, 1995; Wathes *et al.*, 1996). Oxytocin, primarily from the corpus luteum in these species, but also from the pituitary, then interacts with its endometrial receptors to stimulate inositol phosphate production and the second messenger system for diacylglycerol which, in turn, at a precisely timed stage of dioestrus, stimulates the release of the spike-like pulses of $PGF_{2\alpha}$ required for luteolysis (Flint *et al.*, 1990). Furthermore, systemic infusion of oxytocin during the mid-luteal phase inhibits endometrial oxytocin receptor development and prolongs the cycle in both sheep (Flint and Sheldrick, 1985; Ayad *et al.*, 1993) and cattle (Gilbert *et al.*, 1989), suggesting that oxytocin may be involved in regulating its own receptor.

Firm evidence for the involvement of prostaglandins in luteolysis in sheep was demonstrated by the administration of the prostaglandin synthetase inhibitor, indomethacin (Lewis and Warren, 1974), and by passive immunization against $PGF_{2\alpha}$ (Fairclough *et al.*, 1981). Both treatments prolonged the luteal phase in cyclic ewes. The daily oral administration of another prostaglandin synthetase inhibitor, meclofenamic acid, to goats also prevented both the luteolytic action of exogenous $PGF_{2\alpha}$ and the normal increase in peripheral plasma PGFM concentrations in late dioestrus (Cooke and Homeida, 1983). These and many other

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studies in a variety of species have all indicated that $PGF_{2\alpha}$ released from the endometrium is the principal luteolytic agent that causes the demise of the cyclical corpus luteum (see Poyser, 1995).

During early pregnancy in the sheep and cow, luteolysis is inhibited by an interferon secreted by the membranes of the conceptus(Godkin *et al.*, 1984; Ott *et al.*, 1993; Bazer *et al.*, 1994). This embryonic interferon *tau* inhibits the development of oxytocin receptors in the endometrium (Vallet and Lamming, 1991) and, by a local action on the uterine epithelium, inhibits oxytocin-induced luteolytic-type episodes of $PGF_{2\alpha}$ release (Payne and Lamming, 1994).

Camels are allied to ruminants but they are induced ovulators (Musa and Abusineina, 1978; Novoa, 1970). As revealed by serial peripheral plasma progesterone measurements (Marie and Anouassi, 1987; Skidmore *et al.*, 1995), they exhibit a relatively short luteal lifespan of only 8–10 days. Camel embryos, like those of the pig (Bazer and Thatcher, 1977) and horse (Heap *et al.*, 1982), but in contrast to the embryos of sheep, cattle and most other domestic and laboratory animal species (Gadsby *et al.*, 1980), secrete appreciable quantities of oestrogens when cultured *in vitro* from as early as day 10 after ovulation (Skidmore *et al.*, 1994) but they do not produce any detectable protein, or show evidence for the mRNA, of any interferons (Skidmore, 1994). Yet, attempts to prolong luteal lifespan in cyclic camels by administering a range of types and doses of exogenous oestrogens at various times during the luteal phase were uniformly unsuccessful (Skidmore, 1994).

In a study in alpacas, Aba *et al.* (1997) detected occasional pulsatile peaks of PGFM in the peripheral plasma of five pregnant alpacas bled serially for 4 h each day during days 8–13 after mating. But apart from this observation there is little information on the mechanisms of cyclical luteolysis or the maternal recognition of pregnancy in camelids. In this study the experiments were designed to examine the relative roles of $PGF_{2\alpha}$ and oxytocin in bringing about luteolysis in the dromedary camel.

Materials and Methods

Animals

A total of 40 mature female dromedary camels, aged 5–14 years, were used in the experiments which were conducted during the physiological breeding season for camels in the Arabian peninsula, November to March. The camels were all in good physical condition and were fed a diet of mixed concentrates and hay once a day, and water was available *ad libitum*. Three experiments were carried out.

Experiment 1: metabolism of $PGF_{2\alpha}$

For confirmation that endogenous $PGF_{2\alpha}$ is metabolized to 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM) in the camel, four mature females were each injected with two doses of natural $PGF_{2\alpha}$ (Lutalyse; Upjohn Ltd, Purrs, Belgium) on day 6 after an ovulation that had been induced previously by a single i.v. injection of 20 μg of the GnRH analogue, buserelin (Receptal; Hoechst Animal Health, Milton Keynes, Beds), given when a growing dominant follicle of 1.3–1.6 cm diameter was present in the ovaries (Skidmore *et al.*, 1995). The initial i.m. injection of 10 mg $PGF_{2\alpha}$ was followed 2 h later by a second i.m. injection of 50 mg $PGF_{2\alpha}$. Jugular vein blood samples (8 ml) were recovered into heparinized tubes by repeated venepuncture at intervals of 30 min for 2 h before the first injection to obtain baseline pre-treatment PGFM profiles. After each injection the sampling frequency was increased to 10 min intervals for the first hour, 15 min intervals for the next half hour and the final sample was taken 30 min later. The tubes were placed on crushed ice at the point of collection and centrifuged within 30 min at 2000 *g* for 5 min. The plasma was decanted and stored at –20°C until assayed for PGFM concentrations as described below.

Experiment 2: PGFM profiles in pregnant and non-pregnant camels and suppression of luteolysis

Twelve unmated female camels were each given a single i.v. injection of 20 μg buserelin to induce ovulation as described above. Three of them were then mated to a fertile male camel. Ovulation in the mated and unmated camels was detected initially by ultrasonographic examination of the ovaries and confirmed subsequently by measuring a rise in peripheral serum progesterone concentrations (Skidmore *et al.*, 1995). Jugular vein blood samples were taken daily from all 12 camels throughout the experimental period into 10 ml plain vacutainers which were kept at room temperature for 1–2 h to allow the blood to clot. The tubes were then centrifuged and the serum samples decanted for storage at –20°C until assayed for progesterone concentrations.

Serial blood sampling by repeated venepuncture was carried out on three non-pregnant camels on each of days 8, 10 and 12, and three pregnant camels on day 10, after ovulation, with different camels being used at each stage. The samples were taken at 20 min intervals over 8 h to observe basal profiles and any pulsatile episodes. The plasma was collected and stored as described in Expt 1.

At the end of the 8 h serial bleeding programme the uteri of both the mated and unmated camels were flushed with sterile embryo flushing medium (IMV, L'Aigle) using an 18 French gauge flexible, two-way Gibbon balloon catheter (Benkat Instruments, Herts) passed through the cervix as described by Skidmore *et al.* (1992). The medium was recovered by gravity flow and that obtained from each of the mated camels was searched for the presence of an embryo to confirm pregnancy.

Ovulation was induced in nine more camels by an i.v. injection of buserelin. One gram of meclofenamic acid (Arquel; Parke Davis, Gwent) dissolved in 100 ml water was given *per os* twice a day to six of the camels from days 6 to 9 inclusive after ovulation and, thereafter, the dose was reduced to one treatment of 1 g per day until day 15 ($n = 3$), or day 20 ($n = 3$). The three remaining control camels each received 100 ml of water only, twice a day for 15 days.

Jugular vein blood samples were taken daily from all the camels and the serum collected, stored and assayed subsequently for progesterone concentrations to confirm ovulation and monitor the lifespan of the corpus luteum. On day 10 after ovulation serial blood samples were taken at 30 min intervals for 8 h from the six meclofenamic acid-treated animals. The plasma was collected, stored and assayed for PGFM concentrations as described above.

Experiment 3: response to exogenous oxytocin

Ovulation was induced in nine camels as described above and serial blood samples were taken every 20 min for 8 h on day 10 after ovulation. Each camel was then injected i.v. with either 20 iu ($n = 3$), 50 iu ($n = 3$) or 100 iu ($n = 3$) oxytocin and serial blood sampling was continued, at 10 min intervals for the first hour and 20 min intervals for a further 2 h. The decanted plasma samples were subsequently assayed for PGFM concentrations.

Hormone assays

Progesterone. Progesterone concentrations were measured using a commercially available assay kit (Amerlite Progesterone Assay; Kodak Clinical Diagnostics, Amersham) which uses a competitive immunoassay technique based on enhanced luminescence (Whitehead *et al.*, 1983) and which was validated for use with camel serum by Skidmore *et al.* (1996a). The antibody used in the assay exhibited stated cross-reactivities of 5.2%, 4.17% and 1.1% with 5α-pregnane-3,20-dione, 5β-pregnane-3,20-dione and 20α-dihydro-progesterone, respectively. The minimum detection limit of the assay was 0.11 ng progesterone ml^{-1} serum and the intra- and inter-assay coefficients of variation were 7.5% and 8.0%, respectively.

PGFM. Concentrations of PGFM in peripheral plasma were measured using a radioimmunoassay adapted from the method of Kaker *et al.* (1984). In the present assay PGFM was extracted from 0.5 ml camel plasma, using 3 ml acidified diethyl ether, and reconstituted in 0.1 ml assay buffer. The radioactive tracer [13,14-dihydro-15-keto(5,6,8,9,11,12,14(*n*)-^{3}H] $PGF_{2\alpha}$, specific activity 662 TBq ml^{-1}, (Amersham Life Sciences, Amersham, Bucks) was added at 0.1 ml per tube (4500–5000 c.p.m. (0.1 ml)$^{-1}$). The rabbit anti-PGFM serum (kindly supplied by F. W. Bazer, Texas A & M University) used in the assay exhibited crossreactivities of < 0.1% with arachidonic acid, $PGF_{1\alpha}$, $PGF_{2\alpha}$, PGE_2, and was used at a dilution of 1:20 000 The minimum detection limit of the assay was 17.8 pg ml^{-1} plasma and the intra- and inter-assay coefficients of variation were 12% and 18%, respectively.

The assay for camel plasma was validated by assaying pooled blank male camel plasma spiked with PGFM at concentrations of 250, 200, 150, 100 and 50 pg ml^{-1}. Recoveries of 226.5, 177.4, 141.9, 80.7 and 61.6 pg ml^{-1}, respectively, were obtained. Regression analysis of these data showed recovery to be linear ($r^2 = 0.95$, $P < 0.0001$) and mean extraction efficiency across this range was 95.6 ± 7.27%.

Statistical analyses

Experiment 1. The mean baseline PGFM concentration was calculated from the pretreatment data for each animal. The amount of PGFM produced following each injection of $PGF_{2\alpha}$ was calculated as the area under the curve of PGFM concentration against time, expressed in ng ml^{-1}.

Experiment 2. The mean of lowest PGFM concentrations measured in the pre-challenge sampling period and the standard deviation were calculated. Any points falling within this mean plus twice the standard deviation were then included in the above mean calculation and the standard deviation was re-calculated. This process was continued until all points outside the mean calculation were more than twice the standard deviation away from the mean. These outstanding points were considered to be significant pulses only if two or more occurred in succession.

Variation in PGFM concentrations between non-pregnant day groups was determined by the non-parametric Kruskal–Wallis one-way ANOVA on ranks test. Pair-wise comparisons were made using the Student–Newman Keul's test. Variations in PGFM concentrations between day 10 pregnant, day 10 non-pregnant and day 10 meclofenamic acid-treated groups were determined by the Kruskal–Wallis one-way ANOVA test. Multiple comparisons were made using Dunn's test.

Experiment 3. The mean pre-treatment baseline PGFM concentration for each group was calculated using the method described for Expt 2. Post-treatment data were screened for pulsatile responses to the oxytocin administration, defined as peaks of two or more points above the pretreatment mean plus twice the standard deviation. Post-treatment baseline values were also calculated using the method described for Expt 2. *t*-Test comparisons were made between pre- and post-treatment baseline PGFM concentrations.

Results

Experiment 1: metabolism of $PGF_{2\alpha}$

The mean (± SEM) concentration of PGFM measured in the samples of plasma taken from the camels before administering $PGF_{2\alpha}$ was 29.9 ± 1.4 pg ml^{-1} (Fig. 1). After the first injection of 10 mg $PGF_{2\alpha}$, plasma PGFM concentrations increased rapidly in all four camels to a mean (± SEM) peak of 6.4 ± 0.6 ng ml^{-1} by 20 min after injection. Thereafter, the concentrations declined steadily to reach a mean (± SEM) value of 0.25 ± 0.07 ng ml^{-1} by 2 h after injection. After the second injection of 50 mg $PGF_{2\alpha}$, the plasma PGFM concentrations again increased markedly to reach a mean (± SEM) of 30.1 ± 1.4 ng ml^{-1}, again at about 20 min after injection. The concentrations then fell again steadily to a mean (± SEM) value of 2.0 ± 0.4 ng ml^{-1} by 2 h after treatment (Fig. 1).

The amount of PGFM produced from each injection of $PGF_{2\alpha}$ was assessed by measuring the area under the curve. This was calculated to be 64.21 ng ml^{-1} for the 10 mg and 349.41 ng ml^{-1} for the 50 mg doses, respectively, each over 2 h. Thus, a fivefold increase in administered $PGF_{2\alpha}$ resulted in a 5.44-fold increase in measured PGFM (Fig. 1).

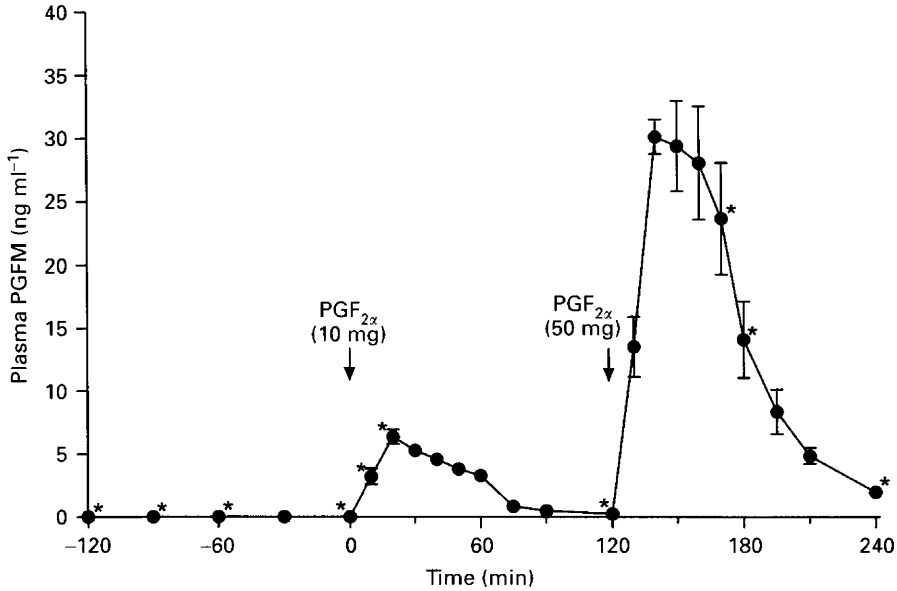

Fig. 1. Mean (± SEM) plasma 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM) concentrations measured in four camels, each treated i.m. with two doses of $PGF_{2\alpha}$: 10 mg at time 0, followed by 50 mg at time 120 min. Measurement of the area under the curve to calculate the amount of PGFM produced after each injection gave 64.95 and 348.75 ng ml^{-1}, respectively. * = mean of three animals.

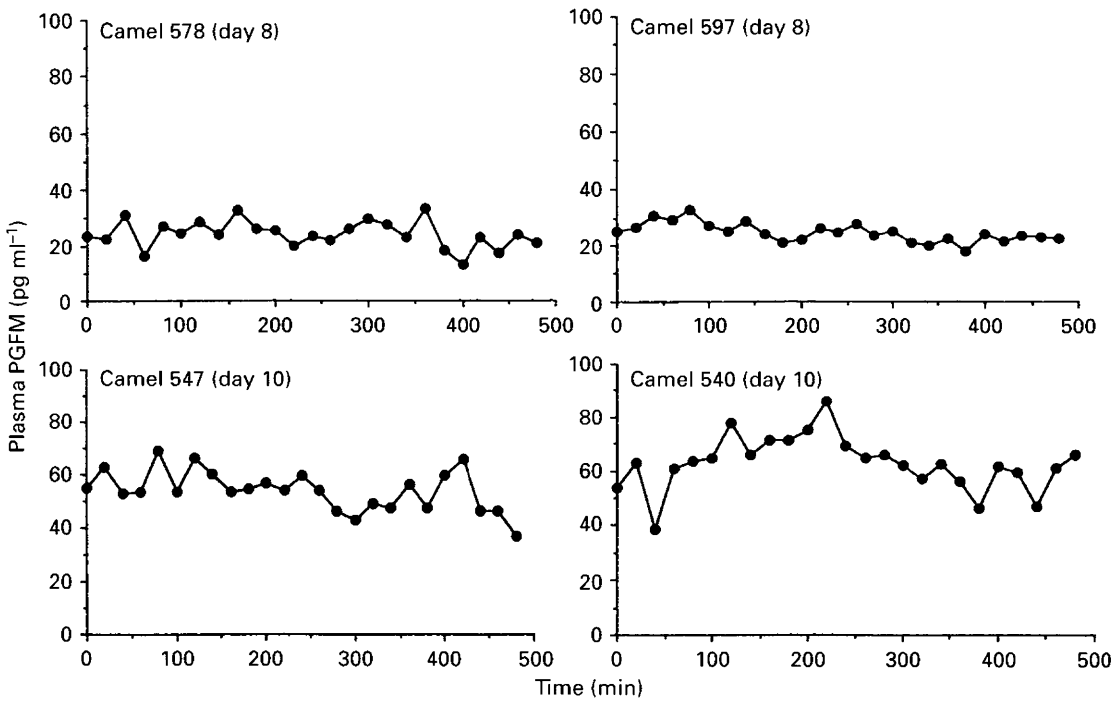

Fig. 2. Peripheral plasma 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM) concentrations measured in four cyclic camels, two on day 8 (nos 578 and 597) and two on day 10 (nos 547 and 540), after ovulation. Note the higher basal concentrations of PGFM in the day 10 camels and the absence of pulsatile releases in any of the profiles.

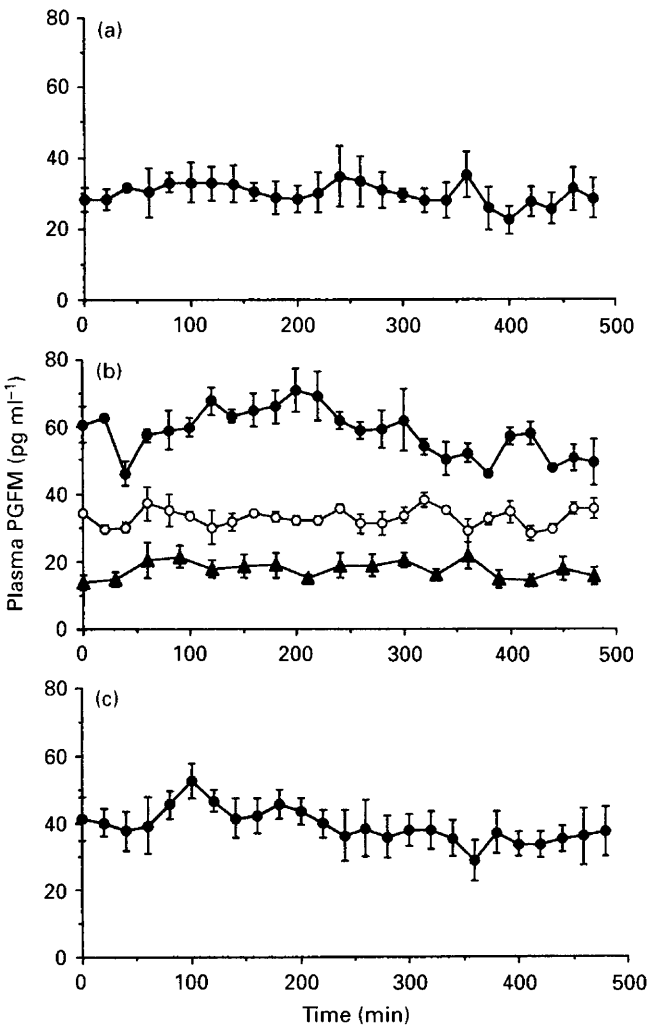

Fig. 3. Mean (± SEM) plasma 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM) concentrations measured over 8 h in camels on (a) day 8 ($n = 3$ non-pregnant), (b) day 10 ((●) $n = 3$ non-pregnant; (○) $n = 3$ pregnant and (▲) $n = 6$ treated with meclofenamic acid) and (c) day 12 ($n = 3$ non-pregnant).

Experiment 2: PGFM profiles in pregnant and non-pregnant camels and suppression of luteolysis

No pulsatile releases of PGFM were detected in any animal in any of the groups (Fig. 2). In the nine non-pregnant camels, the mean (± SEM) basal PGFM concentration on day 8 was 30.02 ± 0.68 pg ml^{-1} (Fig. 3a). A significant ($P < 0.05$) rise to 58.85 ± 1.48 pg ml^{-1} occurred on day 10 (Fig. 3b) and the mean value then declined again significantly ($P < 0.05$) to 39.27 ± 1.01 pg ml^{-1} by day 12 (Fig. 3c). This increase in $PGF_{2\alpha}$ secretion rate in the non-pregnant camels on day 10 coincided with a pronounced fall in their serum progesterone concentrations, from a mean (± SEM) of 3.0 ± 0.3 ng ml^{-1} on day 8 to 0.7 ± 0.1 ng ml^{-1} on day 10. The concentration of PGFM on day 12 was still significantly ($P < 0.05$) higher than that on day 8.

By contrast, the mean (± SEM) plasma PGFM concentration measured in the three pregnant camels on day 10 (32.73 ± 0.54) was not significantly different from the mean concentration on day 8 in the non-pregnant camels, but was significantly lower ($P < 0.05$) than the mean concentration in the non-pregnant camels on day 10 (Fig. 3b).

Meclofenamic acid inhibited $PGF_{2\alpha}$ synthesis and release at all stages between 6 and 20 days after ovulation. The mean (± SEM) plasma PGFM concentration in the day 10 non-pregnant control camels (58.85 ± 1.48 pg ml^{-1}) contrasted significantly ($P < 0.05$) with the mean of only 17.55 ± 0.63 pg ml^{-1} recorded on day 10 in camels treated with meclofenamic acid, and this latter value was appreciably lower than the mean (± SEM) concentration of 32.73 ± 0.54 pg ml^{-1} recorded in the pregnant camels on day 10 (Fig. 3b). The suppression of $PGF_{2\alpha}$ release in the meclofenamic acid-treated animals was associated with an inhibition of luteolysis, as evidenced by the persistence of high serum progesterone concentrations during the period of administration; they fell rapidly to < 1 ng ml^{-1} after treatment ceased, either on day 15 or day 20 after ovulation (Fig. 4). Furthermore, the progesterone concentrations in the meclofenamic acid-treated camels continued to increase steadily after day 10, as is seen in pregnant camels (Skidmore *et al.*, 1996b), thereby indicating that the corpus luteum probably continued to grow in size after this time.

Experiment 3: response to oxytocin

Oxytocin had no discernible effect on $PGF_{2\alpha}$ release, as reflected by the lack of any increase in plasma PGFM concentrations, either pulsatile or tonic, during the 3 h after the i.v. injection of three doses of oxytocin (20, 50, 100 iu) in any of the nine animals treated (Fig. 5a–c).

Discussion

The major blood metabolite of $PGF_{2\alpha}$, 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM), was measured successfully in the peripheral blood of conscious camels at rest, using ether extracts of plasma in a modified radioimmunoassay which gave lower resting values for PGFM in the peripheral plasma of cycling camels (20–90 pgml^{-1}) than the concentrations of 100–300 pg ml^{-1} reported by Skidmore *et al.* (1996c) when using unextracted plasma and a different anti-PGFM serum. These measurements enabled a study of $PGF_{2\alpha}$ release patterns at defined stages of the ovarian cycle in non-pregnant animals, and at day 10 in pregnant animals. A bolus injection of $PGF_{2\alpha}$ resulted in an immediate rise in the concentration of PGFM in peripheral plasma and, since five times the dose of $PGF_{2\alpha}$ produced 5.37 times the amount of PGFM, it is safe to conclude that, as in other species like the cow (Kindahl *et al.*, 1976), PGFM is a principal blood metabolite of $PGF_{2\alpha}$ in the dromedary camel. Thus, measurement of PGFM concentrations in peripheral plasma provides an accurate reflection of the changes in $PGF_{2\alpha}$ secretion rates in the camel.

Concentrations of PGFM in peripheral plasma were monitored in non-pregnant camels on days 8, 10 and 12 after ovulation (Fig. 3a–c). The marked increase in basal concentrations that occurred between days 8 and 10 in

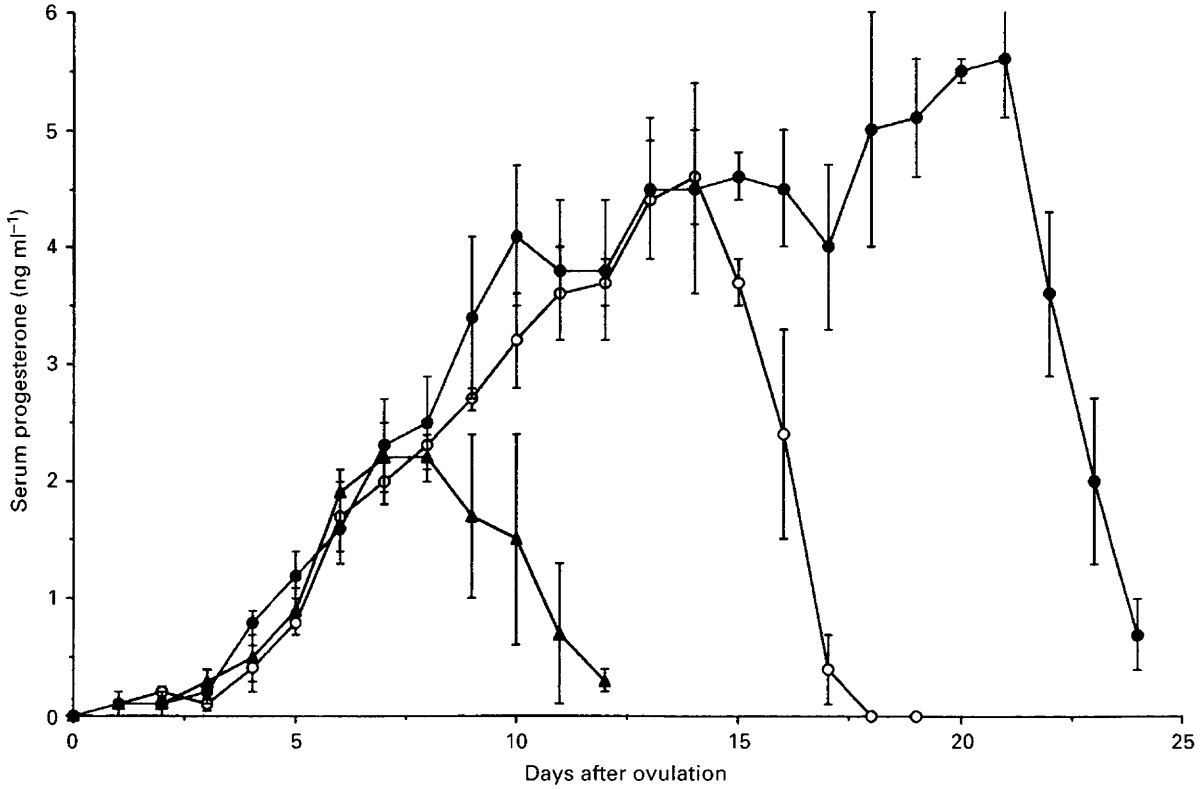

Fig. 4. Comparison of mean (± SEM) serum progesterone concentrations in camels treated daily with meclofenamic acid between days 6 and 15 (n = 3; ○) or days 6 and 20 (n = 3; ●) after ovulation, or with distilled water between days 6 and 15 (n = 3; ▲).

the cyclic animals coincided closely with a decline in serum progesterone concentrations, thereby indicating that luteolysis was occurring simultaneously. PGFM concentrations then declined towards lower basal values by day 12 when progesterone concentrations had also declined. A similar relationship between PGFM and progesterone profiles was demonstrated in cattle by Kindahl *et al.* (1976), who reported low basal concentrations of 40–100 pg PGFM ml^{-1} up to day 18 of the oestrous cycle, after which short duration pulses of PGFM (150–570 pg ml^{-1}) occurred coincidentally with a marked decline in plasma progesterone concentrations. Likewise in ewes, Webb *et al.* (1981) noted that peripheral plasma PGFM profiles indicated a pulsatile release pattern of $PGF_{2\alpha}$, with higher concentrations and more frequent pulses occurring during the period of luteal regression; maximum pulse peaks of 580–720 pg ml^{-1} were reached when progesterone concentrations had fallen to basal values. Subsequently, Schramm *et al.* (1983) argued that five such pulses, each lasting about 1h and over a period of 25 h, are necessary to bring about complete luteolysis in ewes.

In the camels examined in this study, which were sampled at 20 min intervals over 8 h, there was no evidence of any pulsatile releases of $PGF_{2\alpha}$, even on day 10 after ovulation in the non-pregnant animals when baseline values were markedly increased. This is surprising in light of the recent report by Aba *et al.* (1997) of pulsatile rises in peripheral plasma PGFM concentrations in mated alpacas during the period of maternal recognition of pregnancy. The present results suggest that the luteolytic release of $PGF_{2\alpha}$ in the dromedary is tonic, rather than pulsatile, and this tonic release is absent in the pregnant animal. The higher baseline concentrations in the day 10 camels occurred only after serum progesterone concentrations had fallen to < 1 ng ml^{-1} and the same relationship has also been shown to occur in cattle (Kindahl *et al.*, 1976), sheep (Webb *et al.*, 1981) and horses (Neely *et al.*, 1979). Therefore, it is possible that, in the camel as in these other species, progesterone withdrawal serves as a stimulus for continued $PGF_{2\alpha}$ release from, presumably, the uterus, to ensure complete luteolysis.

Further evidence for the involvement of $PGF_{2\alpha}$ in luteolysis in the dromedary was shown by the suppressive effect of meclofenamic acid which inhibits prostaglandin H synthase and thereupon prevents $PGF_{2\alpha}$ synthesis from arachidonic acid. Cooke and Homeida (1983) obtained similar results in goats when they inhibited oxytocin-induced luteolysis by the daily administration of 1g meclofenamic acid. Likewise in heifers, administration of another prostaglandin synthetase inhibitor, indomethacin, prevented oestrogen-induced luteolysis (Lewis and Warren, 1974).

In ewes (Fairclough *et al.*, 1984), cows (LaFrance and Goff, 1985; Lamming and Mann, 1995) and mares (Goff *et al.*, 1993), bolus injections of oxytocin given at about the expected time of luteolysis stimulate a pronounced release of $PGF_{2\alpha}$ from the endometrium, as reflected by a sharp rise in peripheral

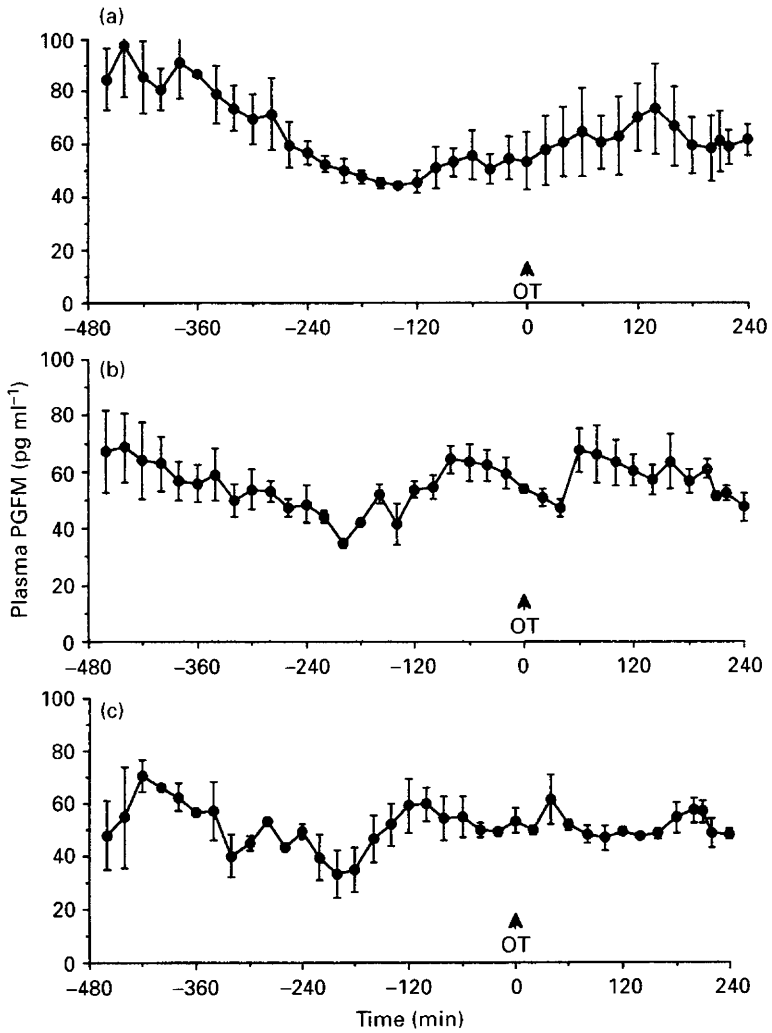

Fig. 5. Mean (± SEM) plasma 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM) concentrations measured on day 10 after ovulation in non-pregnant camels after a single i.v. injection (time 0) of (a) 20 iu ($n = 3$), (b) 50 iu ($n = 3$) or (c) 100 iu ($n = 3$) oxytocin, given at the end of 8 h of serial blood sampling. Oxytocin had no significant effect on $PGF_{2\alpha}$ release in any of the treated camels. OT, oxytocin injection.

plasma PGFM concentrations. By contrast, in the camels in this study, an intravenous injection of an equivalent dose of oxytocin failed to stimulate any discernible increase in plasma PGFM concentrations in any of the treated animals. LaFrance and Goff (1985) suggested that the increased response to oxytocin that occurs at the end of dioestrus in the cow is due to an increase in the sensitivity of the uterus to oxytocin stimulation at this time, resulting either from an increase in the numbers of oxytocin receptors in the endometrium, as in sheep (Roberts *et al.*, 1976; Sheldrick and Flint, 1985; Beard and Lamming, 1994), or from an increase in the capacity of the endometrium to synthesize $PGF_{2\alpha}$. In a recent review of this question, Wathes and Lamming (1995) noted that only the oxytocin receptors present in the luminal epithelial cells of the endometrium in sheep are necessary to achieve a maximal release of $PGF_{2\alpha}$ in response to an oxytocin challenge. The failure of all the camels in this study to respond to exogenous oxytocin may be due to a complete absence, or very low numbers, of oxytocin receptors in the endometrial epithelium. It indicates that oxytocin may not play a significant role in luteolysis in this species.

Pregnancy decreases the response to exogenous oxytocin in cows (LaFrance and Goff, 1985), ewes (Fairclough *et al.*, 1984) and mares (Goff *et al.*, 1987) and the pulsatile peaks of PGFM in peripheral plasma observed during luteolysis in these species are also abolished in pregnancy (Kindahl *et al.*, 1976; Peterson *et al.*, 1976; Webb *et al.*, 1981). The results obtained in the present study showed a similar pattern in the camel in that basal plasma PGFM concentrations remained low on day 10 after ovulation in pregnant animals, while serum progesterone concentrations remained high at 3–5 ng ml^{-1}. Not all investigators have agreed, however, that uterine $PGF_{2\alpha}$ production is reduced or abolished during early pregnancy and some studies in ewes suggested that $PGF_{2\alpha}$

concentrations in uterine vein plasma were either higher than (Wilson *et al.*, 1972), or similar to (Pexton *et al.*, 1975; Lewis *et al.*, 1977), those in the uterine vein of non-pregnant animals at the corresponding stage of the oestrous cycle. However, in these earlier experiments blood samples were collected infrequently and over relatively short periods, which was probably inadequate to detect surges in $PGF_{2\alpha}$ concentrations in the uterine vein, or the resulting increases in PGFM concentrations in peripheral plasma, both of which occur intermittently at intervals of 8–15 h during days 13–15 of the cycle in non-pregnant sheep (Thorburn *et al.*, 1973; Fairclough *et al.*, 1980). More recent experiments, reported by Payne and Lamming (1994), have indicated that the presence of the conceptus in the uterus suppresses the pulsatile releases of $PGF_{2\alpha}$ that are necessary to achieve luteolysis, but does not suppress the synthesis of basal secretion rates of prostaglandin. Indeed, the concentration of $PGF_{2\alpha}$ in the effluent venous plasma from the gravid horn in surgically modified ewes were three times higher than those of the isolated non-gravid horn (Payne and Lamming, 1994).

In summary, the present experiments demonstrated that PGFM is a major metabolite of $PGF_{2\alpha}$ in the camel and can be used as a reliable indicator of changes in the pattern of $PGF_{2\alpha}$ release. The increase in $PGF_{2\alpha}$ release that occurs at about the time of luteolysis in non-pregnant camels, as shown by a significant increase in the mean basal plasma concentration of PGFM but with no evidence of episodic secretion, is absent in pregnant animals in which luteostasis occurs. It can be inhibited by the oral administration of meclofenamic acid but it is unaffected by the i. v. administration of oxytocin. We suggest, therefore, that $PGF_{2\alpha}$ plays a pivotal role in luteolysis in the dromedary camel but there is no evidence to date to indicate that its release is controlled by oxytocin.

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