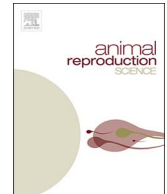




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## Oxytocin is not involved in luteolysis and early maternal recognition of pregnancy (MRP) in alpacas

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### ABSTRACT

Pregnancy maintenance depends on the maternal recognition of pregnancy (MRP), a physiological process by which the lifespan of the corpus luteum is prolonged. This mechanism is not well characterized in camelids. The objectives of the present research were to determine if exogenous oxytocin prolongs the corpus luteum activity in alpacas and to evaluate expression and localization of oxytocin receptors within the endometrium at 9 and 14 days post-mating. In the oxytocin studies, plasma progesterone profiles were determined after ovulation in the same alpacas on 2 cycles: one cycle without oxytocin treatment and one cycle with oxytocin treatment. Oxytocin was administered daily by intramuscular injections (IM) at a dose of 20 IU (experiment 1, n = 6) or 60 IU (experiment 2, n = 7 from day 3 through day 10 after induction of ovulation with GnRH IM). There was no significant difference in the length of the luteal phase (i.e. corpus luteum lifespan) between the treated and control cycles using either 20 or 60 IU of oxytocin. In the final experiment, uteri from open and pregnant alpacas (n = 4 per group) at 9 and 14 days post-mating were evaluated for expressions of oxytocin receptors by immunohistochemistry. No significant difference ( $P \leq 0.05$ ) in the expression of oxytocin receptors was observed between open and pregnant animals in either staining intensity or tissue localization. We conclude that oxytocin is not involved in luteolysis and early MRP in alpacas.

### 1. Introduction

Oxytocin secreted by the corpus luteum (Wathes et al., 1996, 1983) plays an essential role in luteolysis and maternal recognition of pregnancy (MRP) in domestic ruminants (Flint and Sheldrick, 1986). Oxytocin functions to simulate endometrial PGF2 $\alpha$  synthesis. Through a unique counter-current mechanism, endometrium-derived PGF2 $\alpha$  induces further release of oxytocin from the corpus luteum (CL) (Flint and Sheldrick, 1982), as well as release from the hypothalamus (Silva et al., 1991) via positive feedback on these structures. Administration of exogenous oxytocin to cows between day 4 and day 8 after ovulation induces luteolysis (Armstrong and Hansel, 1959). However, oxytocin administration to cyclic heifers from day 10 after ovulation by subcutaneous osmotic mini-pumps lengthened the luteal phase (Gilbert et al., 1989). Similar results were obtained in ewes by Flint and Sheldrick (1985), delaying the return to estrus by 7 days when oxytocin was administered intravenously from day 13 to day 21 after estrus. These authors attributed the results to the high levels of circulating oxytocin preventing the expression and cell surface display of endometrial oxytocin receptors, thus preventing the PGF2 $\alpha$  release necessary for luteolysis (Flint and Sheldrick, 1985). These observations suggest that oxytocin is involved in down-regulating its own receptor when given at the end of diestrus in ruminants (Gilbert et al., 1989). In

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the presence of an embryo, interferon tau inhibits the expression of oxytocin receptors in the endometrium and, by a local action on the uterine epithelium, inhibits oxytocin-induced luteolytic-type episodes of PGF2 $\alpha$  release in sheep (Payne and Lamming, 1994). Similarly, in non-pregnant mares, oxytocin induces the secretion of PGF2 $\alpha$  from the endometrium causing luteolysis between day 14 and 15 post ovulation (Allen, 2000). Release of oxytocin by the neurohypophysis concomitantly with an increased number of endometrial oxytocin receptors in late diestrus is responsible for the release of PGF2 $\alpha$  from the endometrium and induction of luteolysis. However, studies in mares demonstrated that the administration of high doses of oxytocin in mid-diestrus prolongs the corpus luteum lifespan (Vanderwall et al., 2016). Administration of 60 IU of oxytocin twice a day, intramuscularly (IM) on days 7–14 after ovulation maintained progesterone concentration > 1 ng/mL continuously through day 30 (Vanderwall et al., 2007). The same group reported similar results with once daily administration of the 60 IU of oxytocin IM. Luteal function was prolonged in 60% to 70% of treated mares in these experiments (Vanderwall et al., 2012). However, the mechanism that mediates the actions of oxytocin in the mare is likely distinct from that in the cow. In the cow, oxytocin receptors are down-regulated, which does not appear to be the case in the mare. Oxytocin treatment in the mare does not alter the number of oxytocin receptors in late diestrus (Vanderwall et al., 2012).

In camelids, the role of PGF2 $\alpha$  as a luteolysin is well established. The pulsatile production of PGF2 $\alpha$  from the endometrium is responsible of luteolysis beginning on day 7 or 8 and finishing by day 9 or 10 after mating in non-pregnant llamas and alpacas (Aba et al., 2000). However, it remains to be determined whether or not oxytocin plays a role in these physiologic mechanisms in this species. A previous study on dromedaries showed that a single dose of oxytocin (20, 50, or 100 IU) given 10 days post-ovulation did not result in a release of PGF2 $\alpha$  (Skidmore et al., 1998).

The camelid embryo enters the uterus on day 6.5–7 after fertilization allowing for only a few days to signal its presence and avert luteolysis (Picha et al., 2013). In the presence of the conceptus, luteolysis is prevented and the corpus luteum is maintained in the alpaca as the sole source of progesterone for the entire gestation. Similarly to the equine and porcine embryos, camelid embryos have a high aromatization capacity and produce estradiol-17 $\beta$  between days 7 and 15 of pregnancy (Skidmore et al., 1994; Powell et al., 2007). This increase in estradiol production occurs during blastocyst elongation (days 11–13). It is possible that camelid elongation plays an important role in MRP as in ruminants and pigs (Picha et al., 2013). In llamas, although the peak of estradiol is not reached until day 13, blastocysts estradiol production starts at day 7 and by day 9 the levels are three to four-fold higher (Powell et al., 2007). This may provide an adequate signal to prolong luteal lifespan (Powell et al., 2007). Estradiol benzoate (10 mg, IM) administration from days 7–15 after induction of ovulation results in prolonged diestrus and increased progesterone secretion during the period when luteolysis normally occurs in llamas (Powell et al., 2007). Others authors reported that administration of estradiol (200  $\mu$ g/day IM) on days 8 and 9 post-ovulation to embryo recipients improved alpaca embryo survival by 30–50% (Ysaac Chipayo et al., 2003). The involvement of estrogens in MRP in camelids is further supported by the increase in estrogen receptor alpha (ESR1) in the endometrium between Days 8–12 post-mating in pregnant animals and a reduction in the expression of progesterone receptors by Day 12 post-mating (Bianchi et al., 2013). However, attempts to prolong luteal lifespan in cyclic camels by administering a range of types and doses of exogenous estrogens at various times during the luteal phase were unsuccessful (Skidmore et al., 1994).

Migration of the embryo from the right to the left uterine horn is another mechanism that may be involved in the MRP in camelids (Picha et al., 2013). However, this migration is different from the transuterine embryo migration observed in the equine. In the mare, the embryo remains spherical and moves around in the uterus whereas in camelids the embryo elongates. The migration of the embryo from the right to the left horn and the subsequent preponderance of left-horn pregnancies in camelids are attributed to a difference in PGF2 $\alpha$  release between the two uterine horns. PGF2 $\alpha$  release from the right uterine horn is local whereas its release from the left horn is systemic (Tibary et al., 2007). The migration of the embryo originating from an ovulation in the right ovary to the left horn is therefore required to prevent PGF2 $\alpha$  release into the general circulation and may even exert a luteotrophic effect making possible the survival of the embryo (Picha et al., 2013). A recent study in the dromedary camel showed that MRP is not associated with interferons response and that interferon stimulated genes (ISG) expression occurs only during placentation. In addition, differences in expression of some genes were found between the left and right uterine horn only in the preimplantation phase (Abdoon et al., 2017).

There are no studies on the role of oxytocin at the time of MRP in camelids.

The present experiments were designed to determine if oxytocin plays a role in luteolysis in alpacas. Two approaches were taken. The first approach consisted of studying if there is any difference in luteal phase duration in alpacas following treatment with oxytocin after ovulation. The second approach was to determine if there is a difference in oxytocin receptors expression between pregnant and non-pregnant animals at 9 and 14 days post-mating.

## 2. Materials and methods

### 2.1. Animals

All alpacas used for this study were healthy, non-pregnant, non-lactating, between 5 and 16 years of age. Animals enrolled were assessed through an initial physical examination and breeding soundness examination. Alpacas were maintained in outdoor paddocks and fed grass hay and water ad libitum. All procedures were completed in accordance and approval from the institutional animal care and used committee at Washington State University.

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