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Prostaglandin E_1 or E_2 inhibits an oxytocin-induced premature luteolysis in ewes when oxytocin is given early in the estrous cycle

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The objective of this study was to determine whether PGE_1 or PGE_2 prevents a premature luteolysis when oxytocin is given on Days 1 to 6 of the ovine estrous cycle. Oxytocin given into the jugular vein every 8 hours on Days 1 to 6 postestrus in ewes decreased ($P \leq 0.05$) luteal weights on Day 8 postestrus. Plasma progesterone differed ($P \leq 0.05$) among the treatment groups; toward the end of the experimental period, concentrations of circulating progesterone in the oxytocin-only treatment group decreased ($P \leq 0.05$) when compared with the other treatment groups. Plasma progesterone concentrations in ewes receiving PGE_1 or PGE_1 + oxytocin were greater ($P \leq 0.05$) than in vehicle controls or in ewes receiving PGE_2 or PGE_2 + oxytocin and was greater ($P \leq 0.05$) in all treatment groups receiving PGE_1 or PGE_2 than in ewes treated only with oxytocin. Chronic intrauterine treatment with PGE_1 or PGE_2 also prevented ($P \leq 0.05$) oxytocin decreases in luteal unoccupied and occupied LH receptors on Day 8 postestrus. Oxytocin given alone on Days 1 to 6 postestrus in ewes advanced ($P \leq 0.05$) increases in $PGF_{2\alpha}$ in inferior vena cava or uterine venous blood. PGE_1 or PGE_2 given alone did not affect ($P \geq 0.05$) concentrations of $PGF_{2\alpha}$ in inferior vena cava and uterine venous blood when compared with vehicle controls or oxytocin-induced $PGF_{2\alpha}$ increases ($P \leq 0.05$) in inferior vena cava or uterine venous blood. We concluded that PGE_1 or PGE_2 prevented oxytocin-induced premature luteolysis by preventing a loss of luteal unoccupied and occupied LH receptors.

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1. Introduction

Loss of luteal progesterone secretion toward the end of the estrous cycle is *via* uterine secretion of $PGF_{2\alpha}$, which is delivered locally from the uterine vein to the ovarian artery adjacent to the luteal-containing ovary in ewes and cows. Uterine secretion of $PGF_{2\alpha}$ to initiate luteolysis is by increases in estradiol-17β at midcycle, which requires prior progesterone priming (reviewed in [1]). Progesterone given during the first few days of the estrous cycle in ewes causes a premature luteolysis [2–4] in ewes *via* a premature increase in uterine secretion of $PGF_{2\alpha}$ [5]. Exogenous estradiol-17β given early in the estrous cycle of ewes does not cause a premature luteolysis or advance uterine $PGF_{2\alpha}$ secretion. However, estradiol-17β given early in the estrous cycle will increase $PGF_{2\alpha}$ secretion if ewes are first primed with exogenous progesterone given early in the estrous cycle [5].

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Oxytocin given during the first few days of the estrous cycle also shortens estrous cycle length in cows [6], ewes [7], and goats [8], which is associated with an increase in uterine secretion of $PGF_{2\alpha}$ in ewes [9]. The ovary also secretes oxytocin in response to $PGF_{2\alpha}$ [10]. However, oxytocin given too frequently downregulates oxytocin receptors and delays luteal regression [11]. Approximately 6 hours are required for regeneration of oxytocin receptors [11–13]. Moreover, active or passive immunization of ewes against oxytocin delays luteal regression [14,15].

Prevention of luteolysis during early pregnancy in ewes is not via inhibition of $PGF_{2\alpha}$ concentrations in the endometrium or endometrial $PGF_{2\alpha}$ secretion *in vitro*. In addition, transport of $PGF_{2\alpha}$ locally from the uterine vein to the adjacent ovarian artery is not reduced, because concentrations of $PGF_{2\alpha}$ in the uterine vein, in the ovarian artery or ovarian venous blood, $PGF_{2\alpha}$ in luteal tissue, or binding of $PGF_{2\alpha}$ to luteal membranes are not decreased during early pregnancy in ewes (reviewed in [1]). Instead, the corpus luteum was more resistant to $PGF_{2\alpha}$ during early pregnancy, because more $PGF_{2\alpha}$ was required in a dose–response experiment to decrease circulating progesterone than in nonpregnant ewes [16,17]. This resistance is probably mediated via increased PGE_1 and PGE_2 in ovine endometrium on Day 13 postbreeding [18,19], leading to increased PGE (PGE_1 + PGE_2) in uterine venous blood during early pregnancy [20–23]. PGE continues to increase as pregnancy progresses, and by Day 55, PGE_1 or PGE_2 are the luteotropin (reviewed in [1]). Furthermore, either PGE_1 or PGE_2 infused chronically into the ovine uterine lumen adjacent to the luteal-containing ovary prevented a spontaneous [24–26] or premature luteolysis induced by estradiol-17β [27,28], an intrauterine device [29,30], progesterone [31], or $PGF_{2\alpha}$ [32,33]. Acute treatment with PGE_1 into the interstitial tissue of the ovarian vascular pedicle of the ovine luteal-containing ovary increased circulating progesterone for a longer duration than treatment with PGE_2 [32,33]. Thus, PGE_1 and PGE_2 have been reported to be the major direct luteotropic or antiluteolytic signal from the uterine horn to the adjacent luteal-containing ovary to prevent luteolysis during early pregnancy in the ewe (reviewed in [1]). Both PGE_1 and PGE_2 are vasodilators [34] and increase luteal progesterone secretion *in vitro* in cows [35] and ewes [36] as well as *in vivo* [32,33] in ewes and cows [37], whereas $PGF_{2\alpha}$ is a vasoconstrictor [38].

Therefore, the objective of this experiment was to determine whether PGE_1 or PGE_2 infused chronically into the lumen of the uterine horn adjacent to the luteal-containing ovary would prevent an oxytocin-induced premature luteolysis when oxytocin was given during the early luteal phase of ewes.

2. Materials and methods

2.1. Animals and surgery

The experimental protocol was approved by the University of Hawaii Institutional Animal Care and Use Committee. Mature Merino crossbred ewes were checked twice daily (06:00 and 17:00 hours) for estrus with brisket-painted vasectomized rams. Estrus was designated as Day 0 of the estrous cycle. Only ewes in estrus in the morning and with two consecutive interestrous intervals of 16 to 17 days were used. Ewes were fasted for 12 hours before surgery and received 1 mL (0.54 mg) atropine sulfate (Phoenix Pharmaceuticals, Inc., St. Joseph, MO, USA) given im as a preanesthetic followed by pentobarbital sodium anesthesia (Anthony Products Co., Arcadia, CA, USA). A polyvinyl catheter (Cole Parmer, Chicago, IL, USA) was inserted into the jugular vein and secured with 000 silk sutures for administration of treatments and for collection of jugular venous blood for analysis for progesterone and estradiol-17β. A similar cathether was placed into the lumen of the uterine horn adjacent to the ovary containing the corpus luteum to deliver intrauterine treatment with PGE_1 or PGE_2. A polyvinyl catheter (Cole Parmer) was inserted into the inferior vena cava *via* the saphenous vein with the end of the catheter tip positioned 2 cm anterior to the juncture of the ovarian vein and inferior vena cava to quantify $PGF_{2\alpha}$ and PGE (PGE_1 + PGE_2) because the antisera cross reacts equally with PGE_1 or PGE_2.

The uterine horn and inferior vena cava catheters were exteriorized through the flank and secured with 000 silk sutures to the oviduct to administer intrauterine treatments of PGE_1 or PGE_2. Only ewes with one corpus luteum were used.

2.2. Treatments

Treatment groups were as follows: (1) vehicle, 1 mL PBS for intrajugular and intrauterine treatments (N = 5); (2) oxytocin (100 IU; Sigma Chemical Co. Inc., St. Louis, MO, USA) was given into the jugular vein (N = 7); (3) PGE_1 (300 μg; Cayman Chemical Co. Inc., Ann Arbor, MI, USA) was given intrauterine adjacent to the luteal-containing ovary (N = 5); (4) PGE_2 (300 μg; Cayman Chemical Co. Inc.) was given intrauterine adjacent to the luteal-containing ovary (N = 5); (5) PGE_1 + oxytocin (N = 7); and (6) PGE_2 + oxytocin (N = 7). Treatments in 1-mL vehicle were given intrajugular or intrauterine adjacent to the luteal-containing ovary followed by 1-mL PBS to insure treatments were not left in the catheter. Treatment with oxytocin was given intrajugular at 08:00, 16:00, and 24:00 hours from Day 1 through Day 6 postestrus. Treatment with PGE_1 or PGE_2 was given intrauterine adjacent to the luteal-containing ovary at 06:00, 12:00, 18:00, and 24:00 hours from Day 1 through 18:00 hours on Day 8. Ewes were laparotomized at 18:00 hours on Day 8 under pentobarbital anesthesia to collect uterine venous blood and ovarian luteal samples for analyses. PGE_1 and PGE_2 treatments were prepared fresh daily and stored at 4 °C between treatments.

2.3. Sample collection

Samples of jugular venous blood and inferior vena cava blood were collected *via* heparinized syringes at 16:00 hours on Day 0 postestrus and once daily 1 hour after the 24:00 hours treatment for analysis for plasma progesterone by RIA [39] and estradiol by RIA [40] in jugular venous plasma and for PGE (PGE_1 + PGE_2) and $PGF_{2\alpha}$ in inferior venous cava plasma by RIA [41]. Uterine venous

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