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Review

Prostaglandins and reproduction in female farm animals

C.W. Weems [a,*], Y.S. Weems [a], R.D. Randel [b]

[a] Department of Human Nutrition, Food, and Animal Sciences, University of Hawaii, 1955 East West Road, Honolulu, HI 96822, USA
[b] Agricultural Research and Extension Center, Texas A&M University, Overton, TX 75684, USA

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Abstract

Prostaglandins impact on ovarian, uterine, placental, and pituitary function to regulate reproduction in female livestock. They play important roles in ovulation, luteal function, maternal recognition of pregnancy, implantation, maintenance of gestation, microbial-induced abortion, parturition, postpartum uterine and ovarian infections, and resumption of postpartum ovarian cyclicity. Prostaglandins have both positive and negative effects on reproduction; they are used to synchronize oestrus, terminate pseudopregnancy in mares, induce parturition, and treat retained placenta, luteinized cysts, pyometra, and chronic endometritis. Improved therapeutic uses for prostaglandins will be developed when we understand better their involvement in implantation, maintenance of luteal function, and establishment and maintenance of pregnancy.

Keywords: Prostaglandins; Reproduction; Corpus luteum; Pregnancy; Placenta; Ovulation; Implantation; Parturition; Postpartum; Oestrous synchronization

1. Introduction

Prostaglandins (PGs) affect ovulation, luteal regression, the implantation and maintenance of pregnancy, parturition, postpartum physiology, and have been used for synchronization of oestrus alone or with progestins, oestrogens, and gonadotropin releasing hormone (GnRH). To understand PGs and reproduction, knowledge of their metabolism is important.

2. Prostanoid metabolism

Prostanoids (comprising the PGs, leukotrienes [LT], and thromboxanes [TX]) are 20-carbon molecules derived from arachidonic acid (AA) or di-homo-γ-linolenic acid. Most PGs ($PGF_{2\alpha}$, PGI_2, PGE_2) and TXA_2 have double bonds at carbons 5–6 and 13–14 and are derived from AA, while PGE_1 has a double bond only at carbons 13–14 and is derived from di-homo-γ-linolenic acid. Double bonds at carbons 13–14 and an OH group at C-15 are essential for biological activity (Bergstrom et al., 1968; Schneider, 1976; Ramwell et al., 1977).

Leukotrienes are derived from AA, but unlike PGs and TXA do not contain a 5 or 6 member ring (Smith and DeWitt, 1996). Catabolism of PGs can occur within organs, but most occurs in the lung (Piper et al., 1970). This involves reducing the double bond at carbons 13–14 and dehydrogenation of the OH group on C-15 to make the 13-14-dihydro-15-keto-PG catabolite (Samuelsson et al., 1971). Cyclo-oxygenase (COX) occurs as a constitutive (COX-1) and an inducible (COX-2) enzyme for both PG and TXA synthesis. Arachidonic acid is converted by COX to PGG_2 and then to PGH_2, which is then converted by synthases or reductases to a specific PG or TXA (Smith and DeWitt, 1996).

Pharmaceutical agents influence PG metabolism. Aspirin or indomethacin inhibits COX-1 and celecoxib

* Corresponding author. Tel.: +1 808 956 8337; fax: +1 808 956 4883.
E-mail address: weems@hawaii.edu (C.W. Weems).

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inhibits COX-1 and COX-2, while cortisol blocks phospholipase-A_2 release of AA from phospholipids to decrease PG synthesis (Vane and Botting, 1995). Inhibitors of PG synthesis are currently used for understanding reproductive processes, but not for clinical therapy (Murdoch, 1988b; Bridges et al., 1999a). Little information exists on downstream synthases or reductases after PGH_2 formation on reproduction. Lipoxygenases synthesize LT from AA, which can be inhibited by 1-benzo-[b]-thien-2-ylethyl-1-hydroxyurea (Vane and Botting, 1995). Various isoforms of prostaglandin receptors (PG receptors) have been identified in tissues: receptors with low and high affinity binding sites for $PGF_{2\alpha}$ (FP); four isoforms for PGE_1 and PGE_2 (EP_1, EP_2, EP_3, EP_4), and only one isoform each for TXA_2, PGI_2, and PGD_2 (Narumiya, 1995). Effects of PGE_1, PGE_2, and $PGF_{2\alpha}$ on reproduction have been studied, but other PGs may also have roles (Weems et al., 1995).

3. Follicular growth and ovulation

Whether PGs have direct effects on follicular growth prior to the luteinizing hormone (LH) surge to initiate ovulation in livestock is unknown, but $PGF_{2\alpha}$ increases pituitary responsiveness to GnRH to release LH in the postpartum cow (Randel et al., 1996). However, PGs produced by the ovulatory follicle are obligatory for ovulation (Murdoch et al., 1993). Ovulation involves a cascade of changes in follicles and most of the mechanisms for ovulation in livestock have used the sheep model.

In sheep, luteolysis is induced by $PGF_{2\alpha}$ and GnRH is used to time the LH surge for collection of ovulatory follicles. Ovulation occurs 24 h after the LH surge (Murdoch, 1985). The LH surge through alterations in 3′5′ cyclic adenosine monophosphate (c-AMP) levels shifts steroidogenesis in the ovulatory follicle. Androgens and oestradiol-17_β levels decrease and progesterone levels increase, which results in changes in microcirculation and morphology in the follicle wall (Murdoch and Dunn, 1982a,b; Murdoch et al., 1983; Murdoch, 1988a, 1992; Cavender and Murdoch, 1988). Increases in c-AMP occur in the follicle wall 4 h after the LH surge and remain elevated for 12 h, but decline by 16–20 h (Murdoch et al., 1981, 1986). The area of theca interna occupied by blood vessels increases at 4 and 12 h after the LH surge and declines at ovulation to levels lower than those prior to the LH surge, suggesting ischaemia may be a factor in ovulation (Murdoch and Myers, 1983; Murdoch and Cavender, 1987, 1989). Basophil/mast cell numbers in the theca interna decrease by 4 h after the LH surge and neutrophils and eosinophils in ovulatory follicles increase 4 h prior to ovulation (Murdoch et al., 1981, 1986; Murdoch and Steadman, 1991). Follicular fluid volume increases and antihistamines given at the LH surge decrease follicular fluid volume, but do not inhibit ovulation. However, subsequent luteal function is decreased (Halterman and Murdoch, 1986; Murdoch, 1990).

In sheep, concentrations of PGE_2 and $PGF_{2\alpha}$ in follicular fluid do not change after the LH surge (Murdoch et al., 1981, 1986, 1993). In the follicle wall, COX-2 and both PGE_2 and $PGF_{2\alpha}$ increase at 8 h and remain elevated through 12 h, and only PGE_2 decreases by 16–20 h (Murdoch et al., 1981, 1986, 1991, 1993). Intrafollicular injections of LH or follicle stimulating hormone (FSH) in sheep increased PGE_2, but not $PGF_{2\alpha}$, in granulosa cells, while both PGE_2 and $PGF_{2\alpha}$ were increased in the theca (Murdoch and McCormick, 1991; Murdoch et al., 1993). Intercellular space between mural and cumulus cells increases by 12 h and is dependent on PGE_2, but not $PGF_{2\alpha}$ (Murdoch et al., 1993).

Indomethacin inhibition of ovulation can be overcome by PGE_2 or $PGF_{2\alpha}$ (Murdoch, 1988b; Murdoch and Dunn, 1982b; Murdoch and McCormick, 1991; Murdoch et al., 1993). The theca converts PGE_2 to $PGF_{2\alpha}$ to activate collagenolysis, which is dependent on follicular progesterone regulation of 9-keto-PGE_2-reductase to convert PGE_2 to $PGF_{2\alpha}$ (Murdoch and Ferris, 1988; Murdoch et al., 1993). Isoxazol, an inhibitor of progesterone synthesis, also blocks ovulation, which can be restored by progesterone or $PGF_{2\alpha}$, but not by PGE_2 (Murdoch and Cavender, 1987; Murdoch et al., 1993).

Collagenolysis increases by 20 h after the LH surge and until follicular rupture (Murdoch and McCormick, 1991, 1992a; Murdoch, 2000). Collagenolysis is not affected by isoxazol or indomethacin 16 h after the LH surge; however, indomethacin or isoxazol decreases collagenolysis by 24 h (Murdoch et al., 1993). Leukocyte infiltration into the follicle wall may be caused by a chemoattractant produced by collagenolysis (Murdoch and McCormick, 1989, 1991, 1992a,b, 1993). Collagen, collagen -like peptides, LTB_4 (a prostanoid), tumor necrosis factor-α (TNF_α), platelet activating factor (PAF), TXA_2, and plasmin increase leukocyte infiltration in the ovulatory follicle, while antisera to collagen-like peptides prevents leukocyte infiltration (Murdoch, 1986, 1998a, 1999; Murdoch and McCormick, 1989, 1991, 1992a,b, 1993; Alexander et al., 1990; Murdoch, 1997; Murdoch and Lund, 1999; Gottsch et al., 2000).

Nordihydroguaratic acid, a lipoxygenase inhibitor, decreases LT and leukocyte infiltration into the follicle and blocks ovulation, although indomethacin also reduced leukocyte infiltration (Espey, 1992; Carvalho et al., 1989; Murdoch and McCormick, 1991). Remodeling of the extracellular matrix may require other proteases at ovulation, which may be activated by TNF_α (Murdoch, 1999; Murdoch et al., 1999c; Johnson et al., 1999a; Medan et al., 2003). Granulosa cell organelle