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Novel concepts on the role of prostaglandins on luteal maintenance and maternal recognition and establishment of pregnancy in ruminants[1]

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ABSTRACT

In ruminants, the corpus luteum (CL) of early pregnancy is resistant to luteolysis. Prostaglandin (PG)E_2 is considered a luteoprotective mediator. Early studies indicate that during maternal recognition of pregnancy (MRP) in ruminants, a factor(s) from the conceptus or gravid uterus reaches the ovary locally through the utero-ovarian plexus (UOP) and protects the CL from luteolysis. The local nature of the embryonic antiluteolytic or luteoprotective effect precludes any direct effect of a protein transported or acting between the gravid uterus and CL in ruminants. During MRP, interferon tau (IFNT) secreted by the trophoblast of the conceptus inhibits endometrial pulsatile release of $PGF_{2\alpha}$ and increases endometrial PGE_2. Our recent studies indicate that (1) luteal PG biosynthesis is selectively directed toward $PGF_{2\alpha}$ at the time of luteolysis and toward PGE_2 at the time of establishment of pregnancy (ESP); (2) the ability of the CL of early pregnancy to resist luteolysis is likely due to increased intraluteal biosynthesis and signaling of PGE_2; and (3) endometrial PGE_2 is transported from the uterus to the CL through the UOP vascular route during ESP in sheep. Intrauterine co-administration of IFNT and prostaglandin E_2 synthase 1 (PGES-1) inhibitor reestablishes endometrial $PGF_{2\alpha}$ pulses and regresses the CL. In contrast, intrauterine co-administration of IFNT and PGES-1 inhibitor along with intraovarian administration of PGE_2 rescues the CL. Together, the accumulating information provides compelling evidence that PGE_2 produced by the CL in response to endometrial PGE_2 induced by pregnancy may counteract the luteolytic effect of $PGF_{2\alpha}$ as an additional luteoprotective mechanism during MRP or ESP in ruminants. Targeting PGE_2 biosynthesis and signaling selectively in the endometrium or CL may provide luteoprotective therapy to improve reproductive efficiency in ruminants.

Key words: prostaglandin, corpus luteum, endometrium, establishment of pregnancy

PROSTAGLANDINS

Prostaglandins (**PG**), thromboxanes (**TX**), and leukotrienes (**LT**) are classified as eicosanoids (from the Greek *eicosa*, meaning 20), which describe the broad group of compounds derived from C_{20} fatty acids. Prostaglandins are 20-carbon unsaturated hydroxyl fatty acids with a cyclopentane ring. Arachidonic acid, an essential fatty acid, is the principal precursor for PG. In mammals, PG play important roles in several physiological and pathological processes (McCracken, 2005).

Biosynthesis of PG

Phospholipase A_2 (**PLA_2**) liberates arachidonic acid from membrane phospholipids. Cyclooxygenases (**COX**) 1 and 2 convert arachidonic acid into PGH_2, the common intermediate metabolite for biosynthesis of various PG, and PGH_2 is then converted into selective PG including $PGF_{2\alpha}$, PGE_2, PGD_2, PGI_2, and TXA_2 by specific synthases (Smith and Dewitt, 1996; Kudo and Murakami, 1999; Thorén and Jakobsson, 2000; Smith and Song, 2002; Thorén et al., 2003). Prostaglandin F synthase (**PGFS**, such as AKR1B1, AKR1C1, AKR1C2, and AKR1C3) and prostaglandin E synthase (**PGES**-1, -2, and -3) convert PGH_2 into $PGF_{2\alpha}$ and PGE_2, respectively. Catabolism of PG is governed by prostaglandin 15-dehydrogenase (**PGDH**), which catabolizes $PGF_{2\alpha}$ into inactive 15-keto-13,14-dihydro $PGF_{2\alpha}$ (**PGFM**), and catabolizes PGE_2 into inactive 13,14-dihydro-15-keto PGE_2 (**PGEM**; Tai et al., 2002). An overview on PG metabolic pathways is depicted in Figure 1.

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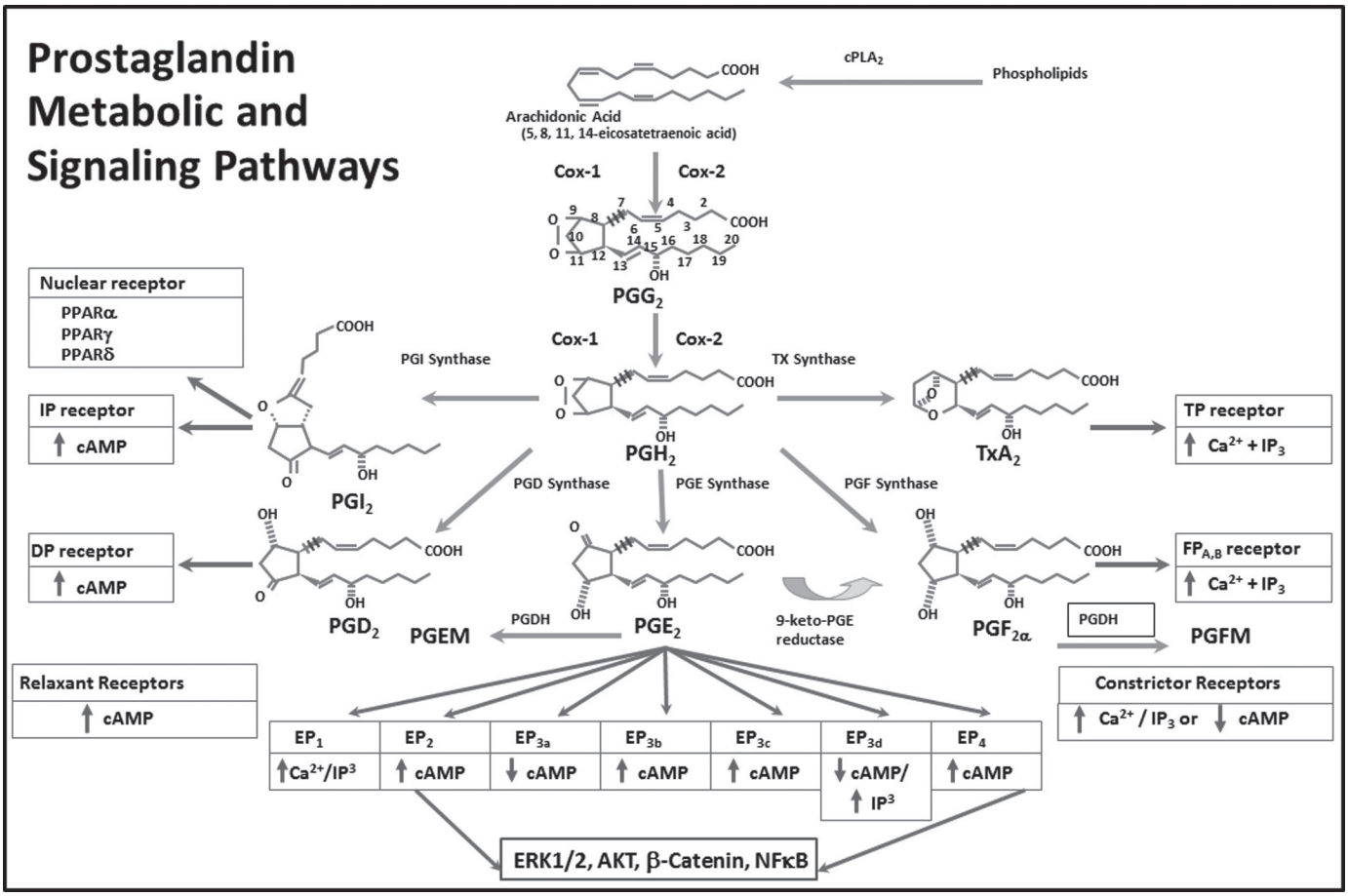

Figure 1. Overview on biosynthesis and signaling of prostaglandins, which is developed based on published information (Kanai et al., 1995; Smith and Dewitt, 1996; Kudo and Murakami, 1999; Narumiya et al., 1999; Narumiya and FitzGerald, 2001; Smith and Song, 2002; Tai et al., 2002; Thorén and Jakobsson, 2000; Thorén et al., 2003; Castellone et al., 2005; Buchanan et al., 2006; Cha and DuBois, 2007). PG = prostaglandin; PPAR = peroxisome proliferator-activated receptor; COX = cyclooxygenase; DP = prostaglandin D_2 receptor; EP = prostaglandin E_2 receptor; FP = $PGF_{2\alpha}$ receptor; ERK1/2= extracellular signal-regulated protein kinases 1 and 2; AKT = protein kinase B; NF-kB = nuclear factor kappa B; IP_3 = inositol trisphosphate; PGDH = prostaglandin 15-dehydrogenase; PGEM = inactive 13,14-dihydro-15-keto PGE_2; *PGFM* = inactive 15-keto-13,14-dihydro $PGF_{2\alpha}$; TX = thromboxane. Color version available online.

Transport of PG

Transport of PG through plasma membranes is poorly understood, with proposed mechanisms including from simple diffusion, passive transport, active transport, counter current exchange, and carrier-mediated transport. The PG are organic anions and cross cellular membranes by simple diffusion; however, the estimated flow rate is too low and insufficient to bring forth their biological effects. In the pulmonary circulation, PGE_2 and $PGF_{2\alpha}$ are catabolized rapidly in one passage through the lungs. Therefore, a carrier-mediated transport mechanism is required for cellular transport of PG. Prostaglandin transporter (**PGT**) is a member of the 12-transmembrane solute carrier organic anion transporter (OATP) 2A1 (SLCO2A1) family (Schuster, 1998, 2002); PGT transports $PGF_{2\alpha}$, PGE_2, PGD_2, and TxA_2 in a competitive manner, with different affinities for each PG. We and others using pharmacological and genomic approaches have shown that inhibition of PGT prevents PGT-mediated transport of PG in various cell types (Kanai et al., 1995; Chan et al., 1998; Banu et al., 2003, 2008).

Signaling of PG

Prostaglandin $F_{2\alpha}$ and PGE_2 elicit their autocrine, paracrine, or endocrine biological actions through FP and EP (EP1, EP2, EP3, and EP4) receptors, respectively, by activating multiple signaling cascades (Coleman et al., 1994; Narumiya et al., 1999; Narumiya and FitzGerald, 2001). The FP and EP1 receptors are coupled to the Gq protein and activate phospholipase C, which generates 2 second messengers: inositol tri-