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The role of progesterone and conceptus-derived factors in uterine biology during early pregnancy in ruminants[1]

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ABSTRACT

This review integrates established and new information on the role of progesterone, interferon tau (IFNT), and prostaglandins in uterine biology of ruminants. Establishment of pregnancy in ruminants encompasses growth of the posthatching blastocyst, elongation of the conceptus (embryo and extraembryonic membranes), and suppression of the endometrial luteolytic mechanism to maintain progesterone production by the ovary. Conceptus elongation involves exponential increases in length of the trophectoderm for pregnancy recognition signaling, implantation, and establishment of pregnancy. Pregnancy recognition signaling is accomplished by IFNT from the trophectoderm that has a paracrine antiluteolytic effect to inhibit upregulation of oxytocin receptors in the endometrial epithelia, thereby inhibiting production of luteolytic $PGF_{2\alpha}$ pulses by the uterus. Survival and growth of the preimplantation blastocyst and elongating conceptus clearly requires embryotrophic factors (AA, carbohydrates, proteins, lipids, and other substances) in the uterine lumen. Individual, interactive, and coordinated actions of progesterone, IFNT, and prostaglandins regulate expression of elongation- and implantation-related genes in the endometrial epithelia that, in turn alter the uterine luminal histotroph and govern conceptus survival and growth. An increased knowledge of progesterone biology and conceptus-endometrial interactions is necessary to understand and elucidate the causes of pregnancy loss and provide a basis for new strategies to improve pregnancy outcome and reproductive efficiency in ruminants.

Key words: progesterone, interferon, prostaglandin, uterus, pregnancy

INTRODUCTION

This review integrates established and new information on the biological role of ovarian progesterone (**P4**), conceptus interferon tau (**IFNT**), and prostaglandins (**PG**) in uterine biology of ruminants during early pregnancy (Spencer et al., 2008; Ulbrich et al., 2013; Lonergan and Forde, 2014; Bauersachs and Wolf, 2015). Establishment of pregnancy in domestic ruminants begins at the conceptus (embryo or fetus and associated extraembryonic membranes) stage and encompasses pregnancy recognition signaling, implantation, and onset of placentation (Guillomot, 1995; Spencer et al., 2007a, 2008; Hue et al., 2012). The morula-stage embryo enters the uterus on d 4 to 6 postmating and then forms a blastocyst that contains an inner cell mass and a blastocoele or central cavity surrounded by a single layer of trophectoderm. After hatching from the zona pellucida (d 8 to 10), the blastocyst slowly grows into an ovoid then tubular and filamentous form and is then termed a conceptus.

In sheep, the ovoid conceptus of about 1 mm in length on d 11 begins to elongate on d 12 and forms a filamentous conceptus of 15 to 19 cm or more in length by d 15 that occupies the entire length of the uterine horn ipsilateral to the corpus luteum (**CL**) with extraembryonic membranes extending into the contralateral uterine horn. In cattle, the hatched blastocyst forms an ovoid conceptus between d 12 and 14 and is only about 2 mm in length on d 13. By d 14, the conceptus is about 6 mm, and the elongating bovine conceptus reaches a length of about 60 mm (6 cm) by d 16 and is 20 cm or more by d 19. Thus, the blastocyst or conceptus doubles in length every day between d 9 and 16 with a significant increase (~30 fold) in length between d 12 and 15 (Betteridge et al., 1980; Berg et al., 2010). Conceptus elongation involves exponential increases in length and weight of the trophectoderm (Wales and Cuneo, 1989), trophectoderm cell proliferation (Wang et al., 2009), and onset of extraembryonic membrane differentiation, including gastrulation of the embryo and formation of the yolk sac and allantois that are vi-

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tal for embryonic survival and formation of a functional placenta (Guillomot, 1995; Hue et al., 2012). Successively, the elongated conceptus begins the process of central implantation and placentation around d 16 in sheep and d 19 in cattle.

Blastocyst growth into an elongated conceptus does not occur in vitro, as it requires secretions supplied by the endometrium of the uterus (Fléchon et al., 1986; Betteridge and Flechon, 1988; Gray et al., 2001b; Brandão et al., 2004; Alexopoulos et al., 2005). Uterine luminal fluid (**ULF**) contains embryotrophic substances, collectively termed histotroph, that drive elongation of the conceptus via effects on trophectoderm proliferation and migration as well as attachment and adhesion to the endometrial luminal epithelium (**LE**) (Gray et al., 2001a; Spencer et al., 2008; Bazer et al., 2010). The ULF is derived primarily from transport and synthesis and secretion of substances by the endometrial LE and glandular epithelia (**GE**), and it is a complex and rather undefined mixture of proteins, lipids, AA, sugars (glucose, fructose), ions, and exosomes or microvesicles (Bazer, 1975, 2012; Gray et al., 2001a; Burns et al., 2014). The recurrent early pregnancy loss observed in uterine gland knockout ewes established the importance of uterine epithelial-derived histotroph for support of conceptus elongation and implantation (Gray et al., 2001b, 2002; Spencer and Gray, 2006). Available evidence in sheep and cattle supports the idea that ovarian P4 induces expression of several genes, specifically in the endometrial epithelia, that are then further stimulated by factors from the conceptus (e.g., IFNT and PG) and endometrium itself (PG; Dorniak et al., 2013a; Brooks et al., 2014; Lonergan and Forde, 2014). In turn, the genes and functions regulated by these hormones and factors in the endometrial epithelia cause specific changes in the uterine histotroph that govern conceptus survival and elongation.

P4 REGULATION OF ENDOMETRIAL FUNCTION AND CONCEPTUS ELONGATION

Progesterone stimulates and maintains endometrial functions necessary for embryonic survival, conceptus growth, implantation, placentation, and development to term. A strong positive association exists between the postovulatory rise in concentrations of P4 and embryonic development in sheep and cattle. The effect of P4 on conceptus growth and elongation in sheep and cattle is indirectly mediated by the endometrium (Spencer et al., 2008; Bazer et al., 2010; Lonergan, 2011; Dorniak et al., 2013a; Lonergan and Forde, 2014). During the estrous cycle and pregnancy, P4 induces a set of genes in the endometrium that establish uterine receptivity, which is the physiological state of the uterus when conceptus growth and implantation is possible. The absence of a sufficiently developed conceptus to signal pregnancy recognition results in those genes being turned off as luteolysis ensues and the animal returns to estrus for another opportunity to mate. The outcome of P4 actions on the endometrium is modification of the composition of the ULF, including an increase in select AA, glucose, cytokines, and growth factors, for support of blastocyst and conceptus survival and growth.

Sheep

Actions of ovarian P4 on the uterus are essential for peri-implantation conceptus survival and growth in sheep (Satterfield et al., 2006). Increasing concentrations of P4 after ovulation enhance conceptus elongation in sheep (Satterfield et al., 2006), whereas lower P4 concentrations in the early luteal phase retard embryonic development (Nephew et al., 1991). Between d 10 and 12 after onset of estrus or mating in cyclic and pregnant ewes, P4 induces the expression of many conceptus elongation- and implantation-related genes in the endometrial epithelia of the uterus (Spencer et al., 2007a, 2008; Bazer et al., 2010; Dorniak et al., 2013a; Figure 1 and Table 1). The initiation of expression of those genes requires P4 action and is temporally associated with the loss of progesterone receptors (**PGR**) between d 10 and 12 in the endometrial LE and between d 12 and 14 to 16 in the GE after onset of estrus (Spencer and Bazer, 2002); however, PGR remain present in the stroma and myometrium in the ovine uterus throughout pregnancy. In the endometrial LE and superficial GE (**sGE**), P4 induces genes that encode secreted attachment and migration factors [galectin-15 (*LGALS15*) and insulin-like growth factor binding protein one (*IGFBP1*)], intracellular enzymes [prostaglandin G/H synthase and cyclooxygenase 2 (*PTGS2*) and hydroxysteroid (11-β) dehydrogenase 1 (*HSD11B1*)], secreted proteases [cathepsin L1 (*CTSL1*)], secreted protease inhibitors [cystatin C (*CST3*) and 6 (*CST6*)], a secreted candidate cell proliferation factor [gastrin releasing peptide (*GRP*)], glucose transporters (*SLC2A1*, *SLC2A5*, *SLC5A1*), and a cationic AA (arginine, lysine, and ornithine) transporter (*SLC7A2*). In the endometrial GE, P4 induces genes that encode for a secreted candidate cell proliferation factor (*GRP*), a glucose transporter (*SLC5A11*), secreted adhesion protein (secreted phosphoprotein one or *SPP1*), a candidate regulator of calcium or phosphate homeostasis (*STC1*), and a potential immunomodulatory factor (*SERPINA14*, also known as uterine milk proteins or uterine serpins). Many of those P4-induced genes in the epithelia are further stimulated by the actions of IFNT and PG, resulting in changes in components of the ULF