韓國家畜繁殖學會誌 23(4) : 365~369(1999)
Korean J. Animal Reprod.

Pregnancy Recognition Signaling for Establishment and Maintenance of Pregnancy

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ABSTRACT

Interferon tau (IFNτ), the pregnancy recognition signal in ruminants, suppresses transcription of the estrogen receptor (ER) gene in the endometrial luminal (LE) and superficial glandular epithelium (sGE) to prevent oxytocin receptor (OTR) expression and pulsatile release of luteolytic prostaglandin $F_{2\alpha}$ (PGF). Interferon regulatory factors one (IRF-1) and two (IRF-2) are transcription factors induced by IFNτ that activate and silence gene expression, respectively. Available results suggest that IFNτ acts directly on LE and sGE during pregnancy to induce sequentially IRF-1 and then IRF-2 gene expression to silence transcription of ER and OTR genes, block the luteolytic mechanism to maintenance a functional corpus luteum (CL) and, signal maternal recognition of pregnancy. The theory for maternal recognition of pregnancy in pigs is that the uterine endometrium of cyclic gilts secretes PGF in an endocrine direction, toward the uterine vasculature for transport to the CL to exert its luteolytic effect. However, in pregnant pigs, estrogens secreted by the conceptuses are responsible, perhaps in concert with effects of prolactin and calcium, for exocrine secretion of PGF into the uterine lumen where it is sequestered to exert biological effects and/or be metabolized to prevent luteolysis.

I. PREGNANCY RECOGNITION SIGNALS IN RUMINANTS

Sheep, cattle and goats, are spontaneous ovulators which undergo uterine-dependent estrous cycles until pregnancy is established. Uterine production of luteolytic prostaglandin $F_{2\alpha}$ (PGF) by lumenal (LE) and superficial glandular epithelia (sGE) is regulated by interactions between progesterone, estrogen, oxytocin and their respective receptors [1, 2, 3]. In cyclic ewes, the endometrial luteolytic mechanism develops between Days 11 and 15 post-estrus after expression of progesterone receptor (PR) mRNA and protein in LE and sGE declines to undetectable levels [4, 5, 6]. With loss of PR expression there is an increase in estrogen receptor (ER) mRNA and protein expression between Days 11 and 15 of the estrous cycle [6] which precedes onset of endometrial oxytocin receptor (OTR) gene expression between Days 13 and 14 of the cycle in LE and sGE [2, 7, 8, 9]. Oxytocin, released in a pulsatile manner from CL and/or posterior pituitary binds endometrial OTR and initiates pulsatile release of luteolytic PGF from LE and sGE [10] to cause CL regression. The female returns to estrus for ano-

ther opportunity to mate and establish pregnancy.

In pregnant ruminants, conceptus trophectoderm produces inteferon tau (IFNτ), the signal for maternal recognition of pregnancy [3]. The IFN tau, a unique subclass of omega (ω) interferons, act as an antiluteolytic hormone on LE and sGE to abrogate the pulsatile production of PGF. Ovine IFNτ, secreted by conceptuses between Days 10 and 21 of pregnancy, exerts paracrine effects on LE and sGE to suppress ER and OTR expression [11-13] and, therefore, secretion of luteolytic pulses of PGF in response to oxytocin [12]. There is no evidence that IFNτ affects expression of PR in uterine endometrium [14].

IFNτ binds Type I IFN receptors on endometrial cells [15] and is assumed to activate an intracellular signaling pathway similar to that of other Type I IFNs [16] including IFN-stimulated gene factor three (ISGF3), interferon regulatory factor one (IRF-1) and IRF-2 [17-19]. In response to IFNτ binding Type I IFN receptors, the ISGF3 complex is formed in the cytoplasm, translocates to the nucleus, binds to IFN-stimulated DNA response elements (ISRE), and increases the rate of gene transcription of IFN-inducible genes such as IRF-1 [16]. The IRF-1 is a transcriptional activator, and IRF-2 is its antagonistic repressor [18,19] which appears to inhibit transcription of genes for ER and OTR.

The unique biological effect of IFNτ is its antiluteolytic activity. Secretion of oIFNτ is developmentally regulated and increases from Day 10 as conceptuses change morphologically from spherical (312 ng/ml uterine flush), to tubular (1,380 ng), and then to filamentous (4,455 ng) forms on Days 12 to 13, reaches peak production on Days 15 to 16 and then decreases to undetectable levels by Days 21 [20]. Successful transfer of embryos to cyclic ewes can occur as late as Day 12, i.e., 48 to 72 h prior to the luteolytic period [21]. Thus, secretion of oIFNτ begins prior to the luteolytic period to block development of the luteolytic mechanism responsible for pulsatile release of PGF. Endometrium of cyclic ewes must be exposed to IFNτ from Days 11 or 12 to Day 14, i.e., 2 to 3 days before expected increases in ER and OTR in LE and sGE of cyclic ewes. During pregnancy recognition, secretion of estrogen by the ovaries and oxytocin by the CL and/or posterior pituitary are similar; therefore, the antiluteolytic effect of oIFNτ is at the level of the uterus to block transcription of ER and OTR genes [19] in both LE and sGE.

Ⅱ. PREGNANCY RECOGNITION IN PIGS

The theory of maternal recognition of pregnancy in pigs [see 23] is based on assumptions that the uterine endometrium secretes luteolytic PGF and that the conceptuses secrete estrogens which are antiluteolytic. For cyclic gilts, PGF is secreted in an endocrine direction, toward the uterine vasculature, and transported to the CL to exert its luteolytic effect. However, in pregnant pigs, secretion of PGF is exocrine, into the uterine lumen, where it is sequestered to exert its biological effects in utero and/or be metabolized to prevent luteolysis. Mean concentrations, peak frequency and peak amplitude of PGF in utero-ovarian vein plasma are lower in pregnant and estrogen-induced pseudopregnant gilts than in cyclic gilts. But, uterine flushings from pseudopregnant and pregnant gilts have significantly higher amounts of PGF than those from cyclic gilts.

The transition from endocrine to exocrine secretion between Days 10 and 12 of pregnancy is

temporally associated with initiation of estrogen secretion by elongating pig conceptuses. The estrogen induces a transient release of calcium into the uterine lumen within 12 hours and re-uptake of that calcium by endometrial and/or conceptus tissues occurs about 12 hour after concentrations of calcium in uterine secretions reach maximum values. The switch in direction of endometrial secretion of PGF from an endocrine to an exocrine is closely associated with the period of release and re-uptake of calcium by the endometrium in pregnant and pseudopregnant gilts and the period when endometrial receptors for prolactin increase [see 23, 24].

Day 15 pig conceptuses secrete proteins (pCSP) that include both delta (25%) and gamma (75%) interferons [see 134]; however, the these IFNs do not appear to be antiluteolytic and do not have an effect on concentrations of progesterone in plasma [see 25]. The pCSP preferentially stimulate endometrial production of PGE, which may influence the establishment and maintenance of pregnancy [see 133]. Inhibition of secretion of prostaglandins between Days 12 and 20 after mating results in pregnancy failure in pigs [see 23]. Available results indicate that estrogens of blastocyst origin are essential for maternal recognition of pregnancy in pigs and that pCSP, including interferons, play other roles during early pregnancy in pigs.

Ⅲ. REFERENCES

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