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Mini-Review Article

Pregnancy-associated changes in uterine-luteal relationships in cows: A mini-review☆,☆☆

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ABSTRACT

The main function of the bovine corpus luteum (CL) is the production of progesterone. Adequate luteal progesterone is crucial for determining the physiological duration of the estrous cycle and for achieving a successful pregnancy. The CL is regulated not only by hypophyseal gonadotropin, but also by a number of intraluteal substances including steroids, peptides and prostaglandins. Although regulation of luteal function throughout the estrous cycle has been intensively studied, studies of the CL during the entire gestation period are limited. Understanding the role of luteal function during pregnancy might lead to ways to improve reproductive efficiencies and reduce the number of defective fetuses. Therefore, the purpose of this review is to summarize our current understanding of the gene expression profiles of bovine CL throughout the gestation period and to focus on recent studies documenting the interactions between the CL, uterus and conceptus in cows.

1. Introduction

The corpus luteum (CL) is a transient ovarian organ established by cells of the follicle following ovulation. The primary product of the CL, progesterone (P4), is required for the establishment and maintenance of pregnancy in many mammals. If pregnancy does not occur, the CL degenerates. When pregnancy is established, the luteal lifespan is prolonged and the CL continues to produce P4 during the gestation period [1]. The mammalian CL is comprised of a heterogeneous mixture of cell types that consists of not only steroidogenic luteal cells but also non-steroidogenic cells, *i.e.*, vascular endothelial cells, fibroblasts, and immune cells such as lymphocytes and monocytes [2–4]. The cells composing the bovine CL produce various intraluteal factors, including

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prostaglandins (PG), growth factors and cytokines/chemokines [1]. During the early phase of pregnancy, the CL is requisite in all mammals. In some species (*e.g.*, cows, pigs, goats and dogs), it is also required for the latter stages of pregnancy [5], whereas in other species (*e.g.*, primates, sheep) it is not required because luteal P4 secretion can be replaced by placental P4 secretion [6]. These findings suggest that the physiological roles and functions of the CL are different between the stages of pregnancy, as well as between species. However, there has not yet been a systematic investigation of functional differences between the CL of pregnancy and non-pregnancy. Therefore, this review focuses on studies documenting the roles of the CL during the entire gestation period, with emphasis on differences in the gene and protein expression profiles in the CL between the estrous cycle and pregnancy. Furthermore, possible mechanisms of interactions between the CL, uterus and conceptus in cows are discussed.

2. Interactions between CL and uterus during luteolysis

It is generally accepted that the ovary and the uterus affect each other. A counter-current mechanism is thought to transfer substances secreted into the utero-ovarian vein to the ovarian artery [7]. At the time of luteolysis, luteal-derived oxytocin (OT) and uterine-derived PGF2α are believed to comprise a positive feedback loop in ruminants, *i.e.*, OT produced by CL stimulates PGF2α secretion by the endometrium, which stimulates OT secretion by the CL [8]. PGF2α secretion by the endometrium is regulated not only by OT but also by one or more other factors in cattle. Previous studies demonstrated that functional tumor necrosis factor-α (TNF) receptors are present in the bovine endometrium, and that TNF possibly plays a role in the regulation of endometrial PGF2α production in cattle [9–11]. Thus, TNF as well as OT increase PGF2α production in bovine endometrium not only by directly stimulating PGF2α but also by inducing the production of PGE2, which is then converted into PGF2α by 9-keto-PGE2 reductase (9K-PGR) at the time of luteolysis [12].

3. Interactions between CL and uterus during early pregnancy

The CL remains functional when animals become pregnant, and the dynamics of PGF2α secretion in the estrous cycle changes in early pregnancy [13–16]. If a conceptus is present in the bovine uterus between Days 14 and 17 after estrus, luteolysis does not occur, and P4 secretion is maintained to establish pregnancy [13]. At the time of recognition of pregnancy, the bovine conceptus produces a signal to prevent luteolysis, which is induced by a pulsatile release of PGF2α from the uterus [15,16]. In ruminants, the conceptus signal is a protein from the trophectoderm, identified as interferon-τ (IFNT) [15,16]. One mechanism by which IFNT inhibits luteolysis is the down-regulation of OT receptor, which prevents OT-stimulated PGF2α secretion [17]. In cattle, IFNT inhibits OT-induced PGF2α secretion from the endometrium not simply by the down-regulation of the OT receptor but by decreasing the expressions of cyclooxygenase-2 (COX-2) and PGF synthase (PGFS) [18]. Since OT appears to play a supplementary role rather than a mandatory role during luteolysis in cattle [19,20], there should be other mechanisms preventing luteolysis, independent of the OT-stimulated PGF2α secretion. IFNT directly inhibits protein kinase (PK) C-regulated PGF2α production and expression of COX-2 and phospholipase (PL) A_2 [18]. IFNT also reduces TNF-induced PGF2α synthesis directly by attenuating COX-2 gene expression in bovine endometrial stromal cells in a dose-dependent manner [21]. Based on these findings, one possible hypothesis is that IFNT plays a luteoprotective role by inhibiting the actions of TNF and OT on endometrial PG production in the cow during early pregnancy.

4. Gene expression profiles in the bovine CL during pregnancy

4.1. *Chemokines*

Our recent microarray analysis [22] demonstrated that the expressions of many genes in the CL of pregnancy differed by a factor of >2-fold from their expressions in the CL of non-pregnancy (day 15) (Table 1). These included 278 genes during days 20–25, 565 genes during days 40–45 and 782 genes during days 150–160 of pregnancy. Remarkably, the expression of *eotaxin* increased by more than three orders of magnitude at

Table 1 – Fold change in mRNA levels of selected genes in the CL of pregnancy *vs.* the CL of non-pregnancy (day 15) evaluated by a microarray analysis.

Gene	Change	Days of pregnancy (number of genes that changed by >2-fold)		
		20–25 (278)	40–45 (565)	150–160 (782)
Chemokines				
Eotaxin	Up	(–)	281	3764
Lymphotactin	Down	4.05	2.35	8.34
Prostaglandin receptors				
PTGER3	Up	4.62	46.9	117
PTGFR	Up	2.49	3.23	4.50
IGFBPs and oxytocin				
IGFBP2	Up	(–)	(–)	29.6
IGFBP6	Up	2.12	2.50	3.30
OT	Down	2.35	21.3	323
Extracellular matrix				
Collagen type I	Down	2.15	4.33	4.26
Collagen type II	Down	3.21	3.79	16.1
Fibronectin type I	Down	3.08	3.67	9.01
Others: >10-fold				
Proenkephalin	Up	35.7	57.4	450
Haptoglobin	Up	25.6	21.6	35.9
Prolactin receptor	Up	5.30	10.1	12.9
OAS1	Up	14.9	(–)	(–)

*Modified from the data from our previous study [22].
(–) Less than 2-fold change.