REGULATION OF ENDOMETRIAL PROSTAGLANDIN F2α SYNTHESIS IN LUTEOLYSIS AND EARLY PREGNANCY IN CATTLE - POSSIBLE ROLE OF TUMOR NECROSIS FACTOR-α-

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Introduction

Prostaglandin (PG) $F_{2\alpha}$, which is primarily secreted from the inter-caruncular region of the surface epithelium of the uterus, is considered as a major contributor in the regulation of reproductive processes in cattle. One of the most important phenomena regulating fertility and reproductive processes is luteolysis. Regression of the corpus luteum (CL) is essential for normal cyclicity as it allows the development of a new ovulatory follicle, whereas prevention of luteolysis is necessary to establish and maintain pregnancy. The purpose of this review is to summarize our current understanding of the endocrine mechanisms that regulate the endometrial $PGF_{2\alpha}$ synthesis in luteolysis and early pregnancy in cattle.

Secretion of $PGF_{2\alpha}$ during the estrous cycle

The ability by the bovine endometrium to secrete prostaglandin (PG)$F_{2\alpha}$ varies during the estrous cycle. $PGF_{2\alpha}$ output reaches the highest value during the follicular phase and at the estrus and declines at the early to the mid-luteal stage of the estrous cycle[1]. Moreover, $PGF_{2\alpha}$ is released from the uterus in several series of pulses of short duration for 2-3 days during and after luteolysis[2]. The CL appears to be particularly sensitive to the luteolytic effects of $PGF_{2\alpha}$, when $PGF_{2\alpha}$ is administered in a pulsatile fashion[3]. The pulsatile pattern of $PGF_{2\alpha}$ is suppressed during early pregnancy in ruminants[4,5], although basal levels of $PGF_{2\alpha}$ are higher than they are in nonpregnant animals. Thus, the nature of the pulsatile release of uterine $PGF_{2\alpha}$ from uterus is more important for luteolysis than the absolute levels of $PGF_{2\alpha}$.

Regulators of endometrial $PGF_{2\alpha}$ secretion

1. Oxytocin

The sensitivity of bovine endometrium to oxytocin (OT) varies during the estrous cycle (Figure. 1). The stimulatory effects of OT on $PGF_{2\alpha}$ secretion by the bovine endometrium were observed at the follicular phase, estrus and early luteal stages of the estrous cycle, whereas OT had no

observed at the follicular phase, estrus and early luteal stages of the estrous cycle, whereas OT had no effect during the mid- to late luteal stages[1]. Although it has been proposed in ruminants that pulsatile $PGF_{2\alpha}$ secretion is generated by a positive feedback loop between luteal and/or hypophyseal OT and uterine $PGF_{2\alpha}$, there is increasing evidence that OT is not essential for the initiation of $PGF_{2\alpha}$ output during luteolysis in the cow[6-8]. Therefore, $PGF_{2\alpha}$ secretion by the endometrium may be regulated not only by OT but also by one or more other factors in cattle. However, the blockade of OT receptors decreased the magnitude of $PGF_{2\alpha}$ release without preventing an increase of PGFM in blood[8]. Therefore, OT may play a supportive and modulatory role as a regulator of the amplitude of pulsatile $PGF_{2\alpha}$ secretion after the initiation of luteolysis in cattle.

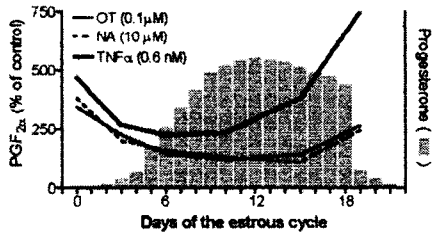

Fig. 1 A schematic illustration of effects of oxytocin (OT), noradrenaline (NA) and tumor necrosis factor-α (TNFα) on PGF2α output by the bovine endometrium in relation to the known serum level of progesterone (P4) during the estrous cycle (based on Miyamoto et al. (2000)[1], and unpublished data - NA).

2. Tumor necrosis factor-α

Our recent studies indicate the presence of functional tumor necrosis factor-a (TNFa) receptors in the bovine cyclic endometrium and suggest a possible role of TNFa in the regulation of endometrial $PGF_{2\alpha}$ production in cattle[1,9,10]. TNFa stimulated $PGF_{2\alpha}$ production only in the stromal cells via the activation of PLA2 and nitric oxide synthase[9]. In contrast to OT action, the stimulatory effects of TNFa on $PGF_{2\alpha}$ output were observed not only at the follicular stage but also at the mid- and late luteal stages (Figure. 1). Moreover, TNFa gene expression, protein concentrations[11] as well as TNFa release[12] from the CL dramatically increase just before luteolysis. Therefore, the overall findings lead us to hypothesize that endometrial and/or luteal TNFa may be a trigger for the output of $PGF_{2\alpha}$ from the uterus in the initiation of luteolysis. Since $PGF_{2\alpha}$ is produced preferentially by epithelial cells[9,13], TNFa-induced $PGF_{2\alpha}$ output from stromal cells is the first component of an auto-amplification cascade within the bovine endometrium and switches on the positive feedback loop between the epithelial $PGF_{2\alpha}$ and the luteal OT to completes luteolysis.

Abrogation of luteolysis in early pregnancy

The functional CL is maintained when a conceptus is present in the bovine uterus between Days 14 and 17 after estrus, and P4 secretion is maintained to establish pregnancy. At the time of

recognition of pregnancy, the bovine conceptus produces a signal to prevent luteolysis, which is induced by pulsatile release of $PGF_{2\alpha}$ from the uterus[13,14]. In ruminants, the conceptus signal responsible for the release of maternal $PGF_{2\alpha}$ at the time of recognition of pregnancy is a protein from the trophectoderm, finally called interferon-t (IFN-t)[13,14].

The first discussed mechanism by which IFN-t inhibits luteolysis was the down-regulation of OT receptor preventing OT-stimulated $PGF_{2\alpha}$ secretion[15]. In ewe, IFN-t inhibits OT-induced $PGF_{2\alpha}$ secretion by reducing the number of E2 receptor and thus preventing the E2-induced increase of OT receptor[16]. However, in cattle, IFN-t inhibits OT-induced $PGF_{2\alpha}$ secretion from the endometrium not simply by the down-regulation of the OT receptor but by decreasing COX-2 and prostaglandin synthase (PGFS) via a mechanism independent on changes in the OT receptor[17,18].

Another mechanism by which IFN-t may inhibit luteolysis is reversing the primary PG production in endometrium from luteolytic $PGF_{2\alpha}$ to luteotropic PGE2. It has been recently demonstrated that IFN-t down-regulates PGFS and PGE2-9-keto (9K-PGR) preventing the production of luteolytic $PGF_{2\alpha}$ in bovine endometrium (28, 29). Furthermore, IFN-t attenuated PG secretion in epithelial cells, which are known to be the primary source of $PGF_{2\alpha}$, by down-regulating COX-2 mRNA[20]. In contrast to the inhibitory effect on $PGF_{2\alpha}$ synthesis in epithelial cells, IFN-t markedly enhanced COX-2 mRNA and PG synthesis in stromal cells[20], which are the primary source of PGE2[9,13,21].

Finally, TNFa may be a trigger for the output of $PGF_{2\alpha}$ by the bovine endometrium in the initiation of luteolysis[1]. Recently, we have found that IFN-t reduced TNFa-induced $PGF_{2\alpha}$ synthesis by bovine endometrial stromal cells in a dose-dependent manner [unpublished data]. Moreover, TNFa may increase the ratio of endometrial PGE2/$PGF_{2\alpha}$ output under the influence of P4[10]. Thus, some interactions between TNFa and IFN-t at the intracellular level may lead to abolishment of $PGF_{2\alpha}$ production during early pregnancy in cattle.

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