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Inter-relationships between endothelin and prostaglandin $F_{2\alpha}$ in corpus luteum function

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In cattle and other species, the corpus luteum plays a central role in the regulation of cyclicity and maintenance of pregnancy. In the absence of fertilization and implantation, the corpus luteum undergoes functional and morphological regression or luteolysis. Luteal regression is initiated in domestic ruminants by surges of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) from the uterus. Despite intensive investigation, the mechanisms by which $PGF_{2\alpha}$ causes luteal regression remain undetermined. Recent studies from several laboratories have demonstrated that endothelial cells and their product, endothelin 1, are required for the manifestation of the luteolytic effects of $PGF_{2\alpha}$. Experimental evidence strongly supports the concept that luteal endothelin 1 inhibits luteal steroidogenesis and mediates the effects of $PGF_{2\alpha}$. Endothelin 1 caused a dose-dependent reduction in both basal and luteinizing hormone-stimulated biosynthesis of progesterone and prostacyclin, and an increase in $PGF_{2\alpha}$ by ovine and bovine luteal cells. Specific receptors for endothelin 1 were identified on large and small bovine luteal cells, and the addition of specific endothelin receptor antagonists abolished the inhibitory effects of endothelin 1. Luteal endothelin 1 content increased as the cyclic corpus luteum aged, and the highest concentrations were observed during luteolysis. The amount of mRNA encoding endothelin 1 was greatly increased during the period of luteolysis. Gene expression for endothelin 1 was increased, in a time-dependent manner, in corpora lutea collected from heifers and ewes after exogenous administration of $PGF_{2\alpha}$. In heifers, exogenous $PGF_{2\alpha}$ resulted in increased luteal output of endothelin 1. In ewes, the luteolytic effects of $PGF_{2\alpha}$ were mitigated by pretreatment with a specific endothelin receptor antagonist. Administration of endothelin 1 or a sub-luteolytic dose of $PGF_{2\alpha}$ to ewes reduced concentrations of jugular venous progesterone but did not shorten luteal lifespan. However, a combination of endothelin 1 and $PGF_{2\alpha}$ acted synergistically to bring about complete luteolysis and reduced lifespan of the corpus luteum. In summary, endothelin 1 appears to have a direct effect on luteal cells in cattle and sheep, and it plays an essential role in mediating the luteolytic effects of $PGF_{2\alpha}$.

The biochemical and endocrine events that regulate the formation, function, maintenance and regression of the bovine and ovine corpus luteum have been studied extensively (see reviews by Niswender *et al*., 1985; Milvae *et al*., 1996). The functional lifespan of the corpus luteum is balanced by luteotrophic and luteolytic factors. LH is considered to be the major luteotrophic hormone, while luteal regression is caused by episodic pulsatile secretion of uterine $PGF_{2\alpha}$ (McCracken *et al*., 1972; Hansel and Convey, 1983). There is a wide variety of endocrine, paracrine and autocrine factors that act in concert with $PGF_{2\alpha}$ to bring about normal corpus luteum function. Despite years of intensive investigation, the intracellular mechanisms by which $PGF_{2\alpha}$ causes luteal regression remain undetermined, and no specific event that can accurately predict the onset of luteolysis has yet been identified.

A number of effects of $PGF_{2\alpha}$ have been observed in domestic ruminants during experiments conducted *in vivo* and *in vitro*. These include: (1) a marked decrease in luteal blood flow; (2) a decrease in the number of small luteal cells; (3) altered activity of steroidogenic enzymes; (4) decreased gene expression for steroidogenic acute regulatory protein; (5) increased gene expression of prostaglandin G/H synthase; (6) inhibition of lipoprotein-stimulated steroidogenesis; (7) changes in membrane fluidity and (8) release of luteal oxytocin (Milvae *et al*., 1996).

The above list of observations is by no means exhaustive, and experiments conducted *in vivo* and *in vitro* often have led to contrasting results. While administration of exogenous $PGF_{2\alpha}$ clearly results in functional luteal regression marked by a cessation of progesterone production, data obtained *in vitro* vary widely depending on species, culture conditions and cell types. $PGF_{2\alpha}$ added to dispersed populations of large and small bovine luteal cells or to small cells alone has been shown to stimulate progesterone production, but has no effect on isolated large cells (Hansel *et al*., 1991). It has been suggested that $PGF_{2\alpha}$ exerts its effect through other cell types, such as endothelial cells (Auletta and Flint, 1988), or through an intracellular mediator such as oxytocin (Rodgers, 1990).

Biology of the endothelins

Adequate blood supply to the corpus luteum is required for the optimal formation, development and function of luteal tissues.

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Alterations in vascular physiology have been implicated in the processes of angiogenesis, synthesis of progesterone, luteolysis, and prostaglandin and peptide action in the corpus luteum. The development of the corpus luteum is accompanied by extensive angiogenesis, resulting in a network of capillaries that serves as the delivery route for biological effectors from within and outside the ovary. These capillaries are lined with endothelial cells, and there are estimates that approximately half the cells within the corpus luteum are endothelial cells (O'Shea *et al*., 1989; Zheng *et al*., 1993). Endothelial cells are also the source of the luteotrophic prostaglandin, PGI-2 (Milvae and Hansel, 1983) and, hence, have the potential to affect corpus luteum function.

Endothelial cells have been shown to modulate vascular resistance via production of the vasodilators, endothelium-derived relaxing factor and PGI-2, as well as the vasoconstrictors, endothelium-derived constricting factor and the endothelins (Vane and Botting, 1990; Stephenson *et al*., 1993). Endothelin contains 21 amino acids and occurs in at least four isoforms: endothelin 1 (ET-1), ET-2, ET-3 and sarafotoxin (Itoh *et al*., 1988; Inoue *et al*., 1989). ET-1 was originally isolated from pig aortic endothelial cells (Fukada *et al*., 1988) and Levin (1996) reported that it is the most potent endogenous vasoconstrictor in mammalian species. The three distinct endothelins are produced in different proportions in non-vascular as well as the vascular tissues, in which production of ET-1 predominates. Tissues other than the vascular endothelium in which ET-1 has been found include the heart, liver, pituitary gland, lung, brain, intestine, stomach, kidney, spleen and adrenal gland. ET-1 is also found in reproductive tissues, including follicular granulosa cells (Iwai *et al*., 1991), endometrial (Economos *et al*., 1992), placental (Economos *et al*., 1992) and luteal cells (Bagavandross and Wilks, 1991; Usuki *et al*., 1991). ET-1 not only affects vascular smooth muscle contraction but also modulates steroidogenesis in Leydig, granulosa and adrenal cells (Hinson *et al*., 1991; Flores *et al*., 1992; Ergul *et al*., 1993).

Endothelin receptors

Two distinct receptor subtypes of the endothelin family have been cloned, sequenced and expressed functionally (Arai *et al*., 1990; Elshourbagy *et al*., 1992; Hosada *et al*., 1992). These receptors have been termed ET_A (for aorta) and ET_B (for bronchus, Maggi *et al*., 1989). The ET_A receptor has a higher affinity for ET-1 and ET-2 than it has for ET-3. ET_B binds all three endothelins with equal affinity (Naruse *et al*., 1994). Endothelin receptors are widely distributed, although the particular expression of ET_A and ET_B varies within tissues and among species. ET_A is relatively abundant in the lung, aorta and heart and is less abundant in the liver, pancreas, kidney, brain and adrenal, whereas ET_B is relatively abundant in the brain, liver, kidney, lung and placenta and less abundant in the gut, heart and skeletal muscle. Multiple regulatory factors, including cytokines and growth factors, affect expression of endothelin receptors, which are subject to up- and downregulation by various vasoactive substances (Levin, 1996).

Multiple endothelin-stimulated signal transduction pathways are likely to contribute to the diversity of the biological responses induced by these peptides. Endothelin stimulates phospholipase C, phospholipase A_2, phospholipase D, cAMP accumulation, arachidonic acid release and prostanoid production, and Na^+–H^+ exchange (Muldoon *et al*., 1989; Resnick *et al*., 1989; VanRenterghem *et al*., 1989).

Endothelin 1 and the function of the corpus luteum

Effects upon luteal progesterone and prostaglandin synthesis

We were the first to report a direct action of endothelin 1 on bovine luteal cells. Physiological concentrations of 10^{-7}–10^{-10} mol ET-1 l^{-1} inhibited both basal and LH-stimulated biosynthesis of progesterone in a dose-dependent manner. The endothelin precursor, Big ET, and various amounts of ET-3 did not affect progesterone production. In addition, exogenous ET-1 resulted in a dose-dependent increase in luteal $PGF_{2\alpha}$ production, while ET-1 had a potent inhibitory effect on the production of PGI-2 by bovine luteal cells (Girsh *et al*., 1996a). The addition of ET-1 had no apparent effect on cell viability.

Cells derived from the corpus luteum and both cultured small and large luteal-like cells were shown to contain high affinity binding sites for ET-1 and identified these receptors as the ET_A subtype.

In the next series of experiments, the hypothesis that ET_A receptors are responsible for the inhibitory actions of ET-1 on progesterone production by bovine luteal cells was tested. A highly selective ET_A receptor antagonist, BQ-610, was preincubated with bovine luteal cells for 20 min before the addition of ET-1. Pretreatment with BQ-610 completely blocked the inhibitory effects of ET-1 on both basal and LH-stimulated progesterone production. An additional study showed that the addition of $PGF_{2\alpha}$ inhibited LH-stimulated progesterone production by slices of the bovine corpus luteum during a 24 h culture period. However, the inhibitory effects of $PGF_{2\alpha}$ were negated when these slices received BQ-610 before addition of other treatments, indicating that the inhibitory effects of ET-1 were mediated via the ET_A receptor. Although ET-1 increased $PGF_{2\alpha}$ secretion, and $PGF_{2\alpha}$ appears to stimulate ET-1 synthesis and release, it is unclear how these compounds interact with one another to bring about decreased biosynthesis of progesterone in luteal cells.

Parallel experiments using the ovine corpus luteum have been conducted. ET-1 was effective in reducing both basal and LH-stimulated progesterone production by dispersed ovine luteal cells during a 2 h incubation. Another highly selective ET_A receptor antagonist, BQ123, was preincubated for 20 min with ovine luteal cells, and totally overcame the ET-1 induced inhibition of progesterone production (Hinckley *et al*., 1997).

In summary, it appears that ET-1 has a direct antisteroidogenic effect on bovine and ovine luteal cells. These effects are mediated through the ET_A receptor. ET-1 alters the normal pattern of prostanoid synthesis and mediates the inhibitory activity of $PGF_{2\alpha}$ on LH-stimulated progesterone synthesis.

Luteal content, production and gene expression of endothelin 1

If our hypothesis that ET-1 is involved in spontaneous and $PGF_{2\alpha}$-induced luteolysis is correct, then concentrations of ET-1 and mRNA encoding ET-1 should be high at times coincident with luteolysis. Bovine corpora lutea were collected on days 5– 6, 9–13, 15–16, and 17–21 of the oestrous cycle, and the

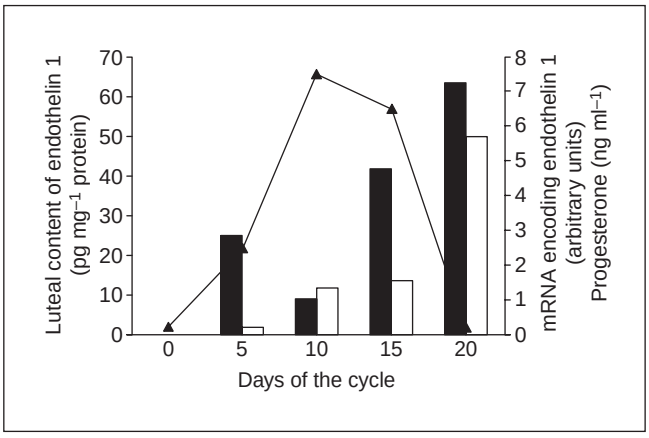

Fig. 1. Relationships between jugular venous progesterone concentrations (▲) and the luteal content of endothelin 1 (□) and luteal endothelin 1 mRNA (■) throughout the bovine oestrous cycle.

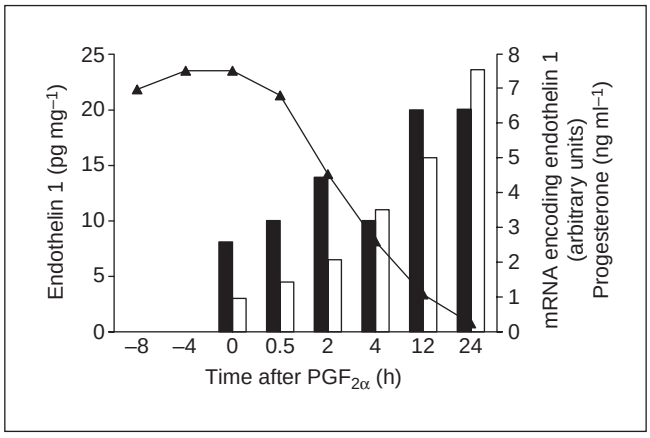

Fig. 2. Changes associated with an injection of a luteolytic dose of $PGF_{2\alpha}$ to heifers on day 10 of the oestrous cycle. There is a rapid decrease in circulating concentrations of progesterone (▲) indicative of functional luteolysis. There is a concomitant increase in both luteal endothelin 1 content (■) and endothelin 1 mRNA (□) associated with the decrease in corpus luteum function.

content of ET-1 was determined. In young (days 5–6) corpora lutea, ET-1 content was low (1.7 pg mg^{-1} tissue) and increased as the corpora lutea matured (12 and 13 pg mg^{-1} in corpora lutea on days 9–13 and 15–16, respectively). The highest concentrations of ET-1 (49 pg mg^{-1}) were measured on days 17–21 of the oestrous cycle. Concentrations of mRNA for ET-1 also varied throughout the oestrous cycle: 2.9, 1.0 and 7.4 units for corpora lutea collected on days 5, 10 and 18 of the oestrous cycle, respectively. Both luteal ET-1 content and mRNA were greatest near the time of functional luteolysis (Fig. 1).

Effects of prostaglandin $F_{2\alpha}$ on luteal endothelin 1 expression and production

The increase in ET-1 expression in the aged corpora lutea could result from uterine $PGF_{2\alpha}$ surges that occur at this time of the oestrous cycle. Therefore, the effects of a luteolytic dose of $PGF_{2\alpha}$ injected into heifers on day 10 on luteal ET-1 expression in corpora lutea collected at various times after treatment were examined. $PGF_{2\alpha}$ increased luteal mRNA encoding ET-1 in a time-dependent manner. A significant increase in mRNA was measured 2 h after $PGF_{2\alpha}$, before the decrease in plasma progesterone concentrations. Concentrations of mRNA encoding ET-1 continued to increase and, by 24 h, reached a value six times greater than that in control corpora lutea (Fig. 2).

Miyamoto *et al*. (1997) reported that intraluteal administration of $PGF_{2\alpha}$ increased bovine luteal output of ET-1 while reducing concentrations of progesterone. In addition, increased jugular venous plasma concentrations of ET-1 were observed during the period corresponding to spontaneous luteolysis and during luteolysis induced by $PGF_{2\alpha}$ administered mid-cycle (Miyamoto *et al*., 1997).

$PGF_{2\alpha}$ increased endothelin content in bovine luteal slices and in microvascular endothelial cells isolated from bovine corpora lutea. The increase in endothelin production was accompanied by induced expression for ET-1, which occurred within 15 min.

Therefore, it appears that $PGF_{2\alpha}$ activates the luteal ET-1 gene, resulting in increased ET-1 production, which, in turn, decreases luteal progesterone synthesis during spontaneous and induced regression of the corpus luteum.

Mitigation of the effects of prostaglandin $F_{2\alpha}$ by BQ-123 in sheep

An experiment was conducted in mid-cycle ewes to test the contention that the effects of exogenous $PGF_{2\alpha}$ are mediated through increased ET-1, which then binds to luteal ET_A receptors to induce luteolysis. Normally cyclic ewes received either intraluteal saline or BQ-123, a highly selective ET_A receptor antagonist, 30 min before administration of a luteolytic dose of $PGF_{2\alpha}$. Pretreatment with BQ-123 mitigated the luteolytic effects of $PGF_{2\alpha}$; plasma progesterone concentrations in ewes treated with BQ-123 were higher than those for saline injected animals at 1, 4, 6, 8, 12 and 24 h after $PGF_{2\alpha}$. Thus, it appears that the effects of exogenous $PGF_{2\alpha}$ are, at least in part, mediated via ET-1 binding to ET_A receptors in the ovine corpus luteum.

Another experiment was designed to determine the effects of ET-1 (100 g i.m.), a subluteolytic dose of $PGF_{2\alpha}$ (7.5 mg i.m.), or a combination of the $PGF_{2\alpha}$ treatment followed after 15 min by ET-1 administration. Ewes that received $PGF_{2\alpha}$ plus ET-1 showed a rapid decrease in concentrations of progesterone and had a mean oestrous cycle duration of 10.3 days. $PGF_{2\alpha}$ and ET-1 given alone resulted in a significant, yet transient, decrease in the concentration of progesterone. However, corpus luteum function recovered, as evidenced by increased plasma progesterone concentrations and normal corpus luteum lifespan (16–17 days). Similar results were reported by Miyamoto *et al*. (1997) when $PGF_{2\alpha}$ or ET-1 was administered via a luteal microdialysis system in heifers. In this study, intraluteal $PGF_{2\alpha}$ resulted in an increase in luteal output of progesterone, while ET-1 administration reduced luteal progesterone release. However, when luteal tissue was exposed to $PGF_{2\alpha}$ before ET-1 infusion, the inhibitory effects on progesterone secretion were much greater. The effects of ET-1 on ruminant luteal function are summarized (Table 1).

Table 1. Effects of endothelin 1 (ET-1) on ruminant luteal function

Experimental condition *in vitro*	Action	Reference
In vitro		
ET-1 via $[ET_A]_R$	↓ basal, LH-stimulated progesterone production by ovine and bovine luteal cells	Girsh *et al*., 1996a
ET-1 + BQ123	No effect on basal, LH-stimulated progesterone production	Hinckley *et al*., 1996
In vivo		
$PGF_{2\alpha}$	↓↓↓↓ plasma progesterone +↑ ET-1 mRNA + ↑ luteal ET-1 release	Girsh *et al*., 1996b
BQ123 + $PGF_{2\alpha}$	↓ plasma progesterone	Hinckley *et al*., 1997
$PGF_{2\alpha}$ (subluteolytic)	↓ plasma progesterone, normal cycle duration	Hinckley *et al*., 1998
ET-1 (100 µg)	↓↓ plasma progesterone, normal cycle duration	
$PGF_{2\alpha}$ (subluteolytic) + ET-1	↓↓↓↓ plasma progesterone, reduced cycle duration	
Microdialysis		
ET-1	↓↓ plasma progesterone	Miyamoto *et al*., 1997; Ohtani *et al*., 1998
$PGF_{2\alpha}$	↑↓↓ plasma progesterone	
Pre-$PGF_{2\alpha}$ + ET-1	↓↓↓↓ plasma progesterone	

Arrows indicate either an increase or decrease in the parameter listed. The number of arrows indicates the relative amount of change.

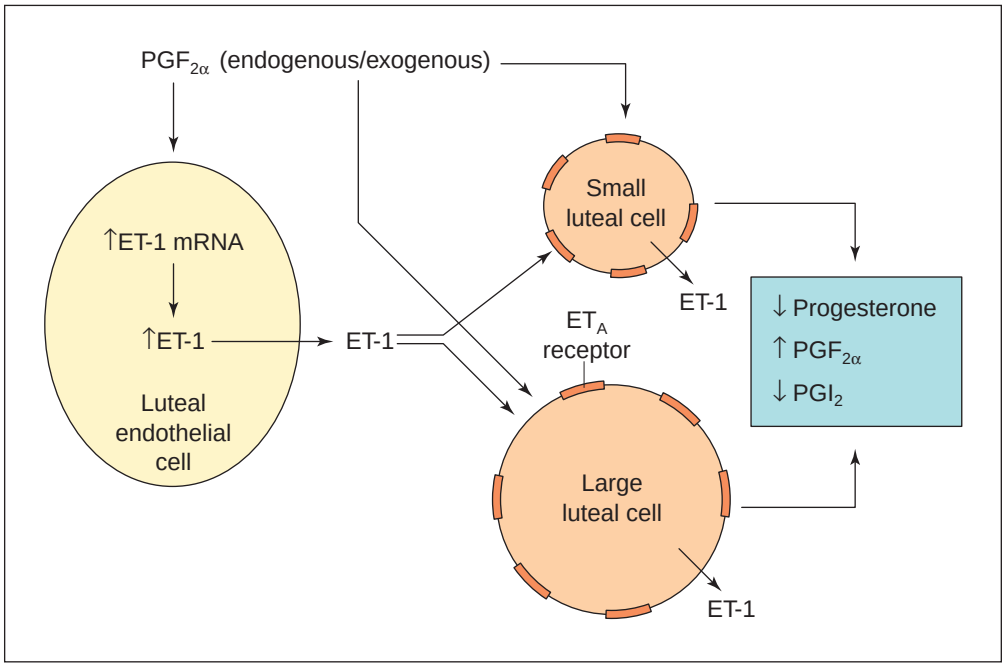

Fig. 3. Model outlining the major interactions among $PGF_{2\alpha}$, luteal endothelial cells (LEC), and small (SLC) and large (LLC) luteal cells in bovine and ovine luteolysis. During either spontaneous (endogenous) or induced (exogenous) luteolysis, $PGF_{2\alpha}$ binds to LEC, SLC and LLC. $PGF_{2\alpha}$ activates the endothelin 1 (ET-1) gene in LEC, and the biosynthesis and secretion of ET-1 are increased. ET-1 binds to specific endothelin receptors of the A subtype (ET_A) located on SLC and LLC, resulting in decreased basal and LH-stimulated progesterone production, decreased production of the luteotrophic prostaglandin, PGI_2, an increase in the luteolytic prostaglandin, $PGF_{2\alpha}$, and probably enhanced ET-1 secretion. The $PGF_{2\alpha}$ produced may act in a paracrine fashion to increase further ET-1 synthesis and release from LEC. There is a greatly reduced blood supply to and within the corpus luteum resulting in complete functional and structural luteolysis associated with these changes occurring at the cellular level.

Conclusions

Endothelin 1 appears to play a critical role in the regulation of ovine and bovine corpus luteum function. The current model outlining the major interactions among $PGF_{2\alpha}$, luteal endothelial cells, and small and large luteal cells in bovine and ovine luteolysis is illustrated (Fig. 3). ET-1, via binding to specific ET_A receptors located on large and small luteal cells, inhibits luteal progesterone synthesis while stimulating luteal $PGF_{2\alpha}$ production. ET-1 plays an important role in mediating the luteolytic effects of $PGF_{2\alpha}$ during both spontaneous and $PGF_{2\alpha}$-induced luteolysis, as indicated by luteal ET-1 content, production and expression. There may be a positive feedback system in which $PGF_{2\alpha}$ stimulates ET-1 production and release, and ET-1 further enhances $PGF_{2\alpha}$ synthesis. These actions of $PGF_{2\alpha}$ and ET-1 probably result in marked decreases in luteal blood flow, and act in concert with numerous other luteal modulators to produce functional and structural luteolysis.

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