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Lives in the balance: responsiveness of the corpus luteum to uterine and embryonic signals

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This review focuses on factors that may affect the sensitivity of the corpus luteum to uterine prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and embryonic signals. The heterogeneity of the types of cell that are present within the corpus luteum results in complex interactions that ensure complete luteal regression in response to $PGF_{2\alpha}$. There is not likely to be a single factor that determines responsiveness. The sensitivity of the corpus luteum depends on the proper balance of a variety of factors that are involved in mediating the effects of $PGF_{2\alpha}$. This balance is achieved as the early corpus luteum undergoes development, but may also be altered by embryonic factors to rescue the corpus luteum during early pregnancy.

Introduction

Communication between the uterus and ovary is essential for normal cyclicity and the maintenance of pregnancy in ruminants. Luteal lifespan is prolonged in hysterectomized animals (Wiltbank and Casida, 1956) because of the lack of prostaglandin $F_{2\alpha}$($PGF_{2\alpha}$), and ovarian steroids regulate the timing and concentrations of uterine $PGF_{2\alpha}$ release. Exogenous $PGF_{2\alpha}$ has been used for many years to regulate the oestrous cycles of ruminant species, but the developing corpus luteum is refractory to the luteolytic actions of $PGF_{2\alpha}$ (Louis *et al.*, 1973). Progesterone synthesis by the corpus luteum is essential for maintenance of pregnancy, and the presence of a healthy embryo is required to rescue the corpus luteum from regression. Clearly, the main role of embryonic interferon τ (IFN-τ) in maternal recognition of pregnancy is to decrease the amount of $PGF_{2\alpha}$ released by the uterus, thus preventing luteal regression. However, alterations in luteal function during maternal recognition of pregnancy also render the corpus luteum less sensitive to the luteolytic effects of $PGF_{2\alpha}$.

The heterogeneous nature of the corpus luteum indicates that there is a complex interaction of different types of cell and paracrine mediators that regulate the sensitivity of the corpus luteum to extraovarian signals. There is increasing evidence that the non-steroidogenic cells may affect the steroidogenic capacity of the corpus luteum and are directly involved in both the formation and demise of the tissue. The rapid angiogenesis that occurs during luteinization and the extensive vascularity within the mature corpus luteum has led a number of investigators to consider the functional significance of capillary endothelial cells to steroidogenesis. Growth factors, such as vascular endothelial growth factor (VEGF), are important

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in the development of the capillary network that will sustain the corpus luteum (Redmer *et al.*, 1996; Berisha *et al.*, 2000) and proliferation of capillary pericytes may be a key factor in achieving full luteal maturation (Redmer *et al.*, 2001). The interactions of the various types of cell and paracrine factors within the corpus luteum, with regard to how these may alter the sensitivity of the corpus luteum to uterine factors, such as $PGF_{2\alpha}$ or embryonic signals, is the subject of this review. Owing to the limited length of the review and the symposium for which it is prepared, the focus is on ruminants, and previous review articles are cited wherever possible.

Local mediators of prostaglandin action in mature corpus luteum

Prostaglandin $F_{2\alpha}$ acts on steroidogenic cells to bring about a rapid decrease in progesterone production. Activation of the phospholipase C–protein kinase C pathway by $PGF_{2\alpha}$ results in an increase in intracellular calcium, a decrease in mRNAs for steroidogenic enzymes and steroidogenic acute regulatory protein (StAR), and inhibition of cholesterol transport through the mitochondrial membrane. The actions of $PGF_{2\alpha}$ on steroidogenic cells to inhibit progesterone production have been reviewed elsewhere (Pate and Townson, 1994; Niswender *et al.*, 2000).

The luteolytic effects of $PGF_{2\alpha}$ may also be advanced by the non-steroidogenic cells within the corpus luteum. Prostaglandin $F_{2\alpha}$ is a more effective inhibitor of progesterone synthesis in the presence of endothelial cells (Girsh *et al.*, 1995), indicating that endothelial cells mediate the antisteroidogenic effects of $PGF_{2\alpha}$. Prostaglandin $F_{2\alpha}$ causes a rapid increase in endothelin 1 (ET-1) mRNA in the mature corpus luteum, and ET-1 acts on luteal cells to decrease progesterone production *in vitro* and *in vivo* (Girsh *et al.*, 1996; Miyamoto *et al.*, 1997; Ohtani *et al.*, 1998; Hinckley and Milvae, 2001). The most convincing evidence that ET-1 may serve as a mediator of $PGF_{2\alpha}$ action in the corpus luteum was reported by Hinckley and Milvae (2001) who demonstrated that administration of ET-1 to ewes in the presence of a subluteolytic dose of $PGF_{2\alpha}$ resulted in luteolysis, and inhibition of the ET-1 receptor, ETA, prevented $PGF_{2\alpha}$-induced luteolysis. The morphology of endothelial cells changes in response to $PGF_{2\alpha}$ before any apparent change in steroidogenic cells (Sawyer *et al.*, 1990), and Gaytan *et al.*, (2002) demonstrated that endothelial cells in the rat corpus luteum undergo apoptosis followed by ischaemic necrosis of the luteal cells. Sufficient development of the microvasculature with adequate numbers of endothelial cells may promote the sensitivity of the corpus luteum to $PGF_{2\alpha}$.

Immune cells are intricately involved in the progression of luteolysis once it has been initiated by $PGF_{2\alpha}$, and they may also contribute to both the continued decrease in progesterone production as well as the structural demise of the tissue (for reviews, see Pate and Townson, 1994; Pate, 1995; Pate and Keyes, 2001). In cows, lymphocytes are present in the fully functional corpus luteum and increase at the time of luteal regression (Lobel and Levy, 1968; Penny *et al.*, 1999; Townson *et al.*, 2002). The increase in immune cells appears to be due to migration of these cells into the tissue as well as proliferation, particularly of macrophages, within the tissue (Bauer *et al.*, 2001). The expression of monocyte chemoattractant protein 1 (MCP-1) in the corpus luteum is likely to be responsible for the recruitment of macrophages into the tissue (Bowen *et al.*, 1996; Townson *et al.*, 1996; Penny *et al.*, 1998). Cytokines, such as tumour necrosis factor α (TNF-α) and interferon γ (IFN-γ), produced by immune cells within the corpus luteum may contribute to the inhibition of steroidogenesis and cell death (Fairchild and Pate, 1991; Benyo and Pate, 1992; Petroff *et al.*, 2001).

Acquisition of luteolytic capacity

The transition from a $PGF_{2\alpha}$ non-responsive, or insensitive state, to a $PGF_{2\alpha}$-responsive state has been termed the 'acquisition of luteolytic capacity' by Diaz *et al.* (2000). Initial suggestions that the developing corpus luteum was insensitive to $PGF_{2\alpha}$ because it lacked $PGF_{2\alpha}$ receptors (FP) were found to be incorrect. Both Rao *et al.* (1979) and Wiltbank *et al.* (1995) demonstrated that there are similar numbers and affinity of $PGF_{2\alpha}$ receptors in early, non-responsive corpora lutea as in mature corpora lutea of cattle. This finding is unlike that in pigs, in which a significant increase in FP receptors occurs at about the time that the corpus luteum becomes responsive to $PGF_{2\alpha}$ (Gadsby *et al.*, 1990). When non-responsive (day 4) or responsive (day 11) bovine corpora lutea were treated with $PGF_{2\alpha}$ *in vivo*, the concentration of luteal ascorbate and mRNAs for 3β-hydroxysteroid dehydrogenase (3β-HSD) and FP receptor were decreased, and insulin-like growth factor binding protein 1 (IGFBP-1) was increased in both day 4 and day 11 corpora lutea, indicating that the day 4 corpora lutea are not completely unresponsive to $PGF_{2\alpha}$ actions (Tsai and Wiltbank, 1998; Sayre *et al.*, 2000). However, day 11 corpora lutea responded to $PGF_{2\alpha}$ with an increase in steady state concentrations of mRNA for prostaglandin G/H synthase-2 (PGHS-2, also known as cyclooxygenase 2), whereas a decrease in PGHS-2 was observed in day 4 corpora lutea (Tsai and Wiltbank, 1998). This finding led the authors to suggest that the ability of the corpus luteum to establish a positive autocrine feedback loop of endogenous prostaglandin synthesis is a key component for the acquisition of luteolytic capacity. This suggestion supports the findings of Milvae (1986), in which it was proposed that stimulation of luteal prostaglandin synthesis is a critical factor in luteal regression, and extends this concept to help explain why the early (developing) corpus luteum is not induced to regress by exogenous $PGF_{2\alpha}$. In fact, multiple $PGF_{2\alpha}$ injections increase luteal PGHS-2 concentrations and also induce luteolysis in the day 4 corpus luteum (Beal *et al.*, 1980; Sayre *et al.*, 2000). The importance of luteal prostaglandins to $PGF_{2\alpha}$-induced luteolysis is further exemplified by the finding that the activity of prostaglandin dehydrogenase (PGDH), which metabolizes $PGF_{2\alpha}$ to its inactive metabolite, PGFM, is greater in the early, non-responsive corpora lutea than in the mid-cycle (fully functional), responsive corpora lutea (Silva *et al.*, 2000).

If endothelial cells and ET-1 secretion are mediators of $PGF_{2\alpha}$-induced luteolysis, then it is reasonable to postulate that the underdeveloped microvasculature characteristic of the early corpus luteum is inadequate to mediate the luteolytic signal. In fact, this hypothesis was first proposed by Levy *et al.* (2000), who demonstrated that mRNAs for ET-1 and ETA were increased by $PGF_{2\alpha}$ in the mid-cycle corpus luteum, but remained unchanged in the day 4 corpus luteum, despite other effects of $PGF_{2\alpha}$ at that time. The difference in the ET-1 response to $PGF_{2\alpha}$ in early and mid-cycle corpora lutea was further corroborated by Wright *et al.* (2001). These investigators also measured endothelin converting enzyme 1 (ECE-1) and found that it was decreased as a result of $PGF_{2\alpha}$ in mid-cycle, but not in early, corpora lutea. In addition to its antisteroidogenic effects, ET-1 is a potent vasoconstrictor. Although vasoconstriction appears to occur after the decline in progesterone, this could be another action of ET-1 to continue the progression of luteolysis (for a review, see Niswender *et al.*, 2000). Acosta *et al.* (2002) used pulsed Doppler ultrasonography to evaluate blood flow in day 4 and day 10 bovine corpora lutea. In the mid-cycle corpus luteum, $PGF_{2\alpha}$ treatment caused an acute increase followed by a gradual decrease in blood flow, whereas no change in blood flow was associated with $PGF_{2\alpha}$ treatment on day 4 of the oestrous cycle. These results lend further support to the concept that endothelial cells and the luteal microvasculature are not sufficiently developed in the early corpus luteum to allow for a complete luteolytic response to $PGF_{2\alpha}$.

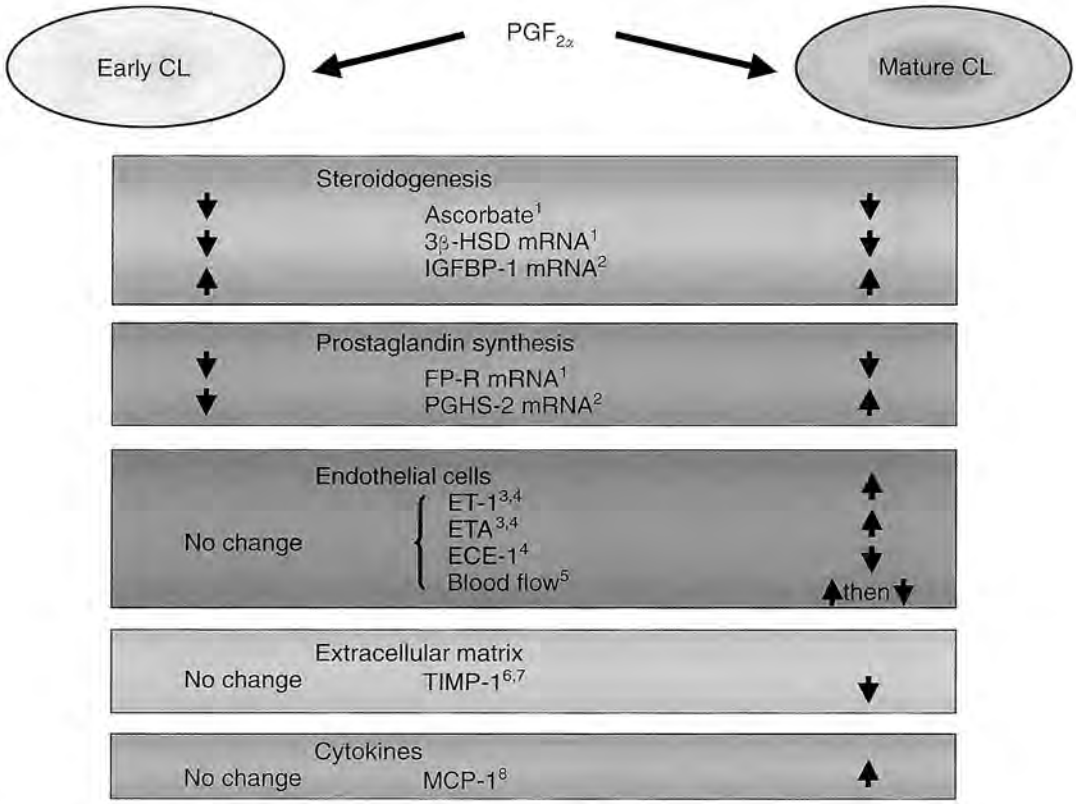

Fig. 1. Effects of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on early (non-responsive) and mid-cycle mature (responsive) corpora lutea (CL). Differences in prostaglandin G/H synthase 2 (PGHS-2) and the inability to effect changes in endothelial cells, extracellular matrix remodelling components and cytokines in the early corpus luteum may prevent the luteolytic effects of $PGF_{2\alpha}$ from being fully manifested. 3β-hydroxysteroid dehydrogenase (3β-HSD); insulin-like growth factor binding protein 1 (IGFBP-1); $PGF_{2\alpha}$ receptor (FP); endothelin-1 (ET-1); ET-1 receptor (ETA); endothelin converting enzyme 1 (ECE-1); tissue inhibitor of metalloproteinase 1 (TIMP-1); monocyte chemoattractant factor 1 (MCP-1). [1]Tsai and Wiltbank (1998); [2]Sayre *et al.* (2000); [3]Levy *et al.* (2000); [4]Wright *et al.* (2001); [5]Acosta *et al.* (2002); [6]Ricke *et al.* (2002); [7]Towle *et al.* (2002); and [8]Tsai *et al.* (1997).

The ability of $PGF_{2\alpha}$ to promote reorganization of the extracellular matrix and tissue degradation may also be a component of the acquisition of luteolytic capacity. When cows or ewes are treated with $PGF_{2\alpha}$ during mid-cycle, there is a rapid and sustained depletion of luteal tissue inhibitor of metalloproteinase 1 (TIMP-1) and an increase of luteal matrix metalloproteinase 2 (MMP-2; Ricke *et al.*, 2002; Towle *et al.*, 2002). However, there is no effect of $PGF_{2\alpha}$ on luteal concentrations of TIMP when administered on day 3 of the oestrous cycle (Ricke *et al.*, 2002). A summary of the responses to $PGF_{2\alpha}$ that occur in early and mid-cycle corpora lutea is presented (Fig. 1).

Other types of cell in the corpus luteum that may influence luteolytic capacity are the immune cells. There are fewer T lymphocytes, monocytes and macrophages in the corpus luteum early in the oestrous cycle compared with later in the oestrous cycle, and the amount of immunoreactive MCP-1 and MCP-1 mRNA in the bovine corpus luteum parallels the number of immune cells present (Townson *et al.*, 2002). Tsai *et al.* (1997) observed that MCP-1 mRNA was increased by a luteolytic injection of $PGF_{2\alpha}$ in mid-cycle corpora lutea, but there was

no MCP-1 response in early corpora lutea. Thus, the inability of the early corpus luteum to respond to $PGF_{2\alpha}$ with an increase in MCP-1, and an insufficient number of immune cells within the tissue may well be an important factor in the luteolytic effect of $PGF_{2\alpha}$ not being fully manifested.

If immune cells are important for the acquisition of luteolytic capacity, it might be expected that cytokine concentrations would be low, or absent, in the early corpus luteum but high in the mid-cycle corpus luteum. Very little has been done to evaluate cytokine concentrations in early compared with mature corpora lutea in ruminants, and the results are not always consistent. This is due, in part, to the lack of reagents for analysis of the bovine or ovine proteins. One of the most studied cytokines in the corpus luteum is TNF-α. The mRNA for TNF-α is present throughout the lifespan of the bovine corpus luteum (Petroff *et al.*, 1999; Sakumoto *et al.*, 2000); therefore, expression of this gene may not be limiting in terms of luteolytic capacity. However, the TNF-α protein is not detected until the corpus luteum is mature (Sakumoto *et al.*, 2000) or until after luteal regression has been initiated by $PGF_{2\alpha}$ (Ji *et al.*, 1991; Shaw and Britt, 1995). The effect of $PGF_{2\alpha}$ on TNF-α synthesis in early and mature corpora lutea has not yet been reported, and is the subject of current investigation in our laboratory. There have been conflicting reports on the presence of the type I TNF receptor (TNF-RI) in luteal tissue. Friedman *et al.* (2000) reported no difference in the mRNA for TNF-RI in luteal tissue of various ages; Sakumoto *et al.* (2000) found the mRNA content to be high early in the oestrous cycle, whereas M. G. Petroff and J. L. Pate (unpublished) observed a lower content in day 5 compared with mid-cycle corpora lutea. Clearly this issue is not resolved, and the relevance of the TNF–TNF-RI system to the acquisition of luteolytic capacity will depend on knowledge of the proteins, not just of the mRNAs. As the pro-inflammatory cytokines, such as TNF-α and IFN-γ, are potent stimulators of luteal prostaglandin synthesis (Fairchild and Pate, 1991; Benyo and Pate, 1992; Townson and Pate, 1996), it is possible that lack of cytokine production in response to $PGF_{2\alpha}$ in the early corpus luteum contributes to its inability to synthesize endogenous prostaglandins and hence its lack of luteolytic capacity.

Another rather novel cytokine, macrophage migration inhibitory factor (MIF), was examined in bovine corpora lutea throughout the oestrous cycle. It was expected that MIF would be absent during luteal development and increase at the time of luteolysis. Surprisingly, the opposite was true. MIF mRNA was consistently high in day 5 corpora lutea, and expression was lower in mid-cycle or day 18 corpora lutea. Immunohistochemistry revealed that MIF was found in the steroidogenic cells, primarily the large luteal cells (Bove *et al.*, 2000). It was hypothesized that MIF is involved in differentiation events during luteinization, and there is now a question as to whether higher concentrations of MIF render the corpus luteum less sensitive to $PGF_{2\alpha}$.

Recent work in our laboratory has focused on the components of the intracellular peptide processing system for presentation of peptides by major histocompatibility complex (MHC) molecules, and the temporal expression of these molecules in the bovine corpus luteum. Processing of peptides presented by MHC class I molecules takes place within the proteosome, and exposure to IFN-γ induces replacement of constitutive proteosome subunits with the IFN-γ-inducible subunits, low molecular weight protein 2 (LMP-2), LMP7 and LMP10. No significant differences were observed in steady state concentrations of LMP7 mRNA, but the LMP10 mRNA content was lower in the day 5 corpora lutea in comparison with corpora lutea at day 11 or day 18 of the oestrous cycle (Cannon and Pate, 2000a). MHC class II molecules present peptides that are processed by the invariant chain and the DM protein. Although no differences were noted in the steady state concentrations of the invariant chain in the bovine corpus luteum throughout the oestrous cycle, both the DMα and DMβ subunits increased from

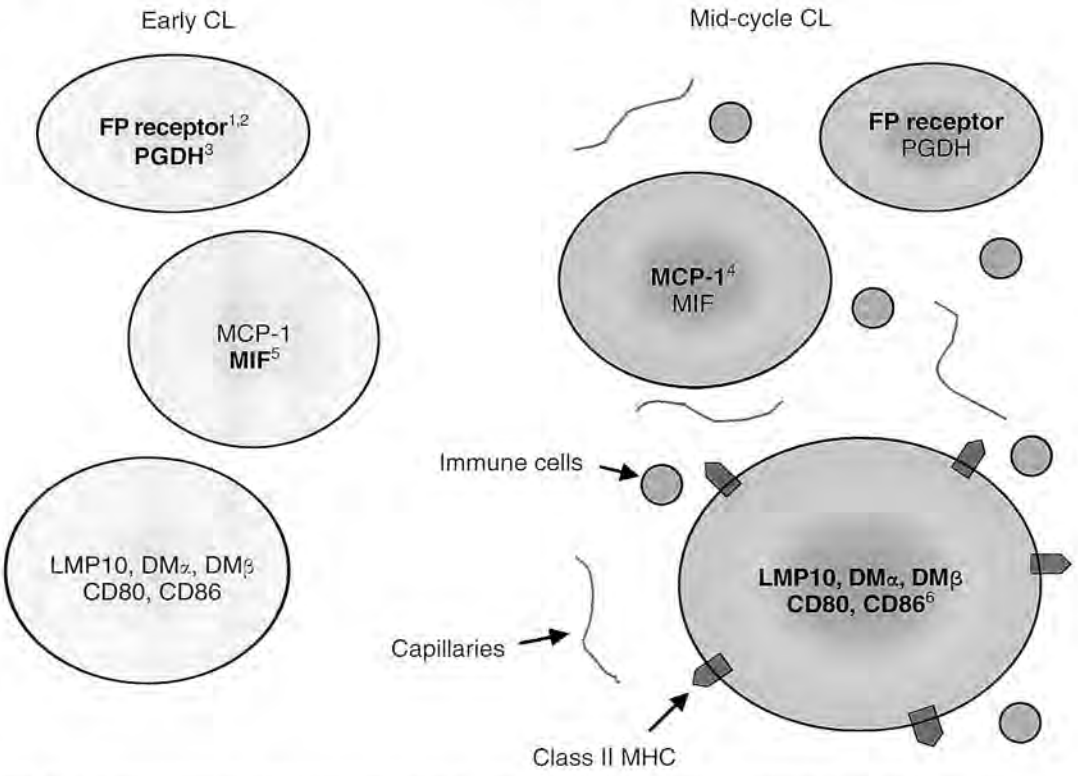

Fig. 2. Components of early prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (non-responsive) and mid-cycle $PGF_{2\alpha}$ (responsive) corpora lutea that may affect acquisition of luteolytic capacity. Bold letters indicate a relatively higher concentration compared with those that are not depicted in bold letters. In addition to relative changes in concentrations of the various components, the mid-cycle corpus luteum contains immune cells, major histocompatibility complex (MHC) class II molecules, and a more developed capillary network. Prostaglandin dehydrogenase (PGDH), monocyte chemoattractant factor 1 (MCP-1), $PGF_{2\alpha}$ receptor (FP), macrophage migration inhibitory factor (MIF), LMP10, DMα and DMβ are antigen processing proteins, and CD80 and CD86 are co-stimulatory molecules. [1]Rao *et al.* (1979); [2]Wiltbank *et al.* (1995); [3]Silva *et al.* (2000); [4]Townson *et al.* (2002); [5]Bove *et al.* (2000); and [6]Cannon and Pate (2000a,b; 2001).

day 5 to day 10 of the oestrous cycle (Cannon and Pate, 2000b). These results are similar to the pattern of MHC class II expression within the corpus luteum that was reported earlier (Benyo *et al.*, 1991), in that MHC class II molecules are absent in the early corpus luteum, but are found in the mid-cycle corpus luteum. Furthermore, fewer of the co-stimulatory molecules that are necessary for MHC-mediated activation of T lymphocytes, CD80 and CD86, were found in early corpora lutea than in mid-cycle corpora lutea (Cannon and Pate, 2001). The addition of CD80 or CD86 antibodies to luteal cell–T cell co-cultures inhibited luteal cell-induced T-cell proliferation, indicating that these costimulatory molecules are necessary for activation of T cells within the corpus luteum (Cannon and Pate, 2001). Lower expression of peptide processing components and co-stimulatory molecules in the early corpus luteum may mean that T-cell activation cannot occur at this stage, and may contribute to the refractory nature of the early corpus luteum to $PGF_{2\alpha}$. In the mid-cycle corpus luteum, which is fully responsive to $PGF_{2\alpha}$, the components necessary for activation of the immune response are in place. Experiments are currently underway to determine whether the increase in expression of these components is correlated with the timing of acquisition of

luteolytic capacity. Components that are differentially expressed in early and mid-cycle corpora lutea that may be critical for the acquisition of luteolytic capacity are summarized (Fig. 2).

Resistance of the corpus luteum to $PGF_{2\alpha}$ during maternal recognition of pregnancy

There is little question that embryonic factors, particularly IFN-τ, act on the endometrium to alter $PGF_{2\alpha}$ secretion during maternal recognition of pregnancy (for a review, see Thatcher, this supplement). In addition to the changes that occur in the endometrial secretion of $PGF_{2\alpha}$ during early pregnancy, it has been suggested that embryonic factors also decrease the sensitivity of the corpus luteum to $PGF_{2\alpha}$ (Pratt *et al.*, 1977).

Silvia and Niswender (1984) demonstrated that the corpus luteum of pregnancy (in sheep) is less sensitive to $PGF_{2\alpha}$ than the corpus luteum of the ovarian cycle, and the number of embryos may be inversely correlated with the sensitivity of the corpus luteum to $PGF_{2\alpha}$. Furthermore, *in vitro* secretion of progesterone by luteal tissue was greater when corpora lutea came from ewes with healthy embryos compared with ewes with abnormal embryos, and both of these were greater than when the corpora lutea came from ewes with no embryos (Abecia *et al.*, 2001). In addition to increasing luteal progesterone production, treatment of luteal cells with conceptus secretory proteins reversed the inhibitory effects of $PGF_{2\alpha}$ on progesterone production (Wiltbank *et al.*, 1992). Therefore, the steroidogenic capacity of the corpus luteum is enhanced, and its sensitivity to $PGF_{2\alpha}$ is reduced, by factors produced by healthy embryos. The ability of immune cells to promote luteolysis may also be impaired during maternal recognition of pregnancy, because there are fewer immune cells and class II MHC molecules within the corpus luteum during early pregnancy than late in the oestrous cycle (Lobel and Levy, 1968; Benyo *et al.*, 1991). Furthermore, IFN-α, which has properties very similar to IFN-τ, protects luteal cells from the cytotoxic effects of TNF-α and IFN-γ, and decreases the ability of these cytokines to stimulate luteal prostaglandin production (Petroff *et al.*, 2001). This result raises the very intriguing question of what changes occur within the corpus luteum to make it less responsive to $PGF_{2\alpha}$, and if these changes rely on mechanisms similar to those found in the early corpus luteum that is not yet responsive to $PGF_{2\alpha}$.

Recently, a new concept has emerged that the lack of sensitivity of the corpus luteum during maternal recognition of pregnancy is due to the ability of the corpus luteum to convert $PGF_{2\alpha}$ to its inactive metabolite, PGFM (Silva *et al.*, 2000). These workers clearly showed that day 13 corpora lutea from pregnant ewes had greater concentrations and activity of PGDH (the enzyme that metabolizes $PGF_{2\alpha}$ to PGFM) than day 13 corpora lutea from cyclic ewes. The greater concentration of PGDH was similar to that at day 4, as mentioned above. Therefore, the ability to metabolize $PGF_{2\alpha}$ may be a common element that renders the corpus luteum less sensitive to the luteolytic effects of $PGF_{2\alpha}$.

What maintains the corpus luteum after IFN-τ declines?

The resistance to $PGF_{2\alpha}$ that is manifested during maternal recognition of pregnancy is lost by day 19 of pregnancy in sheep (Silvia and Niswender, 1986). Little is known about maintenance of the corpus luteum after maternal recognition of pregnancy. When IFN-τ decreases, are there other factors produced by the embryo or placenta that maintain the corpus luteum? Does failure of the embryo to produce adequate luteotrophic signals, or failure of the corpus

luteum to respond to luteotrophins, contribute to late embryonic or fetal loss in ruminants? Although some of these losses are not likely to be due to inadequate luteal function, there is some evidence that late embryos or fetuses can be rescued by induction of a new corpus luteum (for a review, see Inskeep, 2002), implying that some fetal losses are a result of luteal insufficiency.

If the resistance to $PGF_{2\alpha}$ is lost shortly after the period of maternal recognition of pregnancy, additional mechanisms must account for continued luteal function. In ewes and cows, the luteotrophin may shift from LH during the oestrous cycle to PGE_2 during pregnancy (Weems *et al.*, 1998; Kim *et al.*, 2001); thus, an inability to shift from LH to PGE_2 support could result in fetal loss. In rats, placental factors may contribute to luteal maintenance and stimulation of progesterone production by stimulating increases of Cu,Zn-superoxide dismutase (SOD) and Mn-SOD within the corpus luteum (Takiguchi *et al.*, 2000), thus conferring resistance to reactive oxygen species that contribute to the luteolytic actions of $PGF_{2\alpha}$. Additional information obtained from the rat model has been used to indicate that the sensitivity of the corpus luteum to luteolytic agents is dependent on the degree of differentiation of the luteal cells. The corpus luteum of pregnancy is less sensitive to the luteolytic effects of prolactin than the corpus luteum of the ovarian cycle (Gaytan *et al.*, 2001). These authors postulated that the responsiveness of the corpus luteum to the luteolytic effects of prolactin is dependent on the degree of differentiation of the luteal cells, that is, the more differentiated cells in pregnancy were less sensitive than the less differentiated cells during the oestrous cycle. Perhaps having survived luteolysis during maternal recognition of pregnancy, the corpus luteum further differentiates and is less sensitive to additional luteolytic signals. This contention would not be supported by the finding that luteal insensitivity to $PGF_{2\alpha}$ was lost by day 19 of pregnancy (Silvia and Niswender, 1986), unless the factor that causes luteolysis after the period of maternal recognition of pregnancy is something other than $PGF_{2\alpha}$. The question remains whether an additional uterine or embryonic signal is necessary for maintenance of the corpus luteum after the period of maternal recognition of pregnancy, or if the signal during maternal recognition of pregnancy promotes differentiative events within the corpus luteum that, if complete, protect the corpus luteum from subsequent luteolytic insults.

Conclusions

Much has been done to understand the mechanisms by which $PGF_{2\alpha}$ causes luteolysis in ruminants. As this knowledge has unfolded, it has provided insight into the components that affect the sensitivity of the corpus luteum to $PGF_{2\alpha}$. Recent studies have focused on the acquisition of luteolytic capacity as the corpus luteum develops, and it is likely that a continuum of events occurs that culminates in responsiveness to the luteolytic effects of $PGF_{2\alpha}$. These events include changes in expression of genes important for luteal prostaglandin synthesis and metabolism, development of the luteal microvasculature and extracellular matrix, and an influx of immune cells and cytokine expression within the tissue. The sensitivity of the corpus luteum to $PGF_{2\alpha}$ is again reduced during maternal recognition of pregnancy. It remains to be determined whether these mechanisms are similar to those that decrease responsiveness during luteal development, and whether they are sufficient to prevent the fetal loss that is observed in ruminants. The ability of the corpus luteum to survive luteolytic insults is likely to depend on the correct balance of a variety of factors and the cells that produce them. Achieving this balance at the proper time may be the key to luteal survival or luteal regression.

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