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Effect of Prostaglandin E2 on Corpus Luteum Function During Early Luteal Phase in Sheep

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Summary: Prostaglandins (PGs) in particular PGE2 by regulating luteal angiogenesis and steroidogenesis, play an important role in ovarian as well as luteal function in many mammalian species. While the direct luteotrophic effect of PGE2 has been studied intensively, there is still not much information available regarding the indirect effects of PGE2 in ovine corpus luteum (CL). Therefore, in the present study, possible effects of PGE2 stimulation on expression of some steroidogenic hormone receptors (ERα/ER1, ERβ/ER2 and PGR) and growth factors (IGF1, IGF2 and VEGF) were investigated using the isolated primary luteal and -microvascular endothelial cells. Neither the expression of steroidogenic hormone receptors (ERα/ER1, ERβ/ER2 and PGR) nor growth factors (IGF1, IGF2 and VEGF) were affected by PGE2 stimulation in primary luteal cells. However, there was statistically significant difference for the expression of both ERα/ER1 and ERβ/ER2 following PGE2 treatment in primary microvascular endothelial cells. Moreover, while the expression of IGF2 was upregulated, there was no statistically significant change for the expression of IGF1 and VEGF following PGE2 treatment in ovine primary microvascular endothelial cells. In conclusion, by regulating expression of estrogen receptors (ERα/ER1 and ERβ/ER2) and IGF2 in ovine luteal endothelial cells, PGE2 might involve in luteal angiogenesis and vasculogenesis during early luteal phase in sheep.
Key words: Corpus luteum, prostaglandin E2, sheep

Prostaglandin E2`nin Koyunlarda Erken Luteal Dönemde Korpus Luteum Üzerine Etkisi

Özet: Prostaglandinler (PG'ler) özellikle de PGE2 luteal anjiyogenezis ve steroidogenezis'i düzenleyerek, birçok memeli türünde ovaryumun yanı sıra luteal fonksiyonun düzenlenmesinde önemli rol oynamaktadır. PGE2'nin direkt luteotropik etkisi yoğun olarak çalışılsa da PGE2'nin koyun korpus luteumundaki (CL) indirekt etkileri hakkında hala çok fazla bilgi bulunmamaktadır. Bu nedenle, bu çalışmada, korpus luteumdan izole edilen primer luteal ve mikrovasküler endotel hücreleri kullanılarak, PGE2 stimülasyonunun bazı steroidogenik hormon reseptörlerinin (ERα / ER1, ERβ / ER2 ve PGR) ve büyüme faktörlerinin (IGF1, IGF2 ve VEGF) ekspresyonu üzerindeki olası etkileri araştırılmıştır. Primer luteal hücrelerin PGE2 ile stimülasyonunu takiben ne steroidogenik hormon reseptörlerinin (ERα / ER1, ERβ / ER2 ve PGR) ne de büyüme faktörlerinin (IGF1, IGF2 ve VEGF) ekspresyonu etkilendi. Ancak, PGE2 ile primer mikrovasküler endotel hücrelerininin stimülasyonunu takiben ERα / ER1 ve ERβ / ER2`in ekspresyonu belirgin olarak arttı. Aynı zamanda, primer mikrovasküler endotel hücrelerinde IGF2'nin ekspresyonu upregüle olurken, IGF1 ve VEGF'in ekspresyonu PGE2 stimülasyonundan etkilenmedi. Sonuç olarak, PGE2 östrojen reseptörlerinin (ERα / ER1 and ERβ / ER2) ve IGF2`in ekspresyonunu düzenleyerek erken luteal dönemde luteal anjiyogenez ve vaskülogeneze katıldığı düşünülmektedir.
Anahtar kelimeler: Korpus luteum, koyun, prostaglandin E2

Introduction

Following ovulation, the remnants of the granulosa and the theca cell layer of the Graafian follicle turns into a temporary endocrine gland called a corpora lutea (CL) (Channing et al., 1980; Smith et al., 1994; Fraser and Wulff, 2003). Rapid and intense blood vessel formation and supply, which are important for the establishment and maintenance of CL as well as progesterone (P4) production, are observed during formation of CL (Suzuki et al., 1998; Grazul-Bilska et al., 2007; Martelli et al., 2009). In the CL, vascularization and angiogenesis are regulated by a variety of locally produced growth factors such as, fibroblast growth factors (FGFs), vascular endothelial growth factor (VEGF)-system and angiopoietins (Angpts). Furthermore, locally produced luteotropic factors i.e. prostaglandins (PGs), P4 and estrogens (E2) are involved in the maintenance of this temporary endocrine gland (CL).

Prostaglandins are known as a fatty-acid hormone

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synthesized following the liberation of 20-carbon unsaturated fatty acid derivate arachidonic acid from the cellular plasma membrane by phospholipaseA2 (Smith and Dewitt, 1996). Then, this released arachidonic acid is converted into the prostaglandin H2 (PGH2) the main precursor of the different PGs, by means of cyclooxygenases (COXs) (Smith and Dewitt, 1996). While COX1 is constitutively expressed in most of the mammalian cells, expression of PTGS2/COX2 is induced by an inflammatory and proliferative stimulus (Smith and Dewitt, 1996). Prostaglandin E2, prostacyclin (PGI2), PGD2 and PGF2α are produced form the PGH2 with the aid of specific enzymes (Tai et al., 2002).

Among PGs, particularly PGE2 plays important roles in angiogenesis, cellular proliferation and blood supply (Namkoong et al., 2005; Trau et al., 2016). PGE2 mediates its signal through four PGE2 receptors, PTGER1, -2, -3 and -4 (also known as EP1, EP2, EP3 and EP4) (Castellone et al., 2005; Cha et al., 2007). Activation of PTGER2 (EP2) and PTGER4 (EP4) increases production of cyclic adenosine monophosphate (cAMP), an activator of PKA signaling pathway (Narumiya et al., 1999). However, activation of PTGER1 (EP1) and PTGER3 (EP3) induces intracellular Ca2+ release that activates of PKC signaling pathway (Narumiya et al., 1999).

While PGF2α exerts luteolytic effect, PGE2 shows luteoprotective effect in sheep and cows (Weems et al., 1985; Weems et al., 1995; Weems et al., 2006; Wiltbank et al., 2018). Luteotropic effect of PGE2 has been shown in a variety of species such as dog, pig and human as well (Hahlin et al., 1988; Ford and Christenson, 1991; Kowalewski et al., 2013). In accordance with this, high expression of COX2 and PTGES was detected in the dog CL during early luteal phase (Kowalewski et al., 2006). Additionally, PGE2 by inducing expression of ETB and ANGPT2 expression in the dog appears to involve in luteal blood supply and angiogenesis (Gram et al., 2015; Gram et al., 2018). Furthermore, CL, pregnant uterus and conceptus are able to produce PGE2 in sheep. During establishment of pregnancy in ewe, PGE2 seems to be involved in the rescue of the CL (Weems et al., 1995). In sheep, intrauterine infusion of PGE2 mitigates luteolytic action of PGF2α during spontaneous luteolysis (Weems et al., 1985). Administration of PGE2 as well as PGE1 blocks PGF2α induced luteolysis and P4 production in this species as well (Reynolds et al., 1981). Moreover, PGE2 induces production of P4 by activating production of cAMP an activator of PKA signaling pathway in human and rabbit (Boiti et al., 2001; Hahlin et al., 1988). Blockage of the PTGS2/COX2 in vivo with its specific blocker reduces expression of steroidogenic acute regulatory protein (STAR) thereby P4 production in the dog (Janowski et al., 2014).

While the effect of PGE2 on luteal steroidogenesis was intensively investigated in a variety of species, there is little information available regarding the indirect effects of PGE2 in the ovine CL. In order to get more information regarding the potential function of PGE2 in ovine CL and thus to better understand the regulation of its function, in the current study ovine primary luteal and -microvascular endothelial cells were isolated. Thereafter, using the isolated luteal and -microvascular endothelial cells, possible effects of PGE2 stimulation on expression of some steroidogenic hormone receptors (ERα/ER1, ERβ/ER2 and PGR) and growth factors (IGF1, IGF2 and VEGF) were investigated.

Materials and Methods

Tissue collection and isolation of ovine primary luteal and -microvascular endothelial cells

Luteal cells and luteal microvascular endothelial cells were isolated by using our previously described protocol (Gram et al., 2019). Briefly, primary luteal and -microvascular endothelial cells were isolated from CL of clinically healthy and non-pregnant ewes (n=3). Samples for isolation of primary cells were obtained from the local slaughterhouse. Corpora lutea of each animal were separated from the surrounding tissues and washed with sterile phosphate-buffered saline (PBS). Afterwards, they were cut into small pieces with a sterile scalpel blade and incubated for 1h in PBS containing 0.15 % collagenase (Sigma-Aldrich Chemie GmbH). Following digestion of tissues, they were filtered through a sterile 100µm nylon strainer. Then filtrate was centrifuged at 500 g at room temperature. The obtained pellet was subsequently resuspended with PBS containing 1% bovine serum albumin. Then, the endothelial cells were separated from the resulting suspension through affinity purification with magnetic beads. Magnetic tosylactivated beads (Dynabeads M- 450) were coated with (Bandeiraea) Simplicifolia Lectin I (BSL-I) (Vector Laboratories) according to the manufacturer's instruction. Following incubation dispersed cells together with BSL-I labelled magnetic beads, bead adherent cells were separated with the aid of the magnet. Bead-free supernatant that contained the luteal cells were separated and suspended in culture medium ((DMEM/F12, with 10% heat-inactivated FBS, 100 U/ml penicillin and 100 mg/ml streptomycin, and 1% ITS (Insulin-Transferrin-Selenium), seeded immediately into six well plates.

Bead adherent cells, resuspended in endothelial cell culture medium (DMEM/F12, with 10% heat inactivated FBS, containing 100 U/ml penicillin and 100 mg/ml streptomycin and 200 µg/ml Endothelial Cell Growth Supplement (ECGS)) and seeded directly into the six -well plates. Both endothelial and luteal cells were cultured in a humidified incubator at 37^{o}C under 5%

CO_2. To characterize endothelial and luteal cells sterile cover glasses were put into each well and grown on them. When cells reached approximately 90-100% confluency, they were fixed by adding 2% formaldehyde for 10 min at 37°C.

As for stimulation experiments, prior to stimulation, the cells were washed with sterile PBS and replaced by a serum and ECGS-free DMEM/F12 medium containing 1ng/ml PGE2 for 6h. This dosage of the PGE2 is decided based on previously published report.

RNA isolation and semi-quantitative RT-PCR and data evaluation

Total RNA was obtained from primary luteal and -microvascular endothelial cells using TRIzol® reagent according to the manufacturer's instructions (Invitrogen). The concentrations of isolated RNA samples were quantified by spectrophotometrically. DNase treatment was performed using RQ1 RNase-free DNase (Promega). Reverse transcription (RT) of the RNA samples was achieved following the manufacturer's instructions (Applied Biosystems).

Semi-quantitative Real Time (TaqMan) PCR was performed in CFX Connect Real Time system (Bio-Rad). All the reactions were performed in duplicates. Primers and TaqMan® probes labelled with 6-carboxyfluorescein (6-FAM) and 6-carboxytetramethylrhodamine (TAMRA) and are presented in Table 1.

Normalization of the target genes was achieved using two different reference genes, GAPDH and β-ACTIN. Relative gene expression of each target gene was calculated with comparative CT method (ΔΔCT method).

Statistical analyses

Each experiment was performed independently at least three times. All the statistical analyses were performed using the SPSS 16.0 Software. The Effect of PGE2 treatment on expression of ERα/ER1, ERβ/ER2, PGR, IGF1, IGF2 and VEGF in primary luteal and -microvascular endothelial cells was calculated using an unpaired two-tailed Student's t-test. All numerical data are presented as the mean ± standard deviation. $P<0.05$ was considered statistically significant.

Results

Effect of PGE2 stimulation on expression of ERα/ER1, ERβ/ER2, PGR and IGF1, -2 and VEGF in ovine primary luteal and -microvascular endothelial cells

Both primary luteal and -microvascular endothelial cells were isolated from CL of sheep by enzymatic digestion. The expression of all target genes were detected by semi-quantitative RT-PCR. They were

Table 1. List of primers used for Real Time (TaqMan) PCR

Gene	Primer sequence	Product length (bp)	Accession number
ERα/ER1	Forward: 5'- CCTGACGGCTGACCAGATGA-3` Reverse: 5'- CCTCACTGAAAGGGTCTGGTAGGT-3` TaqMan probe: 5'-TGGAGGCTGAGCCCCCCATAATCTATTCT-3`	92	AY033393.1
ERβ/ER2	Forward: 5'- GTCTCCTATAACTGCGGTCAATCC-3` Reverse: 5'- GAGTATTCATGGCGGCTCTCTAC-3` TaqMan probe: 5'-TGGAGCCAGGCCCCATATATTTACCCTCTT-3`	92	NM_001009737.1
IGF1	Forward: 5'- CAGCAGTCTTCCAACCCAAT-3` Reverse: 5'- CAGGGCCAGATAGAAGAGATG-3` TaqMan probe: 5'-AGGTGAAGATGCCAGTCACATCCTCCTC-3`	103	NM_001009774.3
IGF2	Forward: 5'- GGGATGTGTCTGCCTCTACGA-3` Reverse: 5'- GACTGCTTCCAGGTGTCAGATTG-3` TaqMan probe: 5'-TCACAGCATACCCCGTGGGCAAGTT-3`	91	NM_001009311.1
VEGF	Forward: 5'- GGGCTGCTGTAATGACGAAAGT-3` Reverse: 5'- CTGGCTTTGGTGAGGTTTGATC-3` TaqMan probe: 5'-TGTGCCCACTGAGGAGTTCAACATCAC-3`	94	AF071015.1
β-ACTIN	Forward: 5'- AGA GGC ATC CTG ACC CTC AA-3` Reverse: 5'- GTT GTA GAA GGT GTG GTG CCA GAT-3` TaqMan probe: 5'-TAC CCC ATT GAG CAC GGC ATT GTCA -3`	93	U39357.1
GAPDH	Forward: 5'- GGC ACA GTC AAG GCA GAG AAC-3` Reverse: 5'- CAC GTA CTC AGC ACC AGC ATC A-3` TaqMan probe: 5'-AAG GCC ATC ACC ATC TTC CAG GAG C-3`	114	NM_001190390.1

clearly detectable in both stimulated and non-stimulated ovine primary luteal (Fig. 1-2) and -microvascular endothelial cells (Fig. 3-4). There were no statistically significant changes in the expression of investigated steroidogenic hormone receptors (P=0.20 for ERα/ER1, P=0.93 for ERβ/ER2 and P=0.70 for PGR) in primary luteal cells following treatment with 1ng/ml PGE2 treatment (Fig. 2A-C).

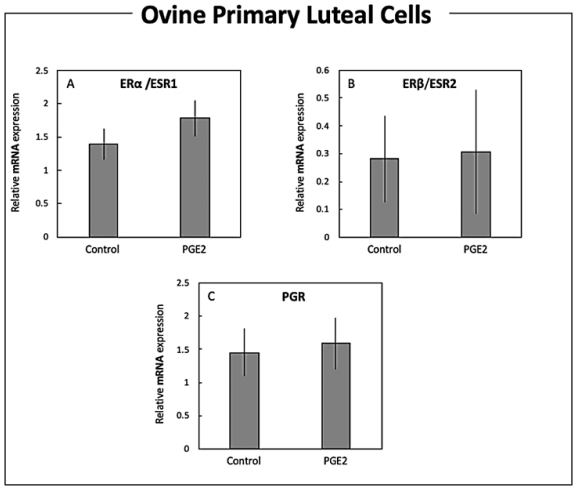

Figure 1. Effect of PGE2 on expression of ERα/ER1, ERβ/ER2 and PGR in ovine primary luteal cells collected from clinically healthy and non-pregnant ewes. Luteal cells were cultured in serum-free DMEM/F12 medium with 1ng/ml PGE2. Non-stimulated cells served as a negative control. (A-C) ERα/ER1, ERβ/ER2 and PGR mRNA expression as determined by real-time (TaqMan) PCR normalized against GAPDH and β-ACTIN. Numerical data are presented as the mean ± standard deviation

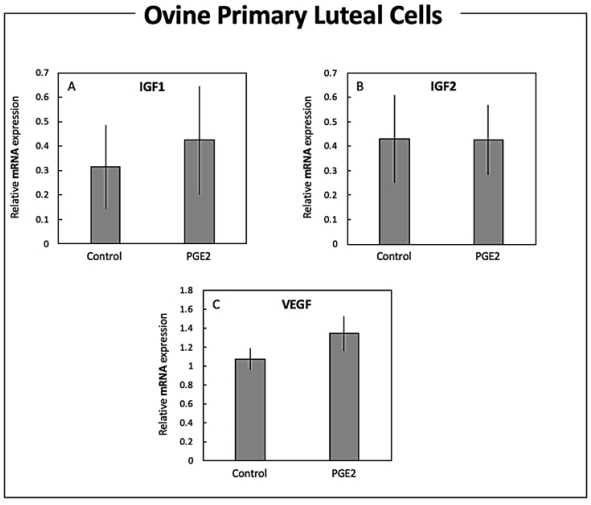

Figure 2. Effect of PGE2 on expression of IGF1, IGF2 and VEGF in ovine primary luteal cells collected from clinically healthy and non-pregnant ewes. Luteal cells were cultured in serum-free DMEM/F12 medium with 1ng/ml PGE2. Non-stimulated cells served as a negative control. (A-C) IGF1, IGF2 and VEGF mRNA expression as determined by real-time (TaqMan) PCR normalized against GAPDH and β-ACTIN. Numerical data are presented as the mean ± standard deviation

Similarly, there was no statistically significant changes in the expression of IGF1, either, (P=0.70) -2 (P=0.70) and VEGF (P= 0.10) in primary luteal cells

Interestingly, the expression of ERα/ER1 and ERβ/ER2 were affected in luteal microvascular endothelial cells following stimulation with 1ng/ml PGE2 (Fig. 3A and B). There was a significant change in expression of both ERα/ER1 (P=0.002) and ERβ/ER2 (P=0.0001) in primary microvascular endothelial cells following treatment with PGE2 (Fig. 3A and B).

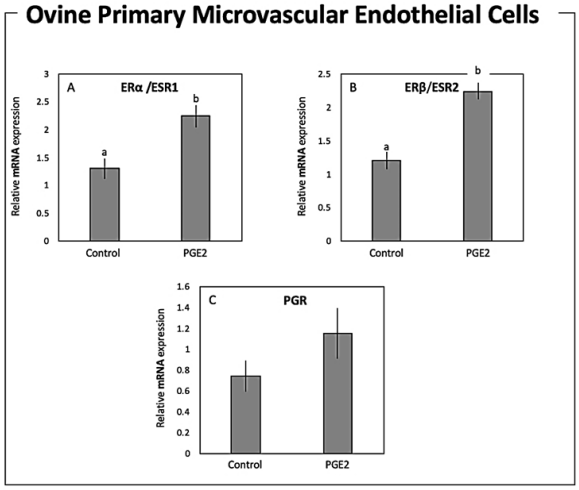

Figure 3. Effect of PGE2 on expression of ERα/ER1, ERβ/ER2 and PGR in ovine primary microvascular endothelial cells collected from clinically healthy and non-pregnant ewes. Microvascular endothelial cells were cultured in serum-free DMEM/F12 medium with 1ng/ml PGE2. Non-stimulated cells served as a negative control. (A-C) ERα/ER1, ERβ/ER2 and PGR mRNA expression as determined by real-time (TaqMan) PCR normalized against GAPDH and β-ACTIN. Bars with different letters differ at P=0.002 (ERα/ER1), P=0.0001 (ERβ/ER2) and P=0.1 (PGR). Numerical data are presented as the mean ± standard deviation

Moreover, the expression of IGF2 (P=0.0005) was also increased significantly (Fig. 4B). On the other hand, the expressions of PGR (P=0.10), IGF1 (P=0.60), and VEGF (P=0.60) did not change signifi-

cantly in primary microvascular endothelial by 1ng/ml PGE2 stimulation (Fig. 3C-4A and C).

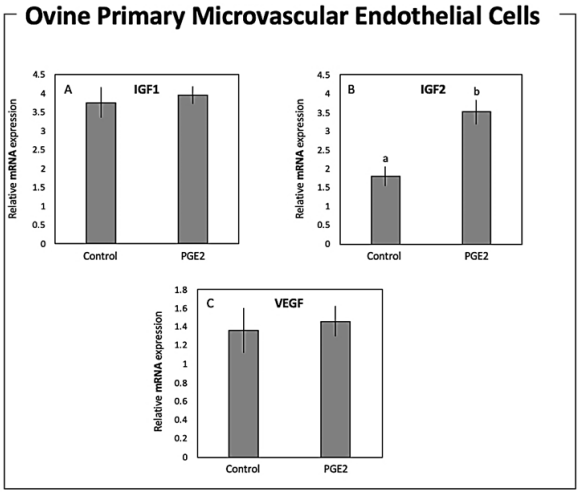

Figure 4. Effect of PGE2 on expression of IGF1, IGF2 and VEGF in ovine primary microvascular endothelial cells collected from clinically healthy and non-pregnant ewes. Microvascular endothelial cells were cultured in serum-free DMEM/F12 medium with 1ng/ml PGE2. Non-stimulated cells served as a negative control. (A-C) IGF1, IGF2 and VEGF mRNA expression as determined by real-time (TaqMan) PCR normalized against GAPDH and β-ACTIN. Bars with different letters differ at (P=0.0005). Numerical data are presented as the mean ± standard deviation

Discussion and Conclusion

Prostaglandin E appears to play an important role in luteal function in domestic animals by regulating angiogenesis, proliferation and steroidogenesis. Luteotrophic effect of PGE2 has been shown in many domestic animal species such as dog, cow, sheep, pig and human (Hahlin et al., 1988; Ford and Christenson, 1991; Kowalewski et al., 2013; Weems et al., 1985; Weems et al., 1995; Weems et al., 2006; Wiltbank et al., 2018). However, indirect effect of PGE2 on luteal function has not yet been investigated in detail. Therefore, aiming to better understand the effect of PGE2 on luteal function, primary luteal and microvascular endothelial cells were isolated from early sheep CL and mRNA expression of ERα/ER1, ERβ/ER2 and PGR and IGF1, IGF2 and VEGF, we investigated in primary luteal and microvascular endothelial cells following treatment with PGE2.

Time dependent expression of both ERα/ER1 and ERβ/ER2 were shown in ovine CL previously (Cardenas et al., 2001; Tomanek et al., 1997). Localization of both receptors in different cellular compartments of the CL such as luteal cells and endothelial cells suggest involvement of estrogen in the regulation of an autocrine/paracrine role of CL (Cardenas et al., 2001; Tomanek et al., 1997). Furthermore, the increase in expression of ERα/ER1 at mid luteal phase, and the decrease ERβ/ER2 expression during mid-luteal phase indicate that the functions of these two receptors in the sheep CL might differ (Cardenas et al., 2001; Tomanek et al., 1997). Interestingly, in the present study, expression of the investigated steroid hormone receptors (ERα/ER1, ERβ/ER2 and PGR) remained unaffected by the PGE2 stimulation. Thus, it seems that there is no functional connection between locally acting PGs, especially PGE2 and ERα/ER1, ERβ/ER2 and PGR in ovine luteal cells.

Interestingly, in ovine primary microvascular endothelial cells, expression of both ERα/ER1 and ERβ/ER2 were upregulated following treatment with PGE2, suggesting an interplay between estrogen and PGE2 in the regulation of the proliferation of endothelial cells as well as vascularization occurring during early CL formation. Nevertheless, further research is required to better understand the mechanisms of PGE2 -mediated effects on endothelial cell proliferation and angiogenesis in ovine CL.

As for PGR, similar to luteal cells, its expression was not affected by PGE2 treatment. On the other hand, the time period that was used to stimulate primary microvascular endothelial cells might be not enough to induce expression of PGR. Moreover, there might be no functional connection between locally produced PGE2 and PGR in ovine luteal endothelial cells. Therefore, further research is required to better understand the effect of PGE2 stimulation on PGR in ovine CL.

Growth hormones (IGF1 and IGF2), like insulin, are also involved in the development, proliferation and regression of the CL in sheep (Juengel et al., 1997; Hastie and Haresign, 2006). By regulating P4 production, IGF1 and IGF2 are involved in steroidogenesis in ovine CL as well (Juengel et al., 1997; Hastie and Haresign, 2006). Furthermore, similar to other domestic animals such as dog and cow, in the sheep early luteal phase is characterized by upregulated expression of VEGF. By regulating angiogenesis this angiogenic growth factor is crucial for the maintenance of the CL. However, in our study neither expression of insulin like growth hormones (IGF1 and IGF2) nor VEGF were affected by PGE2 stimulation in primary luteal cells. Therefore, it appears that there is no functional connection between locally acting PGE2 and IGF1, IGF2 and VEGF in ovine luteal cells. On the other hand, while the expression of IGF2 was upregulated, expression of IGF1 and VEGF were not affected by PGE2 treatment in ovine primary microvascular endothelial cells. This indicates the possible functional interplay among different cellular compartments within the ovine CL. There-

fore, involvement of PGE2 in local autocrine and paracrine regulation of this temporary endocrine gland still needs to be elucidated.

In conclusion, the effects of PGE2 on expression of ERα/ER1, ERβ/ER2 and PGR and IGF1, IGF2 and VEGF have been investigated herein by using the ovine primary luteal and -microvascular endothelial cells. The results presented in the current study suggest that by regulating expression of estrogen receptors (ERα/ER1 and ERβ/ER2) and IGF2 in ovine luteal endothelial cells, PGE2 might involve in luteal angiogenesis and vasculogenesis during early luteal phase in sheep.

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