Reprod Dev Biol 39(1) : 1-6 (2015)
http://dx.doi.org/10.12749/RDB.2015.39.1.1

ISSN : 1738-2432 (Print)
ISSN : 2288-0151 (Online)

Prostaglandin $F_2\alpha$ Controls Reactive Oxygen Species in Bovine Corpus Luteum

Seunghyung Lee[1,2], Boo-Keun Yang[2] and Choon-Keun Park[2,†]

[1]*Institute of Animal Resources, Kangwon National University, Chuncheon 200-701, Republic of Korea*

[2]*College of Animal Life Science, Kangwon National University, Chuncheon 200-701, Republic of Korea*

ABSTRACT

Luteolysis is a cyclical regression of the corpus luteum in many non-primate mammalian species. Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) from the uterus and ovary induces functional and structural luteolysis in bovine. The action of $PGF_2\alpha$ is mediated by $PGF_2\alpha$ receptor located on the luteal steroidogenic and endothelial cell membranes. $PGF_2\alpha$ plays an important role in regulating nitric oxide production in endothelial cells of the bovine corpus luteum. Nitric oxide production and nitric oxide synthase activity are stimulated and induced by $PGF_2\alpha$ in luteal endothelial cells. Moreover, the reactive oxygen species inhibits progesterone secretion in bovine luteal cells and induces apoptosis. Thus, the interaction between $PGF_2\alpha$ and reactive oxygen species provides important aspects in physiology of the corpus luteum forfunctional and structural luteolysis.

(Key words : Prostaglandin $F_2\alpha$, Reactive oxygen species, Corpus luteum, Steroidogenic luteal cell, Endothelial cell)

INTRODUCTION

The oestrous cycle in bovine is characterized by repeated patterns of cellular proliferation, differentiation and transformation that accompany follicular development and the formation and regression of corpus luteum. The derived gonadotropin-releasing hormone and growth hormone from a pituitary are the primary regulation of final follicular maturation and corpus luteum function. The corpus luteum is a transient endocrine gland that produces progesterone, required for the establishment and maintenance of pregnancy. Also, luteolysis, the regression of corpus luteum, is initiated by prostaglandin $F_2\alpha$ ($PGF_2\alpha$) and oxytocin hormones in cattle (Smith *et al.*, 1998; Colazo *et al.*, 2002; Repasi *et al.*, 2005; Wenzinger *et al.*, 2012; Schams *et al.*, 2004). Recently, many studies have reported that reactive oxygen species is occurred in corpus luteum (Lee *et al.*, 2010; Jones *et al.*, 2008; Peltier *et al.*, 2006; Rizzo *et al.*, 2009; Sugino *et al.*, 2006), however, it is unclear how luteolysis regulates with oxidative stress. This review will focus on the mechanisms and regulatory effects of $PGF_2\alpha$ with reactive oxygen species in luteolysis in bovine corpus luteum.

CORPUS LUTEUM IN BOVINE

Corpus luteum, yellow body in Latin, is hormone-secreting body in the female reproductive system. Corpus luteum is formed in an ovary at the site of a follicle,consists of steroidogenic large and small cells, endothelial cells, smooth muscle cells, immune cells, and fibroblasts (O'Shea *et al.*,1989). Specially, steroidogenic and endothelial cells are important factors for the regression of corpus luteum, steroidogenic cells secrete rogesterone and endothelial cells require the formation of new blood vessels and growth of corpus luteum. The main function of corpus luteum is to secrete progesterone during non-pregnant cycle and pregnancy. Luteal regression, luteolysis, is caused by releasing $PGF_2\alpha$ from uterus at the end of the oestrous cycle. The function of formation and regression of the corpus luteum is regulated with many growth factors and hormones. Briefly, vascular and capillaries are up to 80% of the cells in mature corpus luteum (Lee *et al.*, 2009; Rey-

* This work was supported by Grant No. 112145-3 from Korea Institute of Planning and Evaluation for Technology in Food, Agriculture, Forestry and Fisheries (IPET).

† Corresponding author : Phone: +82-33-250-8627, E-mail: parkck@kangwon.ac.kr

nolds *et al.*, 1998). Thus, endothelial cell is potential factor for luteal growth and regression in bovine. In angiogenesis, vascular endothelial growth factor, acidic and basic fibroblast growth factors, insulin- like growth factors, angiopoietins, transforming growth factors family, tumor necrosis factor, vasoactive peptides-like angiotensin II, endothelin-1, and proteins of the extracellular matrix are important factors (Berisha *et al.*, 2000; Augustin *et al.*, 1998; Garrido *et al.*, 1993; Goede *et al.*, 1998; Einspanier *et al.*, 1999; Schams *et al.*, 2001; Schams *et al.*, 2002; Vandehaar *et al.*, 1995; Yancopoulos *et al.*, 2000; Woad *et al.*, 2000). In addition, the primary luteotropic hormones, luteinizing hormone and growth hormone, support corpus luteum for developing and growing. Luteinizing hormone stimulates the production and secretion of progesterone from steroidogenic small cells, also has their receptors (Niswender *et al.*, 1998). Growth hormone is a main mediator for progesterone production in steroidogenic large cells (Niswender *et al.*, 1985). Moreover, oxytocin and $PGF_2\alpha$ are stimulated by growth hormone in bovine corpus luteum (Liebermann *et al.*, 1994; Kobayashi *et al.*, 2001).

PLAY OF PROSTAGLANDIN F_2ALPHA IN LUTEOLYSIS

The luteolysis is crucial to reset the ovarian cycle, has functional luteolysis and structural luteolysis (Hansel *et al.*, 1996; Meidan *et al.*, 1999; McCracken *et al.*, 1999). Functional luteolysis is induced with prostaglandin F_2alpha produced by reducing progesterone from the uterus. Structural luteolysis is processed by tissue degeneration and cell death of steroidogenic and endothelial cells, such as apoptosis.

Functional Luteolysis

A decrease of blood flow in bovine corpus luteum is an initial point for luteal regression. Acosta *et al.* and Knickerbocker *et al.* reported that progesterone concentration and luteal blood flow were low in $PGF_2\alpha$-induced luteolysis (Acosta *et al.*, 2000; Acosta *et al.*, 2002; Knickerbocker *et al.*, 1988). However, $PGF_2\alpha$ does not inhibit progesterone production in steroidogenic luteal cells *in vitro* (Alila *et al.*, 1988; Okuda *et al.*, 1998), but progesterone decreased in co-cultured with luteal endothelial cells and luteal cell (Girsh *et al.*, 1996; Choudhary *et al.*, 2005; Girsh *et al.*, 1995). The above results suggest that endothelial cells in corpus luteum are crucial for inhibiting progesterone in functional luteolysis.

Recently, we reportedluteal endothelial cells isolated from bovine corpus luteum at the mid-luteal phase (days 8~12 of the oestrous cycle) and demonstrated that prostaglandin F_2alpha receptor mRNA and protein expressions in luteal endothelial cell isolated from bovine corpus luteum (Lee *et al.*, 2009). The mRNA of the receptor is not expressed in luteal endothelial cells isolated from early pregnant cow (Cavicchio *et al.*, 2002). On the other hand, the isolated endothelial cells from corpus luteum express $PGF_2\alpha$ receptor mRNA and protein (Cavicchio *et al.*, 2002; Meidan *et al.*, 2005; Mauluk *et al.*, 1998). Endothelial cells in corpus luteum compose more than 50%, the function of luteal endothelial cells may be regulated in luteolysis.

Endothelial cell-regulated factors are vascular endothelial growth factor, acidic and basic fibroblast growth factors, insulin-like growth factors, angiopoietins, transforming growth factors family, tumor necrosis factor, vasoactive peptides-like angiotensin II, endothelin-1, and reactive oxygen species etc. In recent studies, nitric oxide produced by luteal endothelial cells inhibited progesterone secretion in bovine luteal cells (Skarzynski *et al.*, 2000; Klipper *et al.*, 2004). Also, nitric oxide regulates the regression of corpus luteum in many animals and human (Shirasuna *et al.*, 2008; Skarzynski *et al.*, 20000; Korzekwa *et al.*, 2004; Skarzynski *et al.*, 2003; Jaroszewski *et al.*, 2000; Motta *et al.*, 1999; Boiti *et al.*, 2003; Vega *et al.*, 1998). Therefore, our studies and other group studies suggest that nitric oxide has a physiological role for luteolysis in the bovine corpus luteum.

In addition, cytokines, tumor necrosis factor alpha, interlukin-1 beta, and interferon gamma, are increased by $PGF_2\alpha$. And, nitric oxide, angiotensin II, endothelin-1and their receptor, fibroblast growth factors and their receptor are increased by cytokines. To know the mechanism of luteolysis regulating $PGF_2\alpha$, nitric oxide, and cytokines, the apoptotic mechanism is a key in finding functional luteolytic mechanism in the ovary.

Structural Luteolysis

After functional regression of the corpus luteum in bovine, structural luteolysis is continually started by $PGF_2\alpha$ from the uterus and ovary (Lee *et al.*, 2009; Silvia *et al.*, 1991; Horton *et al.*, 1976; Hansel *et al.*, 1986). Vascular endothelial growth factor (VEGF) upregulates prostaglandin F_2alpha in luteal endothelial cells. Neuvians *et al.* reported that vascular endothelial growth factor mRNA and protein level decreased in the collected luteal tissue after injection of $PGF_2\alpha$ analogue (Neuvians *et al.*, 2004). VEGF protein was not detected at 2 hour after prostaglandin F_2alpha, also the mRNA and their receptors after 12 hour were downregulated. That means vascular endothelial growth factor in luteal endothelial cells regulates structural lutoelysis. Also, plasma progesterone decreased from 24

hour in bovine corpus luteum (Acosta *et al.*, 2002).

Generally, luteal steroidogenic cells secrete progesterone. Although, progesterone is not inhibited by $PGF_2\alpha$ in bovine luteal cells, a decrease of progesterone appears during luteal regression, suggesting that progesterone is mediated by other substances locally produced in the bovine corpus luteum, such as reactive oxygen species. In addition, cytokines were up-regulated during luteolysis, the receptors of luteinizing hormone and growth hormone, $P450_{scc}$, and 3beta-hydroxysteroid dehydrogenase were down-regulated during structural luteolysis in bovine.

PROSTAGLANDIN F_2ALPHA AND REACTIVE OXYGEN SPECIES

Reactive oxygen species includehydrogen peroxide, superoxide anion, oxygen, and nitric oxide. Nitric oxide isproduced by endothelial cells from corpus luteum inhibits progesterone and plays a luteolytic role in bovine (Klipper *et al.*, 2004; Shirasuna *et al.*, 2008; Skarzynski *et al.*, 2000; Korzekwa *et al.*,2004; Skarzynski *et al.*, 2003; Jaroszewski *et al.*, 2000; Motta *et al.*, 1999; Boiti *et al.*, 2003; Vega *et al.*, 1998). We also studied that an injection of $PGF_2\alpha$ induces a transient increase in the concentrations of nitric oxide and partial pressure of oxygen in ovarian venous blood (Acosta *et al.*, 2000; Acosta *et al.*, 2002), suggesting nitric oxide from luteal endothelial cells mediates the luteolytic action of $PGF_2\alpha$ in bovine.

Recently, we demonstrated that $PGF_2\alpha$ stimulates nitric oxide production in the isolated luteal endothelial cells from bovine corpus luteum (Lee *et al.*, 2009). Cultured bovine luteal endothelial cells expressed the mRNA of *prostaglandin F2alpha receptor*. Also, nitric oxide was increased by $PGF_2\alpha$ via inducing inducible nitric oxide synthase. Moreover, prostaglandin F_2alpha stimulated nitric oxide synthase activity. In fact, nitric oxide synthase activity has been investigated in many cells, such as macrophages, endothelium, smooth muscle, ovarian stroma cells, and ovarian follicular granulose cells (Stuehr *et al.*, 1985; Ignarro *et al.*, 1987; Busse *et al.*, 1990; Jablonka-Shariff *et al.*, 1997; Van Voorhis *et al.*, 1994). Moreover, nitric oxide regulates progesterone secretion in luteolytic and luteotropic factors in bovine (Boiti *et al.*, 2000; Gobbetti *et al.*, 1999). Therefore, we strongly assume that $PGF_2\alpha$ enhances nitric oxide production by stimulating inducible nitric oxide synthase expression and nitric oxide synthaseactivity in bovine luteal endothelial cells.

In addition, *eNOS* mRNA expression was not changed by $PGF_2\alpha$ in functional luteolysis, but apoptosis can occur. Since cytokines induce inducible nitric oxide synthase and stimulate nitric oxide levels. Thus, nitric oxide may also play a role in early functional luteolysis.

CONCLUSION

$PGF_2\alpha$ regulating reactive oxygen species including nitric oxide in the luteal endothelial cells may play an important role for elucidating the local mechanisms of functional and structural luteolysis in the bovine corpus luteum.

REFERENCES

1. Acosta TJ, Ozawa T, Kobayashi S, Hayashi K, Ohtani M, Kraetzl WD, Sato K, Schams D, Miyamoto A (2000): Periovulatory changes in the local release of vasoactive peptides, prostaglandin $F_2\alpha$, and steroid hormones from bovine mature follicles *in vivo*. Biol Reprod 63:1253-1261.
2. Acosta TJ, Yoshizawa N, Ohtani M, Miyamoto A (2002): Local changes in blood flow within the early and midcycle corpus luteum after prostaglandin $F_2\alpha$ injection in the cow. Biol Reprod 66:651-658.
3. Alila HW, Dowd JP, Corradino RA, Harris WV, Hansel W (1988): Control of progesterone production in small and large bovine luteal cells separated by flow cytometry. J Reprod Fertil 82:645-655.
4. Augustin HG (1998): Antiangiogenic tumor therapy: will it work? Trends Pharmacol Sci 19:216-222.
5. Berisha B, Schams D, Kosmann M, Amselgruber W, Einspanier R (2000): Expression and tissue concentration of vascular endothelial growth factor, its receptors and localization in the bovine corpus luteum during estrous cycle and pregnancy. Biol Reprod 63: 1106-1114.
6. Boiti C, Guelfi g, Zampini D, Brecchia G, Gobbetti A, Zerani M (2003): Regulation of nitric oxide synthase isoforms and role of nitric oxide during prostaglandin $F_2\alpha$-induced luteolysis in rabbits. Reprodcution 125:807-816.
7. Boiti C, Zerani M, Zampini D, Gobbetti A (2000): Nitric oxide synthase activity and progesterone release by isolated corpora lutea of rabbits in the early and mid-luteal phases of pseudopregnancy are modulated differently by prostaglandin E2 and prostaglandin $F_2\alpha$ via adenylate cyclase and phospholipase C. J Endocrinol 164:179-186.

8. Busse R, Mulscha A (1990): Induction of nitric oxide synthase by cytokines in vascular smooth muscle cells. FEBS Lett 275:87-90.
9. Cavicchio VA, Pru JK, Davis BS, Davis JS, Rueda BR, Townson DH (2002): Secretion of monocyte chemoattractant protein-1 by endothelial cells of the bovine corpus luteum: Regulation by cytokines but not prostaglandin $F_2\alpha$. Endocrinology 143:3582-3589.
10. Choudhary E, Sen A, Inskeep EK, Flores JA (2005): Developmental sensitivity of the bovine corpus luteum to prostaglandin $F_2\alpha$ and endothelin-1 (ET-1): Is ET-1 a mediator of the luteolytic actions of progesterone $F_2\alpha$ of a tonic inhibitor of progesterone secretion? Biol Reprod 72:633-642.
11. Colazo MG, Martinez MF, Kastelic JP, Mapletoft RJ (2002): Effects of dose and route of administration of cloprostenol on luteolysis, estrus and ovulation in beef heifers. Anim Reprod Sci 72:47-62.
12. Einspanier R, Miyamoto A, Schams D, Muller M, Brem G (1999): Tissue concentration, mRNA expression and stimulation of IGF-1 in luteal tissue during the oestrous cycle and pregnancy of cows. J Repord Fertil 90:439-445.
13. Garrido C, Saule S, Gospodarowicz D (1993): Transcriptional regulation of vascular endothelial growth factor gene expression in ovarian bovine granulose cells. Growth Factors 8:109-117.
14. Girsh E, Greber Y, Meidan R (1995): Luteotrophic and luteolytic interactions between bovine small and large luteal-like cells and endothelial cells. Biol Reprod 52:954-962.
15. Girsh E, Milvae RA, Wang W, Meidan R (1996): Effect of endothelin-1 on bovine luteal cell function: Role in prostaglandin $F_2\alpha$-induced antisteroidogenic action. Endocrinology 137:1306-1312.
16. Gobbetti A, Boiti C, Canali C, Zerani M (1999): Nitric oxide synthase acutely regulates progesterone production by *in vitro* cultured rabbit corpora lutea. J Endocrinol 160:275-283.
17. Goede V, Schmidt T, Kimmina S, Kozian D, Augustin HG (1998): Analysis of blood vessel maturation processes during cyclic ovarian angiogenesis. Lab Invest 78:1385-1394.
18. Hansel W, Blair R (1996): Bovine corpus luteum: a historic overview and implications for future research. Theriogenology 45:1267-1294.
19. Hansel W, Dowd JP (1986): New concepts of the control of corpus luteum function. J Reprod Fertil 78:755-768.
20. Horton EW, Currie WD, Poyser NL (1976): Uterine luteolystic hormone: Aphysiological role for prostaglandin $F_2\alpha$. Physiol Rev 56:595-651.
21. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G (1987): Endothelium-derived relaxing factor produced and released from artery and veins is nitric oxide. Proc Natl Acad Sci USA 84:9265-9269.
22. Jablonka-Shariff A, Olson LM (1997): Hormonal regulation of nitric oxide synthases and their cell-specific expression during follicular development in the rat ovary. Endocrinology 138:460-468.
23. Jaroszewski JJ, Hansel W (2000): Interaluteal administration of a nitric oxide synthase blocker stimulates progesterone, oxytocin secretion and prolongs the life span of the bovine corpus luteum. Proc Soc Exp Biol Med 224:50-55.
24. Jones LA, Anthony JP, Henriquez FL, Lyons RE, Nickdel MB, Carter KC, Alexander J, Roberts CW (2008): Toll-like receptor-4-mediated macrophage activation is differentially regulated byprogesterone via the glucocorticoid and progesterone receptors. Immunology 125:59-69.
25. Klipper E, Gilboa T, Levy N, Kisliouk T, Spanel-Borowski K, Meidan R (2004): Characterization of endothelin-1 and nitric oxide generation systems in corpus luteum-derived endothelial cells. Reproduction 128:463-473.
26. Knickerbocker JJ, Wiltbank MC, Niswender GD (1988): Mechanisms of luteolysis in domestic livestock. Domest Anim Endocrinol 5:91-107.
27. Kobayashi S, Miyamoto A, Berisha B, Schams D (2001): Growth hormone, but not luteinizing hormone, acts with luteal peptides on prostaglandin $F_2\alpha$ and progesterone secretion by bovine corpora lutea *in vitro*. Prostaglandins Lipid Mediat 63:79-92.
28. Korzekwa A, Jaroszewski JJ, Bogacki M, Deptula KM, Maslanka TS, Acosta TJ, Okuda K, Skarzynski DJ (2004): Effects of prostaglandin $F_2\alpha$ and nitric oxide on the secretory function of bovine luteal cells. J Reprod Dev 50:411-417.
29. Lee S, Acosta TJ, Nakagawa Y, Okuda K (2010): Role of nitric oxide in the regulation of superoxide dismutase and prostaglandin $F_2\alpha$ production in bovine luteal endothelial cells. J Reprod Dev 56:454-459.
30. Lee S, Acosta TJ, Yoshioka S, Okuda K (2009): Prostaglandin $F_2\alpha$ regulates the nitric oxide generating system in bovine luteal endothelial cells. J Reprod Dev 55:418-424.
31. Liebermann J, Schams D (1994): Actions of somatotrophin on oxytocin and progesterone release from the microdialysed bovine corpus luteum *in vitro*. J Endocrinol 143:243-250.
32. Mauluk R, Chen D, Greber Y, Davis JS, Meidan R (1998): Characterization of messenger ribonucleic acid expression for prostaglandin $F_2\alpha$ and luteinizing hormone receptors in various bovine luteal cell types. Biol Reprod 58:849-856.
33. McCracken JA, Custer EE, Lamsa JC (1999): Luteo-

lysis: a neuroendocrine-mediated event. Physiol Rev 79:263-323.
34. Meidan R, Levy N, Kisliou T, Podlovny L, Rusiansky M, Klipper E (2005): The yin and yang of corpus luteum-derived endothelial cells: Balancing life and death. Domest Anim Endocrinol 29:318-328.
35. Meidan R, Milvae RA, Weiss S, Levy N, Friedman A (1999): Intraovarian regulation of luteolysis. J Reprod Fertil 54:217-228.
36. Motta AB, Estevez A, de Gimeno MF (1999): the involvement of nitric oxide in corpus luteum regression in the rat: Feedback mechanism between prostaglandin F_2alpha and nitric oxide. Mol Hum Reprod 5:1011-1016.
37. Neuvians TP, Berisha B, Schams D (2004): VEGF and FGF expression during induced luteolysis in the bovine corpus luteum. Mol Reprod Dev 67:389-395.
38. Niswender GD, Nett TM (1988): The corpus luteum and its control. In Knobil E, Neill J (eds), The Physiology of Reproduction. Raven Press, New York pp. 489-525.
39. Niswender GD, Schwall RH, Fitz TA, Farin CE, Sawyer HR (1985): Regulation of luteal function in domestic ruminants: new concepts. Recent Prog Horm Res 41:101-151.
40. Okuda K, Uenoyma Y, Lee KW, Sakumoto R, Skarzynski DJ (1998): Progesterone stimulation by prostaglandin $F_2\alpha$ involves the protein kinase C pathway in cultured bovine luteal cells. J Reprod Dev 44:79-84.
41. O'Shea JD, Rodgers RJ, D'Occhio MJ (1989): Cellular composition of the cyclic corpus luteum of the cow. J Reprod Fertil 85:483-487.
42. Peltier M, Tee S, Smulian L (2006): Does progesterone lower innate immunity to pathogens associated with preterm birth? Am J Obstet Gynecol 195:S69.
43. Repasi A, Beckers JF, Sulon J, Karen A, Reiczigel J, Szenci O (2005): Effect of the type and number of prostaglandin treatments on corpus luteum, the largest follicle and progesterone concentration in dairy cows. Reprod Domest Anim 40:436-442.
44. Reynolds LP, Redmer DA (1998): Expression of the angiogenic factors, basic fibroblast growth factor and vascular endothelial growth factor in the ovary. J Anim Sci 76:1671-1681.
45. Rizzo A, Roscino MT, Minoia G, Trisolini C, Spedicato M, Mutinati M, Pantaleo M, Jirillo F, Sciorsci RL (2009): Serum levels of reactive oxygen species (ROS) in the bitch. Immunopharmacol Immunotoxicol 31:310-313.
46. Schams D, Berisha B (2001): Regulatory factors for luteolysis in ruminants. Arch Tierz 44:51-53.
47. Schams D, Berisha B (2002): Angiogenic factors (VEGF, FGF and IGF) in the bovine corpus luteum. J Reprod Dev 48:233-242.
48. Schams D, Berisha B (2004): Regulation of corpus luteum function in cattle - an overview. Reprod Dom Anim 39:241-251.
49. Shirasuna K, Watanabe S, Asahi T, Wijayagunawardane MPB, Sasahara K, Jiang C, Matsui M, Sasaki M, Shimizu T, Davis JS, Miyamoto A (2008): Prostaglandin $F_2\alpha$ increases endothelial nitric oxide synthase in the periphery of the bovine corpus luteum: the possible regulation of blood flow at an early stage of luteolysis. Reproduction 135:527-539.
50. Silvia WJ, Lewis GS, McCracken JA, Thatcher WW, Wilson L Jr (1991): Hormonal regulation of uterine secretion of prostaglandin $F_2\alpha$ during luteolysis in ruminants. Biol Reprod 45:655-663.
51. Skarzynski DJ, Jaroszewski JJ, Bah MM, Deptula KM, Barszczewska B, Gawronska B, Hansel W (2003): Administration of a nitric oxide synthase inhibitor counteracts prostaglandin $F_2\alpha$-induced luteolysis in cattle. Biol Reprod 68:1674-1681.
52. Skarzynski DJ, Okuda K (2000): Different actions of noradrenaline and nitric oxide on the output of prostaglandins and progesterone in cultured bovine luteal cells. Prostaglandins Other Lipid Mediat 60: 35-47.
53. Smith ST, Ward WR, Dobson H (1998): Use of ultrasonography to help to predict observed oestrus in dairy cows after the administration of prostaglandin $F_2\alpha$. Vet Rec 142:271-274.
54. Stuehr DJ, Marletta MA (1985): Mammalian nitrate biosynthesis: mouse macrophages produce nitrite and nitrate in response to *Escherichia coli* lipopolysaccharide. Proc Natl Acad Sci USA 82:7738-7742.
55. Sugino N (2006): Roles of reactive oxygen species in the corpus luteum. Anim Sci J 77:556-565.
56. Vandehaar MJ, Sharma BK, Fogwell RL (1995): Effect of dietary energy restriction on the expression of insulin-like growth factor-I in liver and corpus luteum of heifers. J Dairy Sci 78:832-841.
57. Van Voorhis BJ, Dunn MS, Snyder GD, Weiner CP (1994): Nitric oxide: an autocrine regulator of human granulose-luteal cell steroidogenesis. Endocrinology 135:1799-1806.
58. Vega M, Johnson MC, Diaz HA, Urrutia LR, Troncoso JL, Devoto L (1998): Regulation of human luteal steroidogenesis *in vitro* by nitric oxide. Endocrine 8:185-191.
59. Wenzinger B, Bleul U (2012): Effect of a prostaglandin $F_2\alpha$ analogue on the cyclic corpus luteum during its refractory period in cow. BMC Vet Res 8: 220-224.
60. Woad KJ, Baxter G, Hogg CO, Bramley TA, Webb

R, Armstrong DG (2000): Expression of mRNA encoding insulin-like growth factors I and II and the type 1 IGF receptor in the bovine corpus luteum at defined stages of the oestrous cycle. J Reprod Fertil 120:L293-302.

61. Yancopoulos GD, Davis S, Gale NW, Rudge JS, Wiegand SJ, Holash J (2000): Vascular-specific growth factors and blood vessel formation. Nature 407:242-248.

(Received: December 9 2014/ Accepted: January 10 2015)