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Acute Changes in the Concentrations of Prostaglandin F2α (PGF) and Cortisol in Uterine and Ovarian Venous Blood During PGF-induced Luteolysis in Cows

HT Duong[1], HV Vu[1], MM Bah[2], I Woclawek-Potocka[2], TV Dam[3], DJ Skarzynski[2], K Okuda[1] and TJ Acosta[1]

[1]*Laboratory of Reproductive Physiology, Graduate School of Natural Science and Technology, Okayama University, Okayama, Japan;* [2]*Department of Reproductive Immunology and Pathology, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland;* [3]*Faculty of Animal Science, Hue University of Agriculture and Forestry, Phung Hung, Hue, Vietnam*

Contents

Prostaglandin F2α (PGF) is considered to be the main luteolysin in cattle. We have previously demonstrated that cortisol (Cr) suppresses PGF production in non-pregnant bovine endometrium. This study was carried out to test whether exogenous PGF increases ovarian and/or uterine PGF production and to determine the temporal relationship between PGF and Cr in ovarian and uterine circulations during PGF-induced luteolysis in cows. Catheters were inserted into the ovarian vein (OV), uterine vein (UV) and jugular vein (JV) of 10 cows on Day 9 of the oestrous cycle (Ovulation = Day 0) for frequent blood collection. On Day 10, the cows were divided randomly into two groups and treated with a luteolytic dose of a PGF analogue (cloprostenol) or saline solution. Blood samples were collected at −0.25, 0, 0.25, 0.5, 1 and 2 h and then at 2-h intervals until 12 h after treatment (0 h). The basal concentrations of PGF and Cr in OV and UV plasma were not significantly different. Injection of a PGF analogue induced more than twofold increases in the levels of PGF between 0.25 and 1 h in UV plasma, but not in OV plasma. PGF increased ($p < 0.05$) the concentrations of Cr in OV, UV and JV plasma between 0.5 and 1 h. The Cr levels in OV, UV and JV plasma were similar. The PGF levels in UV plasma decreased after Cr reached its highest levels. The overall results suggest that the uterus rather than the ovary increases PGF production in response to PGF injection. Based on the temporal changes of PGF and Cr in the ovarian and uterine circulations, Cr may act to reduce uterine PGF production in non-pregnant cows *in vivo*.

Introduction

In ruminants, PGF is a hormone synthesized and secreted from the uterus (Kim and Fortier 1995; McCracken et al. 1999; Skarzynski et al. 2000). This hormone is involved in the control of the oestrous cycle, ovulation and regression of the corpus luteum (CL) (Poyser 1995; Dubois et al. 1998). In non-pregnant cows, the uterus increases PGF production on Day 17 post-ovulation (Wolfenson et al. 1985). Uterine PGF is transported to the ovary by a countercurrent transfer mechanism (McCracken et al. 1972), which is facilitated by a prostaglandin transporter-mediated mechanism (Lee et al. 2010) to induce the regression of the CL (McCracken et al. 1972; Inskeep and Murdoch 1980).

Cortisol (Cr) is a steroid hormone produced by the adrenal cortex. Cr has been shown to be involved in the regulation of endometrial production of PGF in cattle (Lee et al. 2007). Interestingly, a recent study using cultured bovine endometrial stromal cells demonstrated that PGF increases the expression and enzymatic activity of 11β-hydroxysteroid dehydrogenase 1 (HSD11B1), which converts inactive cortisone to active cortisol (Lee et al. 2009). On the other hand, Cr suppresses PGF production in non-pregnant bovine endometrial stromal cells (Lee et al. 2007). These findings suggest that Cr has a role in regulating uterine PGF production and that a dynamic interrelationship between uterine Cr and PGF exists in bovine endometrium. However, the temporal interrelationship between PGF and Cr in the ovarian and uterine circulations of non-pregnant bovine *in vivo* around the time of luteolysis remains unknown.

Prostaglandin F2α treatment has been shown to increase luteal production of PGF in ruminants *in vitro* (Tsai and Wiltbank 1997). More recent studies have suggested that endometrial/extraluteal PGF triggers intraluteal production of PGF, which induces PGF production in luteal cells by an auto/paracrine action in the regressing CL (Tsai and Wiltbank 1997; Hayashi et al. 2003). Based on the changes in the circulating levels of PGF metabolite, Kotwica et al. (1999) suggested that injection of PGF analogue stimulates the secretion of endogenous PGF from the uterus in cattle. Moreover, PGF could regulate cyclooxygenase 2 (COX-2) expression in an autocrine/paracrine manner to establish a positive feedback system for regulating endometrial tumourigenesis (Jabbour et al. 2005). However, it remains unclear whether exogenous PGF mainly affects uterine and/or ovarian PGF production during the time of luteolysis in cow.

After PGF is released into the circulation, it is rapidly metabolized in the lung, liver and kidney to 13, 14-dihydro-15-keto-prostaglandin F2α (PGFM) (Granstrom and Kindahl 1982; Goff et al. 1984) by the enzyme 15-hydroxy prostaglandin dehydrogenase (Keirse and Turnbull 1975). In cattle, peaks of major pulses of PGF and PGFM during luteolysis occurred concomitantly, based on sampling at 4-h intervals. Therefore, PGFM is often measured to examine the circulating systemic concentrations of PGF (Ginther et al. 2009). However, there is no *in vivo* information available so far on the real-time changes in the concentrations of PGF in the blood plasma collected directly from the uterine vein (UV) and ovarian vein (OV) during PGF-induced luteolysis in cattle.

This study was carried out to test whether exogenous PGF increases ovarian and/or uterine PGF production and to determine the temporal relationship between PGF and Cr in ovarian and uterine circulations during PGF-induced luteolysis in cows.

Materials and methods

All procedures were approved by the Local Animal Care and Use Committee in Olsztyn, Poland (Agreement No. 31/2006/N and 06/2007/N). The experimental animals were conducted at the Faculty of Veterinary Medicine, University of Warmia and Mazury, Olsztyn, Poland.

Animals and surgical procedures

Healthy, normally cycling Polish Holstein Black and White cows were used for this studies. The animals were culled by their owners (Spolka Rolna 'Wroblik', Lidzbark Warminski, and Gospoka Rolne 'Farmer', Zalesie, Szczytno, Poland) from dairy cows herds because of low milk production. Oestrus was synchronized in the cows using implants of a progesterone (P4) analogue (Crestar: Intervet, International B.V. Boxmeer, Holland) with additional intramuscular (i.m.) injection of an analogue of PGF (Cloprostenol; Bioestrophan, Biowet, Gorzow Wielkopolski, Poland), as recommended by the manufacturer for oestrous synchronization of multiparous cows and described previously (Bah et al. 2006). Oestrus was determined by observing external signs (i.e. vaginal mucus, standing behaviour). Before surgery, the ovaries were examined daily by ultrasonography to determine the day and side of ovulation and CL development. The presence of a pre-ovulatory follicle, ovulation and normal CL development were confirmed by a veterinarian using a sectorial rectal probe connected to an ultrasound (Dranminski Animal Profi Scanner, Draminski Electronics in Agriculture, Olsztyn, Poland). The day of ovulation was defined as Day 0 of the oestrous cycle.

The cows were premedicated with an i.m. injection of xylazine at a dose of 25–30 mg per cow (Sedanzin; Biolwet, Pulawy, Poland). Local anaesthesia was induced by s.c. and i.m. injections of 2% procaine hydrochloride (Polocainum Hydrochloricum; Biowet, Drwelew, Poland) in the paralumbar fossa of the side of the CL. On Day 9, catheters (Medicut Catheter Kit; Argyle, Japan Sherwood, Tokyo, Japan) were inserted into the OV, UV and jugular vein (JV) in 10 cows for frequent blood collection. A lateral laparotomy was performed for cannulation of the ovarian and uterine vein. At surgery, 18-gauge catheters were inserted into the ovarian and the uterine vein ipsilateral to the functional CL and fixed to the surrounding connective tissue (Acosta et al. 2000). After surgery, the cows were moved to a barn, where they were fed with grass hay twice daily and were given free access to water. On Day 10, the cows were divided randomly into two groups (n = 5 cows/group). The animals in the first group received an i.m. injection of a luteolytic dose of 500 μg of cloprostenol (Estrumate; Mallinckrodt Burgwedel, Germany), a PGF analogue to induce luteolysis, whereas the second group received an i.m. injection of 5 ml of normal saline solution. Blood samples were simultaneously collected from OV, UV and JV at −0.25, 0, 0.25, 0.5, 1 and 2 h and then at 2 h intervals until 12 h after PGF injection. The time of PGF or saline injection on Day 10 of the cycle was defined as 0 h.

For P4, PGF and Cr measurements, blood samples were collected into sterile 10-ml tubes containing 200 μl of a stabiliser solution (0.3 M EDTA, 1% acid acetyl salicylic, pH 7.4). All tubes were immediately chilled on ice for 10 min, centrifuged at $2000 \times g$ for 10 min at 4°C, and the obtained plasma was stored at −30°C until further analysis.

Progesterone determination

The progesterone concentrations in the plasma samples were assayed using a direct enzyme immunoassay (EIA) as described previously (Piotrowska et al. 2006). The P4 standard curve ranged from 0.05 to 25 ng/ml, and the median effective dose (ED_{50}) of the assay was 2.56 ng/ml. The average intra- and interassay coefficients of variation (CVs) were 4.7% and 6.5%, respectively.

Prostaglandin F2α determination

The concentrations of PGF in the plasma were determined directly with a double-antibody enzyme immunoassay as described previously (Skarzynski and Okuda 2000) using horseradish peroxidase enzyme-labelled PGF as a tracer (1: 75 000 final dilutions) and PGF antibody (kindly donated by Dr Seiji Ito of Kansai Medical University, Osaka, Japan; 1: 100 000 final dilutions). The cross-reactivity of PGF first antibody with cloprostenol injected to induce luteolysis and with PGFM at 50% binding was 0.95% and 0.1%, respectively. The samples (uterine and ovarian venous blood plasma) for the PGF assay were diluted 10 times with EIA assay buffer. The standard curve ranged from 15.6 to 4000 pg/ml, and the ED_{50} of the assay was 400 pg/ml. The intra- and inter-assay CVs were 7.34% and 13.16%, respectively.

Cortisol determination

The concentrations of Cr in the plasma were determined in duplicate after diethyl ether extraction by second antibody EIA as described previously (Acosta et al. 2002), using horseradish peroxidase enzyme-labelled Cr as a tracer (1: 400 000 final dilutions) and Cr antibody (raised in a rabbit against cortisol −3 – CMO; Cosmo Bio Co., Tokyo, Japan; 1 : 80 000 final dilutions). Each plasma sample (200 μl) was extracted by diethyl ether as described previously (Acosta et al. 2000). The residue was evaporated and then dissolved in 200 μl assay buffer (40 mM PBS 0.1% BSA, pH 7.2). To estimate the recovery rate, Cr was added to plasma (1 ng/ml), and the obtained values were on average 75% (n = 5). The standard curve ranged from 0.4 to 400 ng/ml, and the ED_{50} of the assay was 1.6 ng/ml. The intra- and inter-assay CVs were on average 5.4% and 6%, respectively.

Statistical analysis

Experimental data are shown as the mean ± SEM of values obtained from five PGF-treated and five saline-treated cows. The concentrations of PGF and Cr in the blood collected at −0.25 and 0 h were used to calculate

the individual baseline. The statistical significance of differences of P4, PGF and Cr in OV, UV and JV blood plasma between pre- and post-PGF injection period and between OV, UV and JV was assessed by analysis of variance (ANOVA) using GRAPHPAD PRISM version 5.00; San Diego, CA, USA, followed by protected least significant difference (PLSD) as a multiple comparison test. Differences were considered significant when the probability was $<5\%$ ($p < 0.05$).

Results

Effect of an injection of a prostaglandin F2α analogue on the plasma concentrations of progesterone in ovarian venous blood

An injection of a luteolytic dose of PGF induced a significant ($p < 0.05$) decrease in the plasma concentrations of P4 in OV plasma at 2 h, indicating functional luteolysis, as expected (Fig. 1).

Effect of an injection of a prostaglandin F2α analogue on the plasma concentrations of PGF in the ovarian and uterine venous blood

On day 10 of the oestrous cycle, the basal concentrations of PGF in OV plasma were not significantly different from those in UV plasma (Fig. 2). An injection of a luteolytic dose of PGF induced a transient increase in PGF concentrations ($p < 0.05$) in UV blood plasma between 0.25 and 1 h, but not in OV blood plasma (Fig. 2).

Effect of an injection of a prostaglandin F2α analogue on the plasma concentrations of cortisol in the ovarian, uterine and jugular venous blood

On day 10 of the oestrous cycle, the basal concentrations of Cr in OV, UV and JV blood plasma were similar

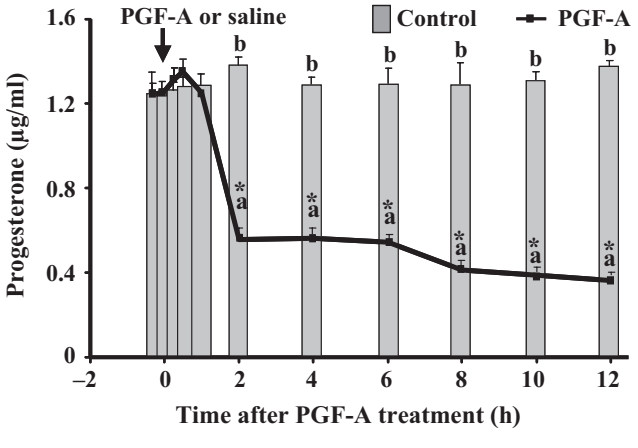

Fig. 1. Concentrations of progesterone (P4) in blood plasma collected from the ovarian vein. Cows were treated intramuscularly with cloprostenol, a prostaglandin F2α analogue (PGF-A, n = 5) or saline solution (Control, n = 5) on Day 10 of the oestrous cycle. Asterisks indicate significant differences ($p < 0.05$) compared with the baseline (pretreatment period). Different superscript letters indicate significant differences ($p < 0.05$) between the cow treated with PGF-A and control groups as assessed by ANOVA followed by protected least significant difference test (PLSD)

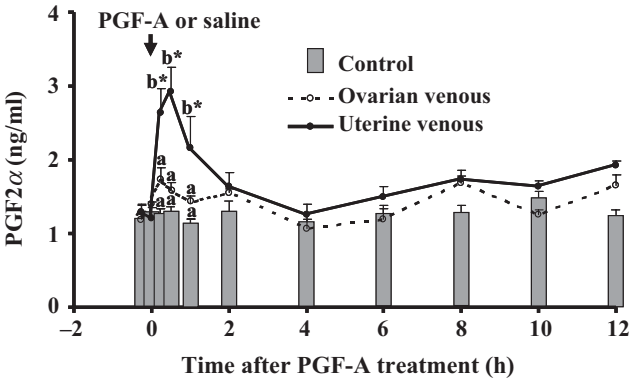

Fig. 2. Concentrations of prostaglandin F2α (PGF2α) in uterine venous blood plasma of saline-treated group (Control), in ovarian and uterine venous blood plasma of cow treated with cloprostenol, a prostaglandin F2α analogue (PGF-A) group. Data are the mean ± SEM for five samples/time-point. Asterisks indicate significant difference ($p < 0.05$) compared with the baseline (before PGF-A or saline injection). Different superscript letters indicate significant differences ($p < 0.05$) between uterine and ovarian venous blood plasma of cow treated with PGF-A group, or between uterine venous blood plasma of cow treated with PGF-A and control groups. Bars show PGF concentration in uterine venous blood of the saline-treated group (n = 5), as determined by ANOVA followed by protected least significant difference test (PLSD)

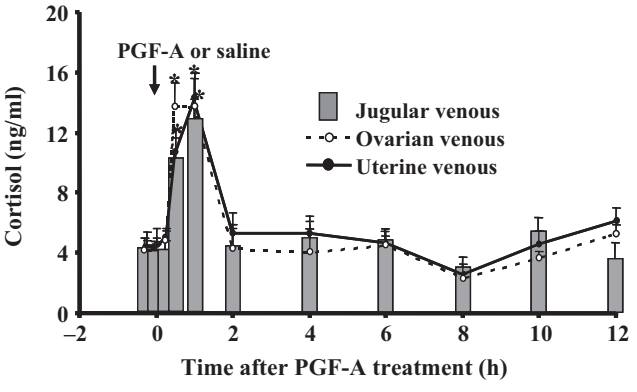

Fig. 3. Concentrations of cortisol (Cr) in jugular, ovarian and uterine venous blood plasma of cows treated with cloprostenol, a prostaglandin F2α analogue (PGF-A). Data are the mean ± SEM for five samples/time-point. Asterisks indicate significant difference ($p < 0.05$) in Cr concentrations compared with the baseline (before PGF or saline injection), as determined by ANOVA followed by protected least significant difference test (PLSD)

Table 1. Acute changes in the concentrations of prostaglandin F2α (PGF) and cortisol (Cr) in uterine venous (UV) and ovarian venous (OV) blood plasma during PGF-induced luteolysis in cows

		Time after prostaglandin F2α injection				
		0 h	0.25 h	0.5 h	1 h	2 h
PGF (ng/ml)	OV	1.4 ± 0.2	1.7 ± 0.2	1.6 ± 0.1	1.4 ± 0.1	1.6 ± 0.3
	UV	1.2 ± 0.2^a	2.6 ± 0.6^b	2.9 ± 0.9^b	2.2 ± 0.4^b	1.6 ± 0.1^a
Cr (ng/ml)	OV	4.2 ± 1.4^a	5.0 ± 0.5^a	13.7 ± 2.6^b	13.6 ± 2.0^b	4.2 ± 1.4^a
	UV	4.4 ± 0.6^a	5.1 ± 0.6^a	10.6 ± 2.1^b	14.1 ± 3.0^b	5.3 ± 1.4^a

Data are the mean ± SEM for five samples/time-point. Different letters indicate significantly different value ($p < 0.05$) in Cr and PGF concentrations among time-points related to PGF injection, as determined by ANOVA followed by protected least significant difference test (PLSD).

(Fig. 3). An injection of a PGF analogue induced an acute increase ($p < 0.05$) in the concentrations of Cr in ovarian, uterine and jugular venous blood plasma between 0.5 and 1 h (Fig. 3). The plasma concentrations of Cr in OV, UV and JV were not significantly different.

The increases in concentrations of Cr in OV, UV and JV blood plasma occurred after the increase in the levels of PGF in UV blood plasma. In addition, the levels of PGF in UV blood plasma decreased after Cr reached its highest levels (Table 1).

Discussion

In cattle, injection of a luteolytic dose of PGF analogue induces luteolysis which is characterized by a decrease in the circulating levels of P4 and a concomitant increase in the levels of PGFM in the jugular venous plasma (Kotwica et al. 1999; Ginther et al. 2009). It is well known that the bovine uterus and ovary both have the capacity to produce PGF (Wiltbank and Ottobre 2003; Arosh et al. 2004). However, it had been unclear whether exogenous PGF affects uterine and/or ovarian PGF production. In the present study, the injection of a PGF analogue induced a significant increase in the levels of PGF in UV plasma within 1 h, whereas the increase in the levels of PGF in OV plasma was not statistically significant. These results suggest that there is an increase in the luteal production of PGF, but the response to an intramuscular injection of PGF analogue is not as great as the observed in UV blood plasma. A recent *in vitro* study also demonstrated that bovine endometrium increases PGF production in response to PGF treatment and that the strongest stimulatory effect of PGF was observed between Days 15 and 17 of the oestrous cycle (Tasaki et al. 2010). These results imply that exogenous PGF increases uterine PGF production and that the endometrium becomes more responsive to PGF at the time of luteolysis.

A study using a micro dialysis system demonstrated that administration of a PGF analogue induces an acute increase in intraluteal PGF secretion during the first 4 h post-treatment (Hayashi et al. 2003). The same study demonstrated that injection of a PGF analogue (Cloprostenol) did not induce a significant increase in PGF levels in OV plasma up to 24 h after treatment, in agreement with the present results. Furthermore, PGF has the ability to activate PGF production within the CL of ewes and cows (Wiltbank and Ottobre 2003; Arosh et al. 2004). These results indicate that the acute increase in the intraluteal production of PGF is not reflected in the profiles of PGF in OV plasma.

Previous *in vitro* studies showed that PGF increases the levels of Cr in cultured bovine adrenocortical cells (Wang et al. 2000) and the conversion of cortisone to cortisol by stimulating HSD11B1 in non-pregnant bovine endometrium (Lee et al. 2009). *In vivo* studies demonstrated that a luteolytic dose of PGF analogue induced an increase in the levels of Cr in the JV blood plasma (Baishya et al. 1994; Shrestha et al. 2010). These findings suggest that PGF has the capacity to stimulate Cr *in vitro* and *in vivo*. Moreover, it has been shown that bovine endometrium (Lee et al. 2007) and corpus luteum tissues (Komiyama et al. 2008) have the capacity to convert cortisone to cortisol. It is of interest to know whether the increase in the levels of Cr in blood plasma collected from the JV, reported by Baishya et al. (1994) and Shrestha et al. (2010), is Cr secreted from the adrenal cortex or converted from cortisone by the ovary or uterus. In the present study, injection of a PGF analogue increased the levels of Cr in ovarian, uterine and jugular venous blood circulation. However, we did not find any significant difference in the levels of Cr among OV, UV and JV blood plasma. These results suggest that PGF stimulates Cr release from the adrenal cortex and that the amount of Cr converted from cortisone by the ovary and uterus is not enough to affect circulating levels of Cr. A recent study demonstrated that PGF stimulates cortisol conversion from cortisone by increasing 11β HSD activity in endometrial tissue and cultured stromal cells (Lee et al. 2009). It is also possible that PGF increases the capacity to convert cortisone to cortisol in other tissues including endothelial cells, making this effect systemic.

It has been demonstrated that PGF is secreted from the uterus in pulses during luteolysis in cattle (Mann and Lamming 2006). The sequential PGF pulses are required to induce natural luteolysis in cattle (Ginther et al. 2009). Although PGF increases Cr levels in JV blood plasma, it is not known how PGF and Cr in ovarian and uterine circulation change with time *in vivo*. Our previous *in vitro* results showed that Cr has the capacity to reduce basal and tumour necrosis factor α-stimulated PGF production in stromal cells of non-pregnant bovine endometrium (Lee et al. 2007). It has been shown that glucocorticoids inhibit PG synthesis by inhibiting the expression of cytosolic phospholipase A2 that converts phospholipids to arachidonic acid (AA) (Newton et al. 1997), the primary precursor of PGF as well as that of COX-2, the enzyme that converts AA to PGH2 (Xue et al. 1996; Rhen and Cidlowski 2005) in most tissues of the body. In the present study, the levels of Cr in OV, UV and JV blood plasma increased immediately after the rise of PGF in UV blood plasma. Interestingly, the present results also showed that the levels of PGF in UV blood plasma decreased after Cr reached its highest levels. These results suggest that Cr inhibits uterine PGF production within a short time period. Thus, Cr may act in reducing the high levels of uterine PGF and may be one of the factors responsible for the generation of PGF pulses in cattle.

In conclusion, exogenous PGF increases uterine PGF production rather than ovarian PGF production. Based on the temporal changes of PGF and Cr in ovarian and uterine circulations, Cr may act to reduce uterine PGF production in non-pregnant cows *in vivo*.

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Conflict of interest

None of the authors have any conflict of interest to declare.

Author contributions

HT Duong-designed study, performed experiments, analysed results, drafted paper; HV Vu-analysed results; MM Bah-designed study, performed surgery; I Woclawek-Potocka-performed experiments, analysed results; TV Dam-reviewed results; DJ Skarzynski-designed study, reviewed results; K Okuda-reviewed manuscript; TJ Acosta-designed study, performed surgery, reviewed paper. All authors have approved the final article.

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Author's address (for correspondence): Tomas J. Acosta, Laboratory of Reproductive Physiology, Graduate School of Natural Science and Technology, Okayama University, Tsushima Naka, Kita-ku 1-1-1, Okayama 700-8530, Japan.
E-mail: acosta@cc.okayama-u.ac.jp