ACTA VET. BRNO 2010, 79: 249-259; doi:10.2754/avb201079020249

Participation of Prostaglandin E_2 in Contractile Activity of Inflamed Porcine Uterus

Barbara Jana[1], Jerzy Jaroszewski[2], Jan Kucharski[1], Marlena Koszykowska[1], Jolanta Górska[1], Włodzimierz Markiewicz[2]

[1]Division of Reproductive Endocrinology and Pathophysiology, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland
[2]Division of Pharmacology, Department of Pathology and Pharmacology, Faculty of Veterinary Medicine, University of Warmia and Mazury, Olsztyn, Poland

Received February 10, 2009
Accepted December 3, 2009

Abstract

The aim of our study was to estimate the participation of prostaglandin E_2 (PGE_2) in the contractile activity of inflamed porcine uterus. On day 3 of the oestrous cycle, 50 ml of saline or 50 ml of *Escherichia coli* suspension, containing 10^9 colony-forming units/ml, was injected into each uterine horn in the control or experimental group, respectively. Seven days later the uteri were collected. Endometritis developed in all bacteria-inoculated gilts. Endometrium/myometrium and myometrium strips were incubated with PGE_2 alone or together with PGE_2 receptor (EP) subtypes (EP_2, EP_4, EP_1 and EP_3) blockers: AH 6809 (BEP_2), ONO-AE_2 (BEP_4), ONO-AE_3-240 (BEP_1) and SC19220 (BEP_3), respectively. In the control group, PGE_2 (10^{-8} and 10^{-7} M) increased the intensity of contractions in endometrium/myometrium, and at the higher dose in myometrium. PGE_2 (10^{-8} M) decreased the contraction intensity of the strips from inflamed uteri. After the use of BEP_2, PGE_2 (10^{-7} M) increased the values of this indicator in endometrium/myometrium and myometrium from the control gilts. In these animals, PGE_2 (10^{-8} M) in the presence of BEP_4 reduced the contraction intensity in endometrium/myometrium. In the bacterial group, PGE_2 (10^{-8} M) in the presence of BEP_2 and BEP_4 enhanced the intensity of contractions in myometrium. Similar reaction was evoked by PGE_2 (10^{-7} M) in endometrium/myometrium of the inflamed uteri in the presence of BEP_4. The intensity of contractions in myometrium from the inflamed uteri significantly decreased after the use of BEP_1 and PGE_2 (10^{-7} M). PGE_2 (10^{-7} M) administered after BEP_3, significantly decreased the intensity of contractions in myometrium of the control gilts. These results show that PGE_2 decreases the contraction intensity of inflamed porcine uteri. Further studies are needed to closely determine the role of PGE_2 and other prostanoids in the contractile activity of inflamed uterine tissue.

Contractile activity, uterus, endometritis, PGE_2, PGE_2 - antagonists, gilts

Endometritis is a common reproductive disorder in female domestic animals with consequences ranging from no effect on reproductive performance to permanent sterility. This pathological state can occur in female domestic animals after parturition as well as in animals that have not yet given birth, following artificial insemination or natural mating. It has been reported that a wide range of bacteria, mainly *Escherichia coli (E. coli), Staphylococcus* spp., *Streptococcus* spp., and in some cases *Actinomyces pyogenes, Pasteurella multocida* and *Klebsiella pneumoniae,* were isolated from uteri of sows with and without endometritis (De Winter et al. 1995; Aas et al. 1998). After labour, the uterine cavity is a target for bacterial flora characteristic of the environment in which the parturition takes place. Microorganisms from the uterus are removed with lochia in a mechanical manner (uterine involution) and/or eliminated by the immune system cells – both occurring simultaneously. However, an impairment of uterine involution and/or immunological response leads to intensive proliferation of microorganisms and consequently to the development of endometritis (Mateus et al. 2003). In the midst of endometritis we can differentiate states of mild progress and those with mucopurulent discharge from uterus and/or pyometra. Cases of endometritis with a mild course cause

Address for correspondence:
Dr. Barbara Jana
Division of Reproductive Endocrinology and Pathophysiology
Institute of Animal Reproduction and Food Research, Polish Academy of Sciences
Tuwima 10, 10-747 Olsztyn, Poland
Phone: +48 (89) 539-31-40
Fax: +48 (89) 535-74-21
E-mail: baja@pan.olsztyn.pl
http://www.vfu.cz/acta-vet/actavet.htm

no serious disturbances of the oestrous cycle. The oestrus in these animals comes in time or with a small delay and the percentage of pregnant females is high. In endometritis with a severe progress, the uterus is filled with mucopurulent secretion and protrudes into the abdominal cavity. In these animals, particularly in cows, the uterine muscular layer is devoid of the ability to contract. In such events, intensive therapy is not always successful. The main cause of these failures is loss of the contraction ability of the uterine muscular layer (Olson et al. 1984; Hussain 1989; Hussain and Daniel 1992; De Winter et al. 1995; Ramadan et al. 1997).

Endometritis generates a considerable increase in the production of prostaglandins (PGs) in uterine tissues. It was indicated that lipopolysaccharide (LPS) released by Gram-negative bacteria in inflamed uterus plays a significant role in the increase of PG synthesis. It has been reported that intrauterine infusions of LPS in postpartum cows and spontaneous or experimental bacterial infections of uteri in heifers and mares increased the concentration of a plasma PGF_2a metabolite, 13,14-dihydro-15-keto-prostaglandin F_2a (PGFM; Neely et al. 1979; Stabenfeldt et al. 1981; Peter and Bosu 1987; Peter et al. 1990). High concentration of PGF_2a even in serious endometritis conditions should cause normal uterine involution and cleaning of the inflammatory exudate from the uterus. During uterus inflammation, in addition to an increase of PGF_2a, concentrations of PGE_2 and PGI_2 also considerably increased (Mateus et al. 2003; Myatt and Lye 2004; Jana et al. 2007). The high PGE_2 and PGI_2 concentrations in inflamed uterus probably inhibit or delimit the contractile activity of PGF_2a in this organ. PGE_2 also has been reported to cause contraction of the uterine muscular layer through two subtypes of PGE_2 receptors (EP): EP_1 and EP_3 and relaxation through other two receptors: EP_2 and EP_4 (Myatt and Lye 2004). We previously reported that PGF_2a may affect the contractile activity of the intact and inflamed uteri through the PGE_2 receptors (Kucharski et al. 2007).

These findings lead us to hypothesize that in the inflamed uterus, PGE_2 may have predominant diastolic activity. To the best of our knowledge, no information is available on the contractile activity of this PG in the inflamed uterus. Therefore, the purpose of the present study was to determine the influence of PGE_2 on the contractile activity of intact and inflamed uteri of gilts. We determined the effect of PGE_2 on the intensity and frequency of the contractions of strips of endometrium/myometrium and myometrium, and the effect of PGE_2 on these indicators in the presence of PGE_2 receptor antagonists.

Materials and Methods

Twelve crossbred gilts (Large White × Landrace) of similar age (7-8 months) and body mass (BM, 100-120 kg) with two controlled subsequent oestrous cycles were used. Oestrous behaviour was detected using the boar-tester. The animals originated from a herd with no abnormal discharge or fertility disorders. The gilts were individually housed in stalls under natural light and temperature conditions. They were fed a commercial grain mixture and tap water *ad libitum*. We followed the principles of animal care (NIH publication No 86-23, revised in 1985) as well as the specific national law on animal protection. The experimental procedures were approved by the Local Ethics Committee, University of Warmia and Mazury in Olsztyn (Agreement No 20/N).

On day 3 of the oestrous cycle (day 0 of the study), the gilts were randomly assigned to one of two groups: group I, control gilts receiving saline (n = 6), and group II, treated with *E. coli* (n = 6). In all the gilts median laparotomy was performed under general anaesthesia induced by azaperone (1 ml/10 kg of body weight; Stresnil Janssen Pharmaceutica, Belgium) and sodium pentobarbital (30-40 ml/100 kg of body weight; Vetbutal, Biowet, Poland). Next, in the animals of group I, 50 ml of saline were injected into each uterine horn (10 ml in five places). Group II received similarly 50 ml of *E. coli* (strain O25:K23/a/:H1; National Veterinary Research Institute, Department of Microbiology, Puławy, Poland) suspension containing 10^9 colony-forming units (cfu)/ml at the same time. In addition, in order to evenly distribute either saline or bacterial suspension within the uterine horn, both horns were carefully massaged. The gilts were not treated with antibiotics during the whole period of the study. The animals were slaughtered seven days after treatment (expected day 10 of the oestrous cycle) and the uteri were collected. Next, the uterine horns were intersected and their macroscopic examination was performed. Fragments of the uterine horns, collected from the middle part of the horns, were transferred to ice and transported to the laboratory within 20 min and immediately processed for examination of contractile activity.

From fragments of the uterine walls two kinds of strips (3 × 5 mm) were prepared: endometrium with myometrium (ENDO/MYO), and myometrium (MYO). The strips were washed in saline and mounted between two stainless steel hooks in 5 ml organ bath (Schuler Organ bath type 809; Hugo Sachs Electronic, Germany) under conditions of resting tension of 5 mN. The strips were kept in Krebs-Ringer solution of the following composition (mM/l): NaCl, 120.3; KCl, 5.9; $CaCl_2$, 2.5; MCl_2, 1.2; $NaHCO_3$, 15.5; glucose, 11.5; and pH 7.4. The solution was maintained at 37 °C and continuously saturated with a mixture 95% O_2 and 5% CO_2. After equilibration the contractile activity of the strips was recorded for at least 60 min. Contraction intensity and frequency of the uterine tissues were measured using a Hugo Sachs Electronic force displacement transducer (HSE F30 type 372), and recorded with HSE-ACADW software for Windows 2000 (Germany). At the beginning of the experiment the strips were incubated with noradrenaline (NA, Polfa, Poland) at doses of 10^{-7} and 10^{-6} M as well as with acetylcholine (ACh, Sigma) at doses of 10^{-5}, 10^{-4} and 10^{-3} M, to determine the viability of tissues and their usefulness to further study. Next, the effect of increasing (10^{-8} and 10^{-7} M) doses of PGE_2 (Sigma) on the contractile activity was studied. The effect of each dose of examined substances was recorded for 7 min. Additionally, the effect of PGE_2 on the contractile activity of uterus was examined in the presence of PGE_2 receptor (EP_4, EP_2, EP_1 and EP_3) antagonists. Before administration of PGE_2 uterine tissues were incubated for 2 min with following receptor antagonists: ONO-AE_2 (Sigma) - BEP_4; AH 6809 (Cayman Chemical, USA) - BEP_2; ONO-AE_3-240 (Sigma) - BEP_1 and SC19220 (Sigma) - BEP_3. BEP_4, BEP_2 and BEP_1 were used at a dose of 10^{-6} M and BEP_3 at a dose of 10^{-7} M. After 2 min incubation of the tissue with antagonists, PGE_2 was added at doses of 10^{-8} and 10^{-7} M. The time of PGE_2 influence lasted 7 min. After the end of every measurement the tissues were washed three times in 15 ml of phosphate buffer at 10 min intervals. In the end, to determine the viability of tissues NA and ACh were administered at doses given above. In the statistical analysis only those results were considered, for which the difference in response to the stimulation by NA and ACh at the beginning and end of the study was lower than 20%.

The numerical values of the contraction activity (intensity and frequency) of tissues before the application of biologically active substances were calculated for 7 min and accepted as 100%. The results calculated for 7-min period after treatments were expressed as a percentage (mean ± SEM) of the contraction intensity and frequency before drug administration. Bonferroni test was USED for calculating the significance of mean differences (ANOVA, InStat Graph Pad, San Diego, CA).

Results

Macroscopic examination of uteri

Inflammatory changes were not observed at slaughter in the ENDO of gilts receiving saline, whereas an inflammatory process involving the entire organ was always found in uteri challenged with *E. coli.* In such animals uterine horns were greatly enlarged and filled with a large amount of a gray-white mucosal exudate. The uterine wall was thickened. ENDO was red and swollen, with distinctly visible blood-injected blood vessels.

Influence of NA and ACh on the contractile activity of uteri

NA at doses of 10^{-6} and 10^{-7} M decreased the intensity of contractions in ENDO/MYO ($p < 0.01$) and MYO ($p < 0.001$) of the control group as compared with the period before treatment. In the *E. coli*-injected gilts, NA at a dose of 10^{-7} caused an increase in the intensity of contractions of ENDO/MYO ($p < 0.05$) and MYO ($p < 0.01$). The frequency of contractions in response to NA did not change significantly in two kinds of the uterine tissues from the control and *E. coli*-treated animals (Fig. 1).

In the control group, ACh increased ($p < 0.05$) the intensity of contractions in ENDO/MYO at a dose of 10^{-3} M and in MYO at doses of 10^{-4} and 10^{-3} M. All doses of ACh led to elevation in the contraction intensity of ENDO/MYO (10^{-5} M – $p < 0.05$, 10^{-4} – $p < 0.01$, 10^{-3} M – $p < 0.001$) and MYO (10^{-5} M – $p < 0.05$, 10^{-4} and 10^{-3} M – $p < 0.001$) from inflamed uteri. In the control group ACh increased the contraction frequency of ENDO/MYO in a dose-dependent manner ($p < 0.01$, $p < 0.001$) and at the highest dose ($p < 0.01$) in MYO. In turn, all doses of ACh caused a decrease (10^{-5} and 10^{-3} M – $p < 0.05$, 10^{-4} M – $p < 0.001$) in the frequency of contractions in ENDO/MYO of inflamed uteri. Similar results ($p < 0.01$) were found in MYO collected from these uteri (Fig. 2).

Influence of PGE_2 on the contractile activity of uteri

In the control group, PGE_2 at doses of 10^{-8} and 10^{-7} M enhanced the contraction intensity in ENDO/MYO ($p < 0.01$) and at the higher dose in MYO ($p < 0.05$). Lower ($p < 0.05$)

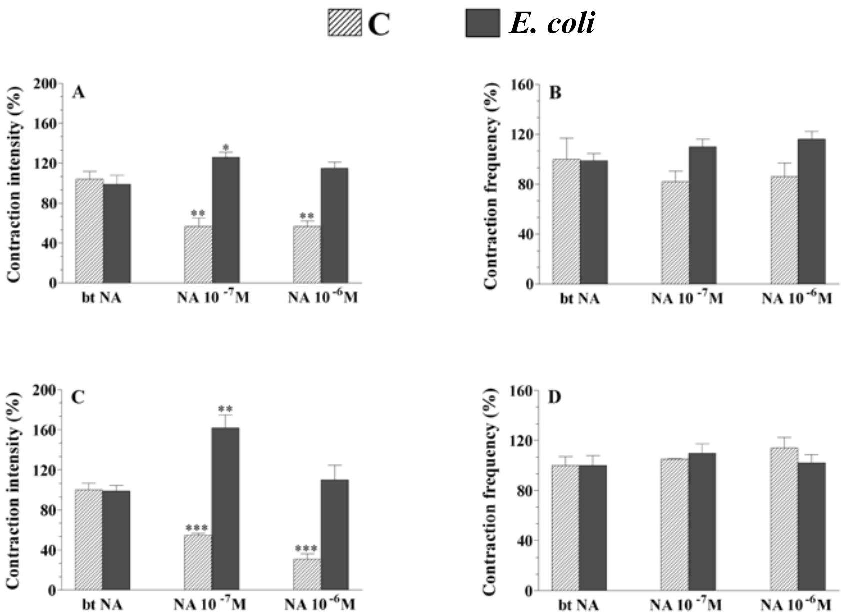

Fig. 1. Effect of NA on the intensity (A, C) and frequency (B, D) of contractions of endometrium/myometrium (A, B) and myometrium (C, D) strips from the control and *E. coli*-treated gilts. Values (mean ± SEM; n = 6) are presented as percentage in relation to the basal (before treatment, bt) intensity and frequency of contractions. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

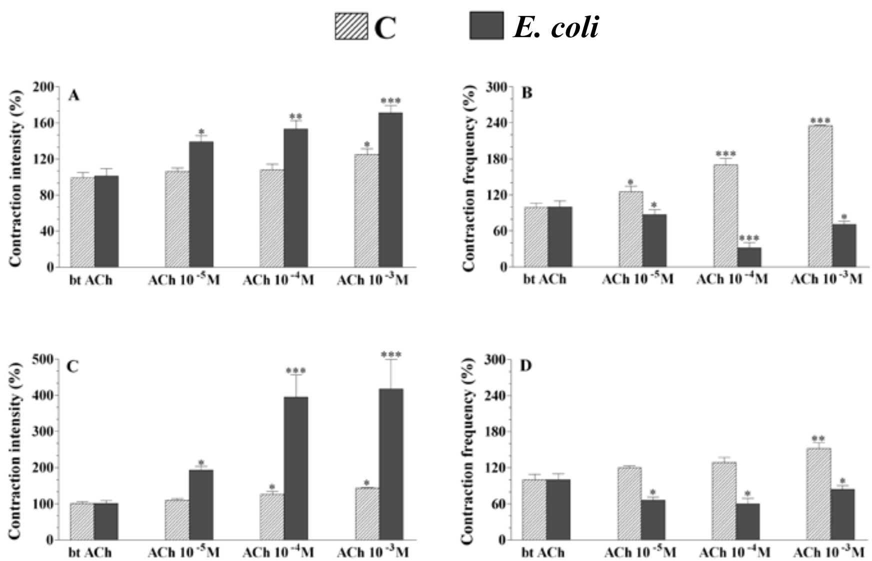

Fig. 2. Effect of ACh on the intensity (A, C) and frequency (B, D) of contractions of endometrium/myometrium (A, B) and myometrium (C, D) strips from the control and *E. coli*-treated gilts. Values (mean ± SEM; n = 6) are presented as percentage in relation to the basal (before treatment, bt) intensity and frequency of contractions. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

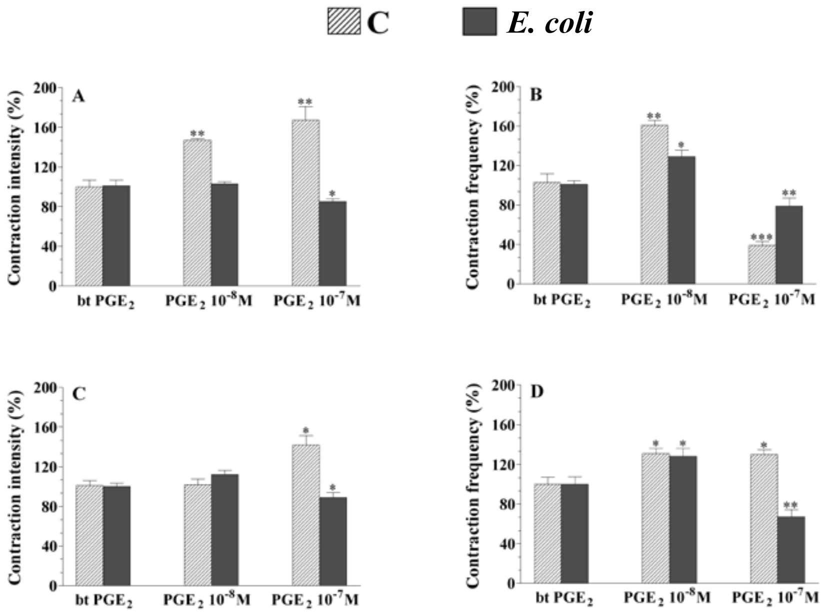

Fig. 3. Effect of PGE_2 on the intensity (A, C) and frequency (B, D) of contractions of endometrium/myometrium (A, B) and myometrium (C, D) strips from the control and *E. coli*-treated gilts. Values (mean ± SEM; n = 6) are presented as percentage in the relation to the basal (before treatment, bt) intensity and frequency of contractions. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

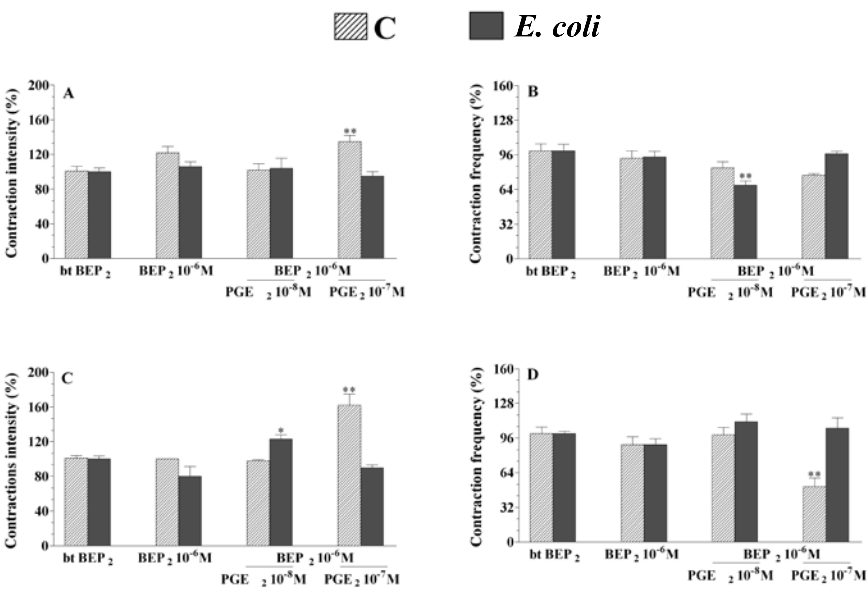

Fig. 4. Effect of PGE_2 on the intensity (A, C) and frequency (B, D) of contractions of endometrium/myometrium (A, B) and myometrium (C, D) strips from the control and *E. coli*-treated gilts in the presence of BEP_2. Values (mean ± SEM; n = 6) are presented as percentage in relation to the basal (before treatment, bt) intensity and frequency of contractions. * $p < 0.05$, ** $p < 0.01$

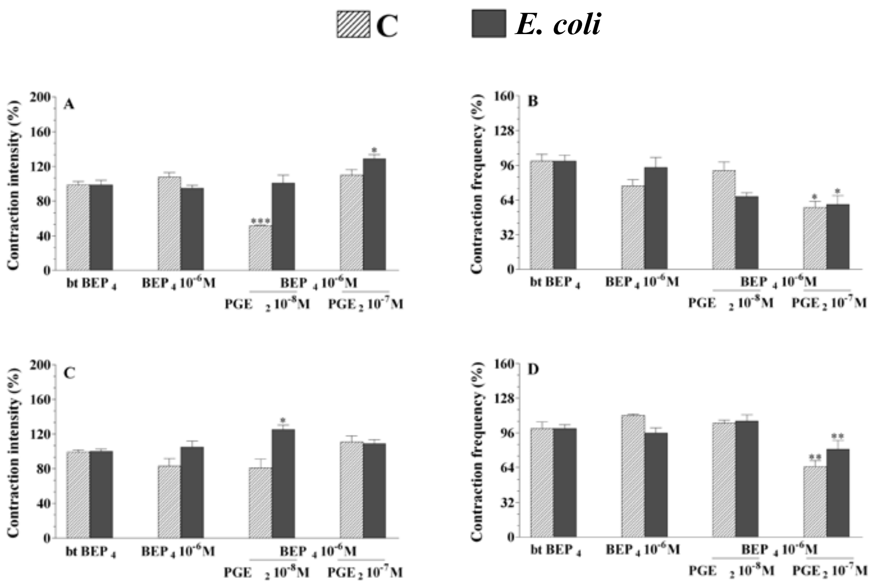

Fig. 5. Effect of PGE_2 on the intensity (A, C) and frequency (B, D) of contractions of endometrium/myometrium (A, B) and myometrium (C, D) strips from the control and *E. coli*-treated gilts in the presence of BEP_4. Values (mean ± SEM; n = 6) are presented as percentage in relation to the basal (before treatment, bt) intensity and frequency of contractions. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

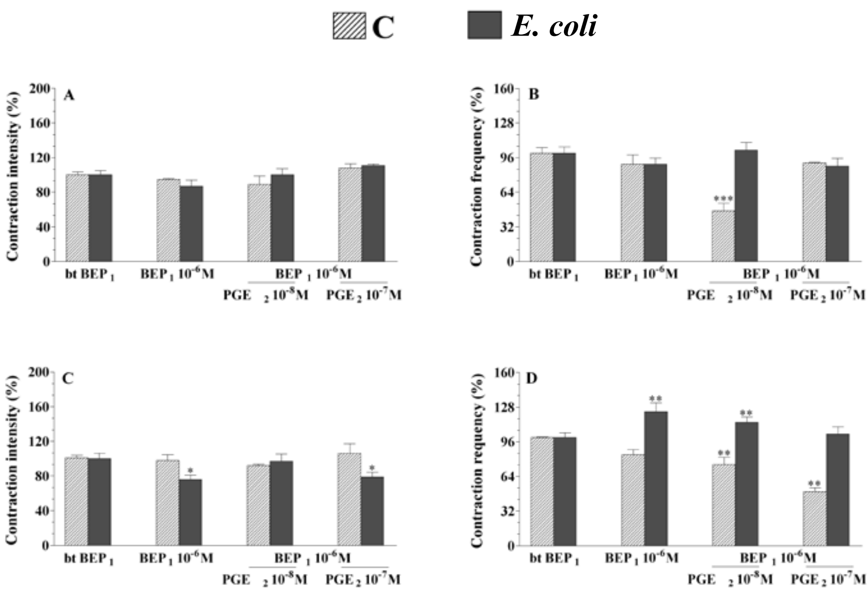

Fig. 6. Effect of PGE_2 on the intensity (A, C) and frequency (B, D) of contractions of endometrium/myometrium (A, B) and myometrium (C, D) strips from the control and *E. coli*-treated gilts in the presence of BEP_1. Values (mean ± SEM; n = 6) are presented as percentage in relation to the basal (before treatment, bt) intensity and frequency of contractions. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

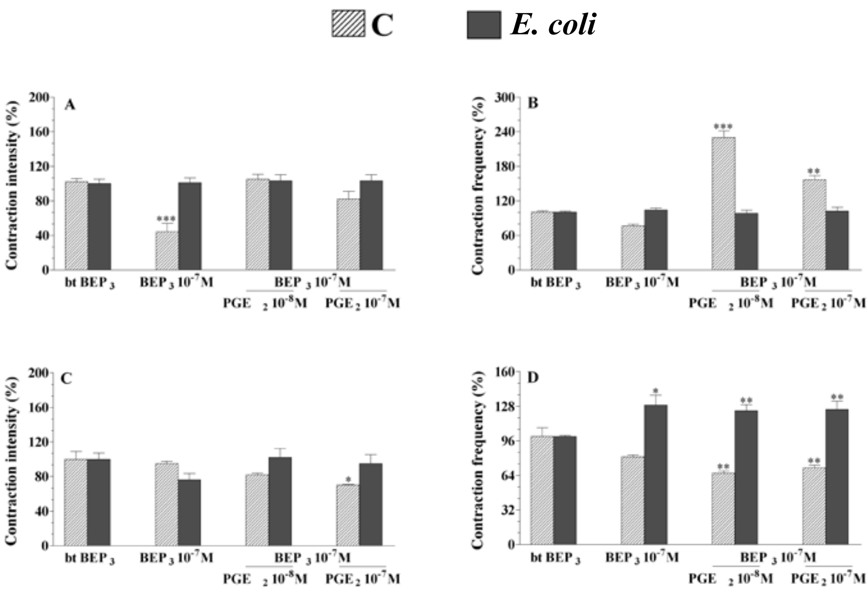

Fig. 7. Effect of PGE_2 on the intensity (A, C) and frequency (B, D) of contractions of endometrium/myometrium (A, B) and myometrium (C, D) strips from the control and *E. coli*-treated gilts in the presence of BEP_3. Values (mean ± SEM; n = 6) are presented as percentage in relation to the basal (before treatment, bt) intensity and frequency of contractions. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

intensity of contractions was found during incubation of two kinds of tissues from inflamed uteri with PGE_2 at a dose of 10^{-7} M. PGE_2 at a dose of 10^{-8} M increased, ($p < 0.01$) and at a dose of 10^{-7} M decreased ($p < 0.001$) the frequency of contractions in ENDO/MYO of the control gilts. In control gilts, PGE_2 at two doses enhanced ($p < 0.05$) the contraction frequency in MYO. Similar effect ($p < 0.05$) was noted in ENDO/MYO and MYO of bacteria-infused animals after PGE_2 treatment at a dose of 10^{-8} M. In contrast, 10^{-7} M of PGE_2 lowered ($p < 0.01$) the frequency of contractions in two kinds of tissues from inflamed uteri (Fig. 3).

Influence of PGE_2 on the contractile activity of uteri in the presence of BEP_2 and BEP_4

The intensity and frequency of contractions in the uterine strips of both intact and inflamed uteri were similar after use of BEP_2 alone. PGE_2 at a dose of 10^{-7} M in the presence of BEP_2 increased ($p < 0.01$) the intensity of contractions in ENDO/MYO and MYO of the control group. BEP_2 and PGE_2 at a dose of 10^{-8} M enhanced ($p < 0.05$) the intensity of contractions in MYO from inflamed uteri. PGE_2 at a dose of 10^{-8} M used in the presence of BEP_2 decreased ($p < 0.01$) the frequency of contractions in MYO of the control gilts. Similar effect ($p < 0.01$) was also observed in ENDO/MYO of inflamed uteri after the use of BEP_2 and PGE_2 at dose of 10^{-8} M (Fig. 4).

BEP_4 alone did not affect significantly the intensity and frequency of contractions in ENDO/MYO and MYO from both studied groups. PGE_2 at a dose of 10^{-7} M used after BEP_4 treatment decreased ($p < 0.001$) the intensity of contractions in ENDO/MYO of the control gilts. In the presence of BEP_4, PGE_2 at doses of 10^{-7} M and 10^{-8} M increased ($p < 0.05$) the contraction intensity of ENDO/MYO and MYO, respectively, from inflamed uteri. In the presence of BEP_4, 10^{-7} M of PGE_2 led to a decrease in the frequency of contractions in ENDO/MYO ($p < 0.05$) and in MYO ($p < 0.01$) from both examined groups (Fig. 5).

Influence of PGE_2 on the contractile activity of uteri in the presence of BEP_1 and BEP_3

In MYO of *E. coli*-treated gilts, BEP_1 alone decreased ($p < 0.05$) the intensity of contractions but increased ($p < 0.01$) the frequency of contractions. In the control group, the intensity of contractions in ENDO/MYO and MYO did not change significantly in the presence of BEP_1 and PGE_2. A decrease ($p < 0.05$) in the contraction intensity in MYO of inflamed uteri was observed in response to BEP_1 and PGE_2 at a dose of 10^{-7} M. In the control group in the presence of BEP_1, PGE_2 at a dose of 10^{-8} M decreased ($p < 0.001$) the frequency of contractions in ENDO/MYO whereas this effect ($p < 0.01$) in MYO was due to two doses of PGE_2. In the presence of BEP_1, the frequency of contractions in MYO of inflamed uteri was increased ($p < 0.01$) by PGE_2 at a dose of 10^{-8} M (Fig. 6).

BEP_3 alone decreased ($p < 0.001$) the intensity of contraction in ENDO/MYO from intact uteri and increased ($p < 0.05$) the frequency of contractions in MYO of inflamed organs. In the control group, a decrease in the intensity of contractions of MYO ($p < 0.05$) was found after the use of BEP_3 together with 10^{-7} M of PGE_2. In two kinds of tissues from inflamed uteri the values of this indicator did not change significantly in response to BEP_3 and PGE_2. In the control gilts, PGE_2 at doses of 10^{-8} and 10^{-7} M in the presence of BEP_3 increased (10^{-8} M – $p < 0.001$, 10^{-7} M – $p < 0.01$) the frequency of contractions in ENDO/MYO but decreased ($p < 0.01$) in MYO. The frequency of contractions in MYO from inflamed uteri were enhanced ($p < 0.01$) under the influence of PGE_2 at doses of 10^{-8} and 10^{-7} M in the presence of BEP_3 (Fig. 7).

Discussion

In the present study we showed that NA decreased the contraction intensity of the tissues from intact uteri and increased it in tissues from inflamed organs. Such response of porcine inflamed uterus to NA has been unknown to date. Relaxation of the uterine wall of the control gilts was anticipated. It is generally accepted that NA leads to an inhibition of uterine contractile activity that is probably connected with numerical superiority of β-adrenergic receptors in comparison with α-adrenergic receptors (Taneike et al. 1991; Kitazawa et al. 2001) and also with the lower sensitivity threshold of β-receptors (Kaneko et al. 1996). Although the mechanism responsible for the increase of contractile activity in the inflamed uterus after NA treatment is unknown, it may be a consequence of the highest expression or lower threshold excitability for α-adrenergic receptors. In our study, the changes in contraction intensity of the uterine tissues from both studied groups, in response to NA, were not connected with significant alterations in the frequency of contractions.

In turn, ACh increased the contraction intensity of the uterine tissues of both the control and *E. coli*-treated groups. This observation corresponds with the report of Kitazawa et al. (1999). However, the intensity of contractions in inflamed uteri was higher than in intact organs. We suggest that differences in response to ACh stimulation in intact and inflamed uteri are consequences of the changes in expression and sensitivity of muscarinic receptors during the inflammatory process embracing the uterine wall.

It is known that PGE_2 may both stimulate or inhibit the contractile activity of the uterus depending on its concentration and the physiological stage of the uterus (Crankshaw and Gaspar 1995; Popat and Crankshaw 2001; Cao et al. 2002). PGE_2 is also considered a potent vasodilator and relaxant acting on MYO and thus an important mediator of inflammation, and a factor contributing to the development of pathological process and its maintenance (Slama et al. 1991; Slama et al. 1994). Our earlier study showed that in inflamed porcine uterus, enhanced production of PGE_2 and PGF_2a was connected with increases in the expressions of cyclooxygenase-2 (Jana et al. 2007), microsomal PGE synthase-1 and 9-ketoreductase (converting PGE_2 to PGF_2a; Jana et al. unpublished). Particularly, a high PGE_2 level (four times higher than PGF_2a) was found on day 17 after intrauterine infusion of *E. coli* (Jana et al. 2007). In cows with *endometritis* an increase in PGE_2 plasma level was observed a few days after parturition (Mateus et al. 2003). In the present study, we demonstrated that PGE_2 increased the uterine contraction intensity in the control gilts (with the exception of the lower dose in MYO). This is probably because the uterine tissue has more receptors responsible for contraction (EP_1, EP_3) than for relaxation (EP_2, EP_4) and/or differences in their distribution, as was earlier shown in human (Popat and Crankshaw 2001) and porcine (Cao et al. 2005) uteri. On the other hand, the intensity of contractions in two kinds of tissues from inflamed uteri decreased after PGE_2 treatment at the higher dose. This may suggest that in inflamed uterine tissues the content of EP_1 and EP_3 receptors responsible for the contractions diminished compared to representation and/or activity of EP_2 and EP_4 receptors causing a diastola-like relaxing effect. It may be also presumed that the relaxing effect of PGE_2 on inflamed uterine tissues could be stronger in conditions of fully developed pathological process. The seven-day period between *E. coli* inoculation and investigation in our study could be too short to induce big changes in the content/distribution of PGE_2 receptors. Moreover, it is known that in cows MYO loses its contractile activity usually in serious and prolonged endometritis.

PGE_2 administered in the presence of EP_2 and EP_4 receptor blockers did not evoke significant changes in the contraction intensity of the tissues from both examined groups or increase the values of this indicator except for ENDO/MYO of the control gilts (the lower dose of PGE_2 and BEP_4) where the contraction intensity decreased. Moreover, the changes in enhancement of the contraction intensity found in intact and inflamed uteri were dependent on the type of the blocked receptor. The application of PGE_2 (at the higher dose) in the presence of BEP_2 enhanced the contraction intensity in two kinds of tissues of the control gilts. In contrast, in inflamed uteri such a reaction occurred only in MYO after the use of BEP_2 and the lower dose of PGE_2. Moreover, in these uteri, PGE_2 at the lower or higher dose in the presence of BEP_4 increased the contraction intensity in MYO or ENDO/MYO, respectively. The differences probably result from the various expressions/distributions of EP_2 and EP_4 receptors in intact and inflamed uteri. Based on these results, we suggest that PGE_2 causes dilatation in the intact uterus mainly by EP_2 receptors, whereas in inflamed uteri it causes dilatation mainly through EP_4 receptors, the content of which can be greater in inflamed than in intact uteri. In terms of uterine strip contraction frequency, PGE_2 after the treatment of EP_2 and EP_4 blockers did not significantly affect or decrease the number of contractions in both intact and inflamed uteri.

PGE_2 administered in the presence of EP_1 and EP_3 receptor blockers whose stimulation leads to uterine contraction, usually failed to evoke significant changes in the contraction intensity in uterine tissues in both studied groups. However, in the control gilts, PGE_2 at a higher dose in the presence of BEP_3 decreased the contraction intensity in MYO. A similar reaction was found in MYO of inflamed uteri in response to PGE_2 used also at a higher dose but after prior BEP_1 treatment. These results indicate that the concentration and/or sensitivity of EP_3 receptors was higher in intact uteri, whereas those of EP_1 receptors in inflamed uteri. It can be presumed that inflammation also changes the expression/distribution of two types of contractile receptors for PGE_2. Moreover, it should be emphasised that the contractile activity of uteri changed after the use of only BEP_1 and BEP_3. In the presence of BEP_1, the contraction intensity decreased in MYO from inflamed uteri, while BEP_3 caused the same reaction in ENDO/MYO of intact uteri. In turn, both blockers increased the contraction frequency in MYO of inflamed organs. These data indicated that uterine strips produce endogenous PGE_2, and its action is inhibited by PGE_2 receptor antagonists. PGE_2 acted differently in the presence of BEP_1 and BEP_3 on the frequency of contractions in the uterine tissues from both groups of gilts. In the intact uteri this indicator mainly decreased, while in inflamed uteri it increased in most cases.

In conclusion, the presented data demonstrate, for the first time, that PGE_2, acting through EP_2 and EP_4 receptors, decreased the contraction intensity of endometrium/myometrium and myometrium collected from gilts on day 7 after intrauterine injection of an *E. coli* suspension. Our data also suggest that PGE_2, through its effect on the contractile activity of inflamed uteri, can be important for the course and/or consequences of this pathological state in females of domestic animals. However, further studies should be performed to closely determine the role of PGE_2 and other prostanoids in the contractile activity of uterine tissues with more advanced inflammation.

Acknowledgments

The authors are grateful to Marta Wasielak for editorial assistance.

References

Aas AHG, Sunde M, Karlberg K, Hofmo PO 1998: Bacteriological and histological examination of urogenital organs from sows culled after weaning. 2nd Conf. Eur. Soc. Dom. Anim. Reprod., 2nd Central Eur. Conf. Anim. Reprod. 26-28. 10. Keszthely, Hungary, p. 46

Cao J, Shaibuzhati M, Tajima T, Kitazawa T, Taneike T 2002: In vitro pharmacological characterizartion of the prostanoid receptor population in the non pregnant porcine myometrium. Eur J Pharmacol **442**: 115-123

Cao J, Yosida M, Kitazawa T, Taneike T 2005: Uterine region-dependent differences responsiveness to prostaglandin in the non pregnant porcine myometrium. Prostaglandins Other Lipid Mediat **75**: 105-122

Crankshaw DJ, Gaspar V 1995: Pharmacological characterization in vitro of prostanoid receptors in myometrium of non pregnant ewes. J Reprod Fertil **103**: 55-61

De Winter PJJ, Verdonck M, De Kruif A, Devriese LA, Haesebrouck F 1995: Bacterial endometritis and vaginal discharge in the sow: prevalence of different bacterial species and experimental reproduction of the syndrome. Anim Reprod Sci **37**: 325-335

Hussain AM 1989: Bovine uterine defense mechanisms: a review. J Vet Med Ser B **36**: 641-651

Hussain AM, Daniel RCW 1992: Effects of intrauterine infusion of *Escherichia coli* in normal cows and in cows with endometritis-induced by experimental infection with Streptococcus agalactiae. Theriogenology **37**: 798-810

Jana B, Kucharski J, Dzienis A, Deptuła K 2007: Changes in prostaglandin production and ovarian function in gilts during endometritis induced by *Escherichia coli* infection. Anim Reprod Sci **97**: 137-150

Kaneko Y, Tsukamoto T, Kawarabayashi T, Ikeda M, Sugimori H 1996: Characteristics of beta-adrenergic receptors in longitudinal muscle membranes of rat uterus: changes in kinetic properties of the receptor during gestation. J Mol Recognit **9**: 233-238

Kitazawa T, Nakagoschi K, Teraoka H, Taneike T 2001: 5-HT(7) receptor and b(2)-adrenoreceptor share in the inhibition of porcine uterine contractility in a muscle layer- dependent manner. Eur J Pharmacol **433**: 187-197

Kitazawa T, Uchiyama F, Hirose K, Taneike T 1999: Characterization of the muscarinic receptor subtype that mediates the contractile response of acetylcholine in the swine myometrium. Eur J Pharmacol **367**: 325-334

Kucharski J, Jaroszewski J, Jana B, Górska J, Kozłowska A, Markiewicz W 2007: The influence of inflammatory process on prostaglandin $F_2\alpha$ contractile activity in porcine uterus. J Anim Feed Sci **16**: 654-667

Mateus L, Lopes DA, Costa L, Diniz P, Zięcik A 2003: Relationship between endotoxin and prostaglandin (PGE_2 and PGFM concentration and ovarian function in dairy cows with puerperal endometritis. Anim Reprod Sci **76**: 143-154

Myatt L, Lye SJ 2004: Expression, localization and function of prostaglandin receptors in myometrium. Prostaglandins Leukot. Essent. Fatty Acids **70**: 137-148

Neely DP, Kindahl H, Stabenfeldt GH, Edqvist LE, Hughes JP 1979: Prostaglandin release pattern in the mare: physiological, pathophysilogical, and therapeutic responses. J Reprod Fert Suppl **27**: 181-189

Olson JD, Ball L, Mortimer RG, Farin PW, Adney WS, Huffman EM 1984: Aspects of bacteriology and endocrinology of cows with pyometra and retained fetal membranes. Am J Vet Res **45**: 2251-2255

Peter AT, Bosu WTK 1987: Effects of intrauterine infection on the function of the corpora lutea formed after first postpartum ovulation in dairy cows. Theriogenology **127**: 593-609

Peter AT, Bosu WTK, Gilbert RO 1990: Absorption of *Escherichia coli* endotoxin from the uterus of postpartum dairy cows. Theriogenology **33**: 1011-1014

Popat A, Crankshaw DJ 2001: Variable responses to prostaglandin E_2 in human nonpregnant myometrium. Eur J Pharmacol **416**: 145-152

Ramadan A, Johnson GI, Lewis D 1997: Regulation of the uterine immune function during the estrous cycle and in response to infection bacteria in sheep. J Anim Reprod Sci **75**: 1621-1632

Slama H, Vaillanciurt D, Goff AK 1991: Pathophysiology of the puerperal period: relationship between prostaglandin E_2 (PGE_2) and uterine involution in the cow. Theriogenology **36**: 1071-1090
Slama H, Vaillancourt D, Goff AK 1994: Effect of bacterial cell wall and lipopolysaccharide on arachidonic acid metabolism by caruncular and allantochorionic tissues from cows that calved normally and those with retained fetal membranes. Theriogenology **41**: 923-942
Stabenfeldt GH, Kindahl H, Hughes JP, Neely DP, Liu I, Pascoe D 1981: Control of luteolysis in the mare. Acta Vet Scand Suppl **77**: 159-170
Taneike T, Miyazaki H, Nakamura H, Ohga A 1991: Autonomic innervation of the circular and longitudinal layers in swine myometrium. Biol Reprod **45**: 831-840