The influence of inflammatory process on prostaglandin F$_2$α contractile activity in porcine uterus

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ABSTRACT

The aim of this study was to determine the influence of prostaglandin F$_2$α (PGF$_2$α) on the contractile activity of intact and inflamed porcine uteri. On day 3 of the oestrous cycle, gilts were randomly assigned to group I (control; n = 6) or II (treated with E. coli; n = 6). In all gilts median laparotomy was performed and 50 ml of saline or 50 ml of E. coli containing 10$^9$ colony-forming units/ml were injected into each uterine horn in groups I and II, respectively. After seven days (on day 10 of the oestrous cycle) the gilts were slaughtered and uterine horns collected. After macroscopic examination, contractile activity of uterine strips: endometrium+myometrium (ENDO/MYO) and myometrium (MYO) was examined using noradrenaline (NA), acetylcholine (ACh), PGF$_2$α alone or together with EP$_2$, EP$_4$, EP$_1$, EP$_3$ receptor blockers (BEP$_2$, BEP$_4$, BEP$_1$ and BEP$_3$, respectively). NA decreased (P<0.01, P<0.001) the intensity of contractions in ENDO/MYO and MYO of the control group but increased (P<0.05, P<0.01) in the inflamed uterus. ACh at doses 10$^{-5}$, 10$^{-4}$ and 10$^{-3}$ M increased (P<0.05-0.001) the intensity of contractions in ENDO/MYO and MYO from the bacteria group and intact group (P<0.05) at doses 10$^{-4}$ and 10$^{-3}$ M. ACh at all of the tested doses increased (P<0.05-0.001) the frequency of contractions in the control and decreased (P<0.05, P<0.001) in the experimental group. NA and ACh treatment revealed that uterine strips were living and suitable for further investigations. PGF$_2$α at a dose of 10$^{-7}$ M increased (P<0.05, P<0.01) the intensity of contractions in ENDO/MYO and MYO of both control and experimental groups. PGF$_2$α at doses 10$^{-8}$ and 10$^{-7}$ M used in the presence of BEP$_2$ or BEP$_4$ increased (P<0.05-0.001) the intensity of contrac-

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tions in both the control and bacterial groups. However, PGF\(2\alpha\) did not significantly influence the frequency of contractions with the exception of the stimulatory effect in ENDO/MYO (P<0.001) strips of the control groups. PGF\(2\alpha\) at doses of 10^{-8} and 10^{-7} M administered after BEP\(_1\) and BEP\(_3\) treatment decreased (P<0.05-0.001) or did not significantly influence the intensity and frequency of contractions in uterine tissues in both examined groups. The presented findings revealed that PGF\(2\alpha\), besides affecting the contractile activity of uterine tissues, may also act through the PGE\(_2\) receptors. However, thorough interpretation of these results requires determination of the role of other prostanoids in this process.

KEY WORDS: contractile activity, uterus, endometritis, PGF\(2\alpha\), PGE\(_2\) - antagonists, gilts

INTRODUCTION

By acting though specific receptors, prostanoids regulate many physiological processes in different organs: the brain (Cao et al., 1996; Sehic et al., 1996; Resch and Millington, 2001; Moore et al., 2004), kidneys (Harris et al., 1998) and gastrointestinal tract (Wallace, 1990; Dubois et al., 1998). Prostaglandins (PGs), mainly from series E and F, control most processes in the reproductive organs, particularly: sperm migration, ovulation, luteolysis, fertilization, egg implantation, foetal growth and the uterine activity in the postpartum period (Herschman, 1996).

The presence of pathogenic microorganisms in the uterus increases considerably PG concentrations in both uterine tissues and venous blood outflow from this organ. Endotoxin (lipopolysaccharide; LPS) released from the bacterial wall, as well as proinflammatory cytokines, stimulate the enzymatic activity of cyclooxygenase-2 (COX-2). The metabolism of mucous membrane phospholipids into PGs is connected with phospholipase A\(_2\) (cPLA\(_2\)) and phospholipase C (PLC) activity. In the inflammatory changed uterus independent of phospholipase, phospholipid metabolism is more active, and high PG concentrations are the results of intensified COX activity (Chong-Jeh et al., 1996; Gijon and Leslie, 1999).

In veterinary practice, long-lasting uterine inflammatory stages characterized by mucopurulent discharge or pyometra cause long-term problems. Under these conditions the uterine muscular layer loses its contractile ability and the uterus filled with inflammatory exudate hangs in the abdominal cavity. The high PGF\(2\alpha\) concentration in the uterus is caused by the presence of pathogenic microorganisms and should ensure contractile activity of the uterine muscular layer even in long-lasting endometritis. During inflammation of the uterus, besides an increase in PGF\(2\alpha\) levels, there is also a rise in concentrations of PGE\(_2\) (Mateus et al., 2003; Jana et al., 2007) and PGI\(_2\) (Kołaczkowska, 2002). In accordance with Jana et al. (2007) after intrauterine \textit{E. coli} infusions the level of PGE\(_2\) was four times higher than of PGF\(2\alpha\) in gilts on day 17. We accept that during development of
endometritis, besides distinctly increasing their concentrations, PGs change their mutual relation (Jana et al., 2007). The concentrations of PGE$_2$ and PGI$_2$ increase and the level of PGF$_2\alpha$ decreases. The high PGE$_2$ and PGI$_2$ concentrations in the inflamed uterus probably inhibit or delimit the contractile activity of PGF$_2\alpha$. It has been reported that PGE$_2$ operates on the uterine muscular layer during contraction (though EP$_1$ and EP$_3$ receptors) and diastole (though EP$_2$ and EP$_4$ receptors) (Myatt and Lye, 2004). Importantly, apart from PGE$_2$, progesterone is one factor that, under physiological conditions, acts diastolicly on the uterine muscular layer. Moreover, PGF$_2\alpha$ in the human uterus has been reported to act not only by its receptors but also through receptors for PGE$_2$ (Myatt and Lye, 2004). The literature to date lacks data concerning the influence of PGF$_2\alpha$ on contractile activity in intact and inflamed porcine uteri.

Therefore, the aim of this study was to determine the effect of PGF$_2\alpha$ on the intensity and frequency of uterine contractions in intact and inflamed uteri of gilts. We studied the influence of PGF$_2\alpha$ on the contractile activity of endometrium+myometrium (ENDO/MYO) and myometrium (MYO) uterine strips and the effect of PGF$_2\alpha$ on the contractile activity of the uterine tissues in the presence of PGE$_2$ receptor antagonists (EP$_2$, EP$_4$, EP$_1$ and EP$_3$).

MATERIAL AND METHODS

Animals

Twelve crossbred gilts (Large White × Landrace) 7-8 months old, weighing 100-120 kg and with at least two regular oestrous cycles were used in this study. The animals originated from a herd with no abnormal discharge or fertility disorders and were not treated with antibiotics before, during or after surgery. The gilts were individually housed in stalls under conditions of natural light and temperature. They were fed a commercial grain mixture and tap water ad libitum. All experimental procedures followed the principles of animal care (NIH publication No 86-23, revised in 1985) and were approved by the Local Ethics Commission for Animal Experiments (Agreement No 20/N). On day 3 of the oestrous cycle the gilts were randomly assigned to one of two groups: group I (n = 6) control receiving saline and group II (n=6) treated with E. coli. In all the gilts median laparotomy was performed under general anaesthesia using Stresnil (Janssen Pharmaceutica, Belgium) at a dose of 1 ml/10 kg BW and Vetbutal (Biowet, Poland) at a dose 30-40 ml/100 kg BW. Next, group I had 50 ml of saline injected into each uterine horn (10 ml in five places). Group II received 50 ml of an E. coli (strain O25:K23/α::H1; National Veterinary Research Institute, Department of Microbi-
ology, Puławy, Poland) suspension containing $10^9$ colony-forming units (cfu)/ml, the same way. The animals were slaughtered seven days after surgery (on day 10 of the oestrous cycle) and the uteri were collected. The uterine horns were then cut off and a macroscopic examination was performed. Fragments of the uterine horns were transferred on ice, transported to the laboratory within 20 min and immediately processed for examination of contractile activity.

**Determination of contractile activity**

Strips $3 \times 5$ mm were prepared (in an identical way and from the same site) from two kinds of uterine wall fragments: endometrium with myometrium (ENDO/MYO) and myometrium (MYO) from the middle part of the uterine horns. They were separated, 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 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 study the strips were incubated (7 min) with noradrenaline (NA) (Polfa, Poland) at a concentration of $10^{-7}$ and $10^{-6}$ M and acetylcholine (ACh) (Sigma) at concentrations of $10^{-5}$, $10^{-4}$ and $10^{-3}$ M to determine the strips’ contractile activity and their qualification for further study. Afterwards, the influence of increasing ($10^{-8}$ and $10^{-7}$ M) doses of PGF$_2\alpha$ was examined. PGF$_2\alpha$ was tested alone or after two min of preincubation with AH 6809 (Cayman Chemical, USA), BEP$_2$; ONO-AE$_2$; BEP$_4$; ONO-AE$_3$-240 (Sigma), BEP$_1$; and SC19220 (Sigma), BEP$_3$; selective antagonists of EP$_2$, EP$_4$, EP$_3$ and EP$_4$ receptors, respectively. BEP$_2$, BEP$_4$ and BEP$_1$ were used at a dose of $10^{-6}$ M, while BEP$_3$, at a dose of $10^{-7}$ M. The effective dose of each substance was tested in pilot studies on uterine tissue collected at a local slaughterhouse from gilts in the luteal phase of the oestrous cycle. At the end of the study NA and ACh were administrated in the same doses as at the beginning to assess the contractile activity of the strips.

**Statistical analysis**

For the statistical analyses, the numerical values of the contraction activity (intensity and frequency) of tissues before the application of the biologically ac-
tive substances were calculated for seven min and taken as 100%. The results calculated for the seven min period after treatments were expressed as a percentage (mean ± SEM) of the contraction intensity and frequency before drug administration. The Bonferroni test was applied for calculating the statistical significance of mean differences (ANOVA, InStat Graph Pad, San Diego, CA) and P value of < 0.05 was considered statistically significant for all tests.

RESULTS

Macroscopic examination of uteri. Macroscopically, inflammatory changes were not observed in the endometrium of the gilts receiving saline. The administration of *E. coli* into the uterus induced inflammation involving the entire organ. The endometrium was red, swollen with distinctly visible blood vessels. The uterine horns were enlarged and a grey-white mucosal exudate was found inside them.

Figure 1. Influence of noradrenaline (NA) on the intensity of contractions (A, C) and frequency of contraction of endometrium and myometrium (A, B) and myometrium (C, D) strips collected 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, pp) intensity and frequency of contractions. * P<0.05, ** P<0.01, *** P<0.001
Effect of NA and ACh on the contractile activity of uteri. NA at doses of $10^{-7}$ and $10^{-6}$ M decreased the intensity of contractions of ENDO/MYO (P<0.01) and MYO (P<0.001) from the control group. In the animals receiving bacteria, NA at a dose of $10^{-7}$ M increased the intensity of contractions in ENDO/MYO (P<0.05) and MYO (P<0.01) as compared with the period before treatment. The frequency of contractions in response to NA was similar in the two kinds of uterine tissue from both groups of gilts and insignificant (P>0.05) as compared with the period before treatment (Figures 1 A-D).

In the control group ACh elevated (P<0.05) the intensity of contraction in ENDO/MYO at a dose of $10^{-3}$ M and in MYO at doses of $10^{-4}$ and $10^{-3}$ M. In the strips from the inflamed uterus, ACh increased the intensity of contractions in both ENDO/MYO (P<0.05, P<0.01 and P<0.001 after dose of $10^{-5}$, $10^{-4}$ and $10^{-3}$ M, respectively) and in MYO (P<0.05, P<0.01 and P<0.001 after dose of $10^{-5}$, $10^{-4}$ and $10^{-3}$ M, respectively). Moreover, in the control group ACh increased the frequency of contractions in ENDO/MYO in a dose-dependent manner (P<0.01, P<0.001) and at the highest dose (P<0.01) in MYO strips. In contrast, in the strips collected from the *E. coli*-treated group, a decrease was observed (P<0.05) in the frequency of contractions after all tested doses of ACh (Figures 2 A-D).
Effect of PGF$_2$α on the contractile activity of uteri. PGF$_2$α at a dose of 10$^{-7}$ M increased the intensity of contractions in both ENDO/MYO and MYO strips of the control (P<0.05) and _E. coli_-treated (ENDO/MYO-P<0.01, MYO-P<0.05) gilts. Instead, PGF$_2$α at a dose of 10$^{-8}$ M did not significantly influence the intensity of contractions in the uterine tissues in both examined groups. The frequency of contractions in ENDO/MYO decreased (P<0.05) in the control group after treatment of PGF$_2$α at a dose of 10$^{-7}$ M. In the MYO, PGF$_2$α did not significantly influence the frequency of contractions (Figures 3 A-D).

Effect of PGF$_2$α on the contractile activity of uteri in the presence of BEP$_2$ and BEP$_4$. BEP$_2$ employed alone increased (P<0.01) the intensity of contractions in ENDO/MYO of the intact group but decreased (P<0.01) the frequency of contractions in ENDO/MYO of the bacteria group. PGF$_2$α at a dose of 10$^{-7}$ M in the presence of BEP$_2$ increased (P<0.05) the intensity of contractions in both uterine tissues of the control group. At doses of 10$^{-8}$ and 10$^{-7}$ M PGF$_2$α increased (P<0.001) the frequency of contractions in the ENDO/MYO of the control group. In contrast, in the ENDO/MYO of the bacteria group and also in the MYO of both examined
groups, PGF$_2$α did not significantly influence the intensity and frequency of contractions in the presence of BEP$_2$ (Figures 4 A-D).

BEP$_4$ applied alone did not significantly influence the intensity and frequency of contractions in uterine strips of both healthy and inflamed uteri. PGF$_2$α at a dose of $10^{-8}$ M in the presence of BEP$_4$ decreased ($P<0.05$) the intensity of contractions in ENDO/MYO of the control group. Inversely, PGF$_2$α given at a dose of $10^{-7}$ M increased ($P<0.01$) the intensity of contractions in MYO of the control group. In the MYO of the bacteria group, PGF$_2$α dose dependently ($10^{-8}$ or $10^{-7}$ M) increased ($P<0.05$ and $P<0.001$) the intensity of contractions. However, in the ENDO/MYO of the bacteria group, PGF$_2$α caused no significant changes. PGF$_2$α did not significantly influence the frequency of contractions in uterine tissues in both examined groups in the presence of BEP$_4$ (Figures 5 A-D).

**Effect of PGF$_2$α on the contractile activity of uteri in the presence of BEP$_1$ and BEP$_3$.** BEP$_1$ applied alone decreased ($P<0.05$) the intensity and frequency of contractions in MYO of the bacterial group and the frequency of contractions in ENDO/MYO in both examined groups. PGF$_2$α at a dose of $10^{-8}$ and $10^{-7}$ M used in the presence of BEP$_1$ decreased ($P<0.05$) the intensity of contractions in the
ENDO/MYO of the control group, whereas it did not significantly influence the intensity of contractions in both ENDO/MYO and MYO of the E. coli-treated group. PGF$_2\alpha$ at a dose of $10^{-8}$ M in the presence of BEP$_4$ reduced the frequency of contractions in ENDO/MYO in both intact (P<0.001) and bacterial (P<0.01) groups. However, in the MYO strips in both examined groups such changes were not observed (Figure 6 A-D).

BEP$_3$ administered alone decreased the intensity and frequency of contractions in ENDO/MYO (P<0.05, P<0.01) and MYO (P<0.01, P<0.001) of the intact group. In the group after E. coli infusions such changes were not observed. PGF$_2\alpha$ at a dose of $10^{-8}$ M used in the presence of BEP$_3$ decreased the intensity of contractions in MYO of the control (P<0.05) and experimental (P<0.01) groups. Instead, PGF$_2\alpha$ at a dose of $10^{-7}$ M decreased (P<0.01) the intensity of contractions in MYO of the control group. In ENDO/MYO, PGF$_2\alpha$ did not significantly influence the intensity of contractions in both examined groups. PGF$_2\alpha$ at a dose of $10^{-8}$ M in the presence of BEP$_3$ reduced the frequency of contractions in the ENDO/MYO of the control (P<0.05) and experimental (P<0.01) groups. Instead, PGF$_2\alpha$ at a dose of $10^{-7}$ M decreased (P<0.01) the frequency of contractions in the

Figure 5. Influence of prostaglandin F$_2\alpha$ (PGF$_2\alpha$) on the intensity of contractions (A, C) and the frequency of contractions (B, D) of endometrium and myometrium (A, B) and myometrium (C, D) strips collected from the control and E. coli-treated gilts in the presence of BEP$_4$. Values (mean±SEM; n=6) are presented as percentage in the relation to the basal (before treatment, pp) intensity and frequency of contractions. * P<0.05, ** P<0.01, *** P<0.001
Figure 6. Influence of prostaglandin F$_2$α (PGF$_2$α) on the intensity of contractions (A, C) and the frequency of contractions (B, D) of endometrium and myometrium (A, B) and myometrium (C, D) strips collected from the control and E. coli-treated gilts in the presence of BEP$_1$. Values (mean±SEM; n=6) are presented as percentage in the relation to the basal (before treatment, pp) intensity and frequency of contractions. * P<0.05, ** P<0.01, *** P<0.001

Figure 7. Influence of prostaglandin F$_2$α (PGF$_2$α) on the intensity of contractions (A, C) and the frequency of contractions (B, D) of endometrium and myometrium (A, B) and myometrium (C, D) strips collected from the control and E. coli-treated gilts in the presence of BEP$_3$. Values (mean±SEM; n=6) are presented as percentage in the relation to the basal (before treatment, pp) intensity and frequency of contractions. * P<0.05, ** P<0.01, *** P<0.001
ENDO/MYO of the bacterial group. In the MYO strips the influence of PGF$_2\alpha$ on the frequency of contractions in the presence of BEP$_3$ differed. Both doses of PGF$_2\alpha$ decreased (P<0.01) the frequency of contractions in the healthy group and increased (P<0.01) this indicator in the inflamed uterus group (Figures 7 A-D).

DISCUSSION

Whereas according to the generally held assumption, NA should relax the uterine tissues in both intact and inflamed uteri of gilts, it actually decreased contraction intensity only in healthy uterine tissues. Inversely, in the inflamed uterus, NA caused a significant increase in the contraction intensity of the uterine strips. Such NA activity in the inflamed porcine uterus has been unknown to date. Generally, we can accept that NA activity leads to inhibition in uterine contractile activity, which is probably connected to the numerical superiority of $\beta$- over $\alpha$-adrenergic receptors (Williams and Leffkowitz, 1977; Garbuliński, 1984; Kitazawa et al., 2001) and also with the lower threshold excitability for $\beta$-receptors (Kubikowski and Kostowski, 1983). In this study, increased uterine contractile activity may result in increased expression of $\beta$-receptors or lower threshold excitability for $\alpha$-adrenergic receptors. Moreover, NA did not significantly influence uterine contraction frequency in either control or experimental groups.

ACh, as was to be expected, increased the contractile intensity of uterine tissues in both intact and inflamed uteri. However, the intensity of contractions was greater in $E.\ coli$-treated gilts in comparison with control animals. It is difficult to explain this difference in activity of ACh in healthy and inflamed uteri. We suppose that during the inflammatory process expression of muscarine receptors probably increases in uterine tissues. Finally, we can add that besides a contractile reaction in the smooth uterine muscles (Dynarowicz, 1987; Fogel and Maśliński, 2000), ACh may act diastolicly and dilate pulmonic lumen and coronal vessels and decrease the intensity of contractions of the cardiac muscle (Fogel and Maśliński, 2000). The application of NA and ACh as control substances in healthy and inflamed uteri revealed that uterine sections were living and suitable for further investigation.

PGF$_2\alpha$ added to the uterine tissues increased the intensity of contractions in both control and experimental groups. The contractile activity of PGF$_2\alpha$ in healthy uterine tissues is generally known and accepted by different authors (Kindahl et al., 1982, 1996; Lindell and Kindahl, 1983; Slama and Vaillancourt, 1991; Cao et al., 2002, 2005). On the other hand, high PGF$_2\alpha$ contractile activity in the inflamed porcine uterus requires explanation. One reason may be the short period (seven
days) between intrauterine *E. coli* infusion and investigation. The inflammatory stage created in the uterus probably was incapable of causing changes in the distribution and expression of PGF$_2\alpha$ receptors in uterine tissues. Because of this the intensity of contractions of the uterine tissues in both control and experimental groups was similar. Moreover, in comparison with cows we can accept that the uterine muscular layer loses its contractile activity only in heavy and prolonged *endometritis*.

PGF$_2\alpha$ treated in the presence of EP$_2$ and EP$_4$ receptor blockers whose stimulation leads to uterine relaxation caused increased contractile activity in the uterine muscular layer of the healthy gilts. In the gilts with inflamed uteri, only in the presence of EP$_4$ blocker did PGF$_2\alpha$ have a stimulatory effect on the intensity of contractions in the *myometrium*. In terms of uterine strip contraction frequency, PGF$_2\alpha$ acted differently in the presence of the blockers. In the presence of BEP$_2$, the frequency of contractions increased in the *endometrium* of the control group. The use of BEP$_4$ did not significantly influence the frequency of contractions in the examined groups. The stronger activity of PGF$_2\alpha$ in the *myometrium* after prior BEP$_4$ treatment is certainly caused by the increased concentration of contractile receptors in this tissue. The ineffective reaction or lack of response in the intensity of contractions of the uterine tissues in the *E. coli*-infused gilts to PGF$_2\alpha$ treatment in the presence of BEP$_2$ was probably caused by the presence of the inflammation in this organ.

PGF$_2\alpha$ administered in the presence of EP$_1$ and EP$_3$ receptor blockers decreased the intensity of contractions or failed to evoke a response in uterine tissues in both examined groups. However, stronger PGF$_2\alpha$ activity was observed in the *myometrium* after prior of BEP$_3$ blocker treatment. Similarly, the contraction frequency decreased except for the *myometrium* of the bacterial group where this parameter increased. The presented findings revealed that PGF$_2\alpha$ may act on the uterine muscular layer through non-specific PGE$_2$ receptors. However, thorough interpretation of these results requires determination of the role of other prostanoids in contractile activity in pathologically-changed uterine tissues. This study is one of the first to deal with this problem.

**CONCLUSIONS**

NA and ACh used as control substances in healthy uterine tissues acted consistently as expected; NA caused relaxation and ACh contraction of the uterine wall. However, in the gilts with inflamed uteri both substances caused strong contraction of the uterine tissues. PGF$_2\alpha$ in both healthy and inflamed uteri increased contraction intensity. The application of PGE$_2$ (EP$_2$ and EP$_4$) receptor blockers
prior to PGF$_2\alpha$ treatment caused an increase in contractile activity in the myometrium of the healthy gilts and in EP$_4$ of E. coli-infused gilts. The application of PGF$_2\alpha$ in the presence of PGE$_2$ (EP$_1$ and EP$_3$) receptor blockers caused a significant decrease in the intensity of contractions or no reaction in the uterine tissues of both healthy and inflamed-uterus gilts.

The investigations revealed that PGF$_2\alpha$ contractile activity in uterine tissues was present in both healthy and inflamed uteri. However, its ability to contract uterine tissues is probably dependent on the intensity of the inflammatory process. The application of PGE$_2$ receptor blockers demonstrated that PGF$_2\alpha$ in uterine tissues may act in a non-specific manner through PGE$_2$ receptors.

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