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Original article

Influence of β_2- and β_3-adrenoceptor agonists on contractile activity of the porcine myometrium in the luteal phase and the first days of pregnancy

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Abstract

This study analysed the relaxant properties of salbutamol (β_2-adrenoceptors agonist) and BRL 37344 (β_3-adrenoceptors agonist) regarding the contractility of porcine myometrium on days 10-14 of the oestrous cycle (cyclic group; n = 10) and on days 3-5 of pregnancy (early pregnant group; n = 6). The activity of myometrial strips (tension, frequency and amplitude) was recorded under isometric conditions using force transducers. The contractility was assessed further following the administration of increasing concentrations of the agonists (10^{-9}-10^{-4} M), both with and without β-adrenoceptor antagonists (butaxamine – a selective β_2- adrenoceptor antagonist, propranolol- a non-selective β_1- and β_2-adrenoceptor antagonist and bupranolol – a non-selective β_1-, β_2- and β_3-adrenoceptor antagonist) at a concentration of 10^{-4} M. Although neither salbutamol nor BRL 37344 caused changes in the tension, at the highest concentrations they decreased the frequency and amplitude of contractions. These changes were more evident after salbutamol treatment and in the early pregnant group. Antagonists given alone did not cause changes in the parameters examined but changed some activity of the agonists. Butoxamine reduced the decrease in frequency and amplitude induced by salbutamol and produced a decrease in the tension after BRL 37344 treatment in the early pregnant group. Propranolol reduced the decrease in frequency and amplitude induced by salbutamol in both examined groups and did not cause significant changes in BRL 37344 activity. The administration of bupranolol before salbutamol treatment caused an increase in the tension and reduced the decrease in the frequency in the cyclic group. Moreover, bupranolol eliminated a decrease in frequency and induced an increase in amplitude caused by BRL 37344 in both groups and these changes were more evident in the early pregnant group. The data indicates that both β_2- and β_3-adenoreceptors are involved in the regulation of the contractility in both groups, but the changes after agonists and antagonists treatment are more evident in the early pregnant myometrium.

Key words: beta adrenoceptors, cyclic pigs, early pregnancy, uterine contractility

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Introduction

Uterine contractile activity in gilts undergoes changes during the oestrous cycle (Kitazawa et al. 2001, Cao et al. 2002, Kucharski et al. 2007, Jana et al. 2010, Jana et al. 2013) and pregnancy (Kitazawa et al. 2003, Kurowicka et al. 2005, Markiewicz et al. 2016). It is regulated by many factors, including the autonomic nerve system (Taneike et al. 1995, Kitazawa et al. 1999, Kitazawa et al. 2001). It was initially believed that β_2-adrenoceptors play a predominant role in the relaxation of rat (Engstrom et al. 1997) and human (Liu et al. 1998) myometrium. However, the presence of functional β_3-adrenoceptors has been demonstrated in human near-term (Bardou et al. 2000) and non-pregnant myometrium (Rouget et al. 2005) as well as in the myometrium of pregnant rats (Minorics et al. 2009) and mice (Parida et al. 2013). This may suggest a predominant role of the β_3-adrenoceptor in human myometrium contractility (Rouget et al. 2005, Ursino et al. 2009).

Since it is generally acknowledged that β_2-adrenoceptors are inhibitory in nature, their agonists, i.e. ritodrine and salbutamol, are used clinically in the treatment of pre-term labour (de Heus et al. 2009, Motazedian et al. 2010, Parida et al. 2013). Recently, an increased interest in the role of β_3-adrenoceptors in the regulation of myometrium contractile activity in humans (Bardou et al. 2000, 2007, Dennedy et al. 2001, 2002, Rouget et al. 2005, Pędzińska-Betiuk et al. 2011), rats (Yurtcu et al. 2006, Clouse et al. 2007, Minorics et al. 2009) and mice (Parida et al. 2013) has been observed. The above studies have demonstrated the species variability of β_3-adrenoceptor pharmacology, as well as the heterogeneous responsiveness to β_3-adrenoceptor stimulation. Moreover, in gilts there are differences in myometrial activity between cyclic and pregnant gilts (Kitazawa et al. 2001, Markiewicz et al. 2016).

Uterine contractile activity of the non-pregnant uterus has an important influence on semen transport in the reproductive tract and movement and positioning of the embryos in the uterine cavity. Fanchin et al. (1998) showed that women with high uterine contractile activity have a lower pregnancy rate after in-vitro fertilization than women with low uterine activity. Therefore, the elimination of excessive uterine contractile activity in the post-conception period may play an important role in successful implantation. Moreover, conducting research on the contractile activity at different stages of the oestrous cycle and pregnancy will accurately reveal the contraction regulation mechanisms of this organ and may increase the probability of successful pregnancy.

The early pregnancy in the pig is divided into three periods: post-conception (days 1-10 of pregnancy), the maternal recognition of pregnancy (days 11-13) and implantation (days 14-19) (Zięcik et al. 2011). In our previous study (Markiewicz et al. 2016) we showed that the presence of embryos increased contractile activity in the porcine myometrium on days 12-14 of pregnancy. Moreover, it has been shown that β_3-adenoceptors are involved in the regulation of smooth muscle contractility in the swine uterus in the peri-implantation period and their activation triggers relaxation of the myometrium to a lesser extent than the activation of the β_2-adrenoceptors (Markiewicz and Jaroszewski 2016). To date, the role of β_3-adrenoceptors in the regulation of the myometrium contractility in post-conception period has not yet been described. Therefore, the aim of the study was to verify whether β_3-adrenoceptors are involved in the regulation of the contractile activity of the porcine uterine smooth muscle contractility in the first days of pregnancy and to compare the relaxative effect of selective β_2- and β_3-agonists in the luteal phase and post-conception period.

Materials and Methods

Tissue collection

In the first group (cyclic group), the uteri (n=10) from days 10-14 of the estrous cycle were collected from mature crossbred (about seven-month-old) gilts at a local slaughterhouse. The assessment of ovarian and uterine morphology was performed to confirm the day of the estrous cycle as described previously (Leiser et al. 1988).

In the second group (early pregnant group), pre-pubertal crossbred gilts from the same herd (n=6) with an average weight of 101-110 kg were used. The gilts were treated hormonally by an intramuscular injection of 750 I.U. of eCG (Folligon, Intervet, Poland) and 500 I.U. of hCG (Chorulon, Intervet) given 72 h later. 16-18 days after hCG administration, gilts were treated with prostaglandin $F_{2\alpha}$ analogue (Dinolytic, Pfizer Trading, Poland) and again 24 h later with eCG followed with hCG after 72 h. Subsequently, 24 h after last hCG administration, the gilts were inseminated twice at a 12 h interval. The day of the second insemination was the first day of pregnancy. The gilts were slaughtered on days 3-5 of pregnancy. To confirm pregnancy, the embryos were collected by flushing the oviducts (to collect 4-celled embryos) or oviducts with the tips of the uterine horns (to collect ≥ 8-celled embryos) with 20 ml of phosphate-buffered saline (PBS). The recovered flushings were then evaluated under a stereo-microscope for

the presence of embryos at the respective stage of development to confirm the relevant day of pregnancy (day 3-4-celled embryos, day 4-8-celled embryos and day 5 – > 8-celled embryos) (Wasielak et al. 2016). The experiment was approved by the Local Ethics Commission of the University of Warmia and Mazury in Olsztyn, Poland.

Segments of the uterine horns (about 2 cm in length), collected from the middle part of the horns were transferred to ice and transported within 30 min to the laboratory and immediately processed for contractility analysis.

Preparation of the uterine strips for contractile activity measurement

The contractile activity was examined according to the method described previously (Markiewicz et al. 2012, Jana et al. 2013). Briefly, after removal of the endometrium, the strips of myometrium (3 × 5 mm) were isolated, washed in saline and suspended vertically in 5 ml of organ bath (Schuler Organ bath type 809; Hugo Sachs Electronic, Germany) containing 37°C Krebs-Ringer solution of the following composition (mol/L): NaCl, 120.3; KCl, 5.9; $CaCl_2$, 2.5; $MgCl_2$, 1.2; $NaHCO_3$, 15.5; glucose, 11.5; pH 7.4. The solution was continuously bubbled with 95% O_2 and 5% CO_2. The tension, frequency and amplitude were measured using a Hugo Sachs Elektronic (Germany) force displacement transducer (HSE F-30 type 372), a type 570 bridge coupler and recorded with HSE-ACAD W software for Windows.

The strips were loaded at 10 mN initial tension and the recording was started after prior equilibration for at least 60-90 min.

Schedule of contractile activity examination

At the beginning of the examination, the strips were incubated with increasing (10^{-6}-10^{-4} M) concentrations of acetylcholine (ACh; Sigma, St. Louis, MO, USA) to determine the viability of tissues and their usefulness for further study. Thereafter, the effects of cumulatively (10^{-9}-10^{-4} M) applied salbutamol, a selective β_2-adrenoceptor agonist (Sigma, St. Louis, MO, USA) or BRL 37344, a selective β_3-adrenoceptor agonist (Tocris Bioscience, United Kingdom) given alone and in the presence of antagonists, were examined. Three antagonists: butoxamine (a selective β_2-adrenoceptor antagonist; Sigma), propranolol (a non-selective β_1- and β_2-adrenoceptor antagonist, Sigma), and bupranolol (a non-selective β_1-, β_2- and β_3-adrenoceptor antagonist, LGC Standarts GmbH, Germany), each at concentration of 10^{-4} M, were added to the organ bath 15-min before the administration of agonists. Between each examination set, the tissue chambers were washed three times with 15 ml of the incubation solution at 10-min intervals. ACh was administered again in concentrations of 10^{-6}-10^{-4} M at the end to determine the viability of tissues. Only those results for which the difference in response to the stimulation by ACh at the onset and termination of the trial was less than 20% were included in the statistical analysis. The spontaneous contractile activity measured 10-min before the addition of agents was regarded as the control level.

Statistical analysis

The contractile activity values (tension – resting/baseline tension expressed in mN; amplitude – difference between minimum and maximum value for a single contraction expressed in mN; frequency – the number of observed peaks) of the myometrial strips before the application of the examined substances (pre-treatment period), were calculated for 10 min and accepted as 100%. The results calculated for a 10-min period after treatments were expressed as a percentage (mean ± SD) of the contraction tension, amplitude and frequency before drug administration. The statistical significance of the obtained differences was assessed by a one-way analysis of variance ANOVA (Graphpad PRISM 3.1; Graphpad Software, USA) followed by Bonferroni's Multiple Comparison Test (to compare differences with the pre-treatment period) and a Student t test (to compare differences between the same concentrations of the drug used for stimulation of the strips from cyclic and early pregnant gilts). The differences were considered significant when a p value was less than 0.05.

Results

Examinations were only performed on myometrial strips which showed regular spontaneous contractile activity (Fig. 1) and an increase in tension after ACh stimulation.

Effect of salbutamol and BRL 37344

Salbutamol in all examined concentrations did not cause significant changes in the tension in either of the examined groups (Fig. 2A) compared to the pre-treatment period. However, its administration significantly ($p<0.05$–0.001) decreased the frequency of

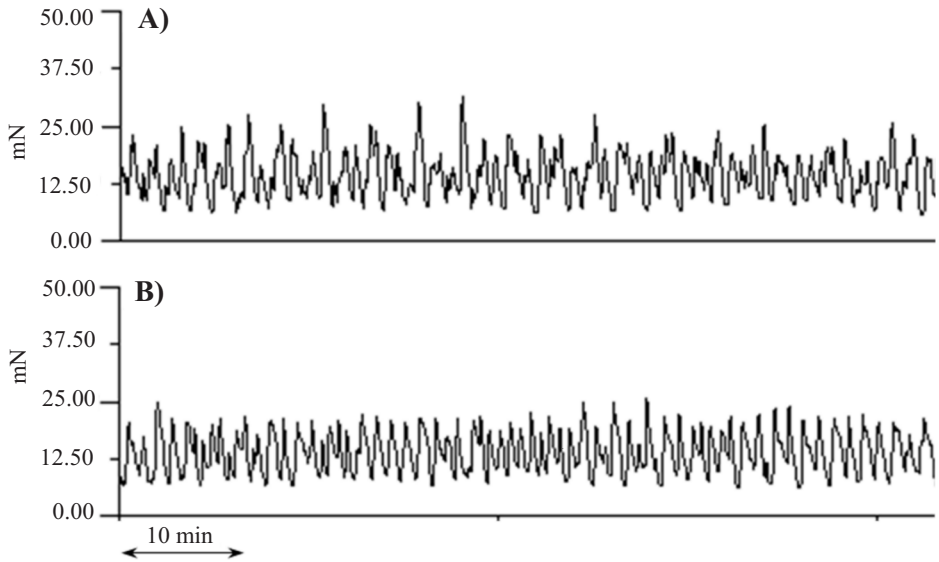

Fig. 1. Representative diagrams showing the spontaneous, regular activity of porcine myometrial strips collected on days 10-14 of the oestrous cycle (A) and on days 3-5 of early pregnancy (B).

contractions at 10^{-6}-10^{-4} M concentrations in both groups (Fig. 2B). In the cyclic group, the decrease in contraction frequency was significantly lower after treatment at the 10^{-6} M ($p<0.01$) and 10^{-5} M ($p<0.001$) concentrations compared to the early pregnant group. Salbutamol also decreased ($p<0.05$–0.001) the amplitude of contractions at 10^{-5} and 10^{-4} M and 10^{-6}-10^{-4} M concentrations in the cyclic and early pregnant groups, respectively (Fig. 2C), compared to the pre-treatment period. The decrease was significantly ($p<0.01$) lower in the cyclic group after treatment at the 10^{-5} M concentration compared to the early pregnant group.

BRL 37344 did not cause significant changes in the tension in either of the examined groups (Fig. 2A'), but caused a significant decrease in the contraction frequency at the 10^{-4} M concentration ($p<0.001$) in the cyclic group and at the 10^{-6}-10^{-4} M concentrations ($p<0.01$–0.001) in the early pregnant group (Fig. 2B') compared to the pre-treatment period. The decrease was significantly ($p<0.01$–0.001) lower in the cyclic group after treatment at the 10^{-6} and 10^{-5} M concentration compared to the early pregnant group. The amplitude decreased significantly after BRL 37344 administration at the 10^{-4} M ($p<0.001$) concentration in the cyclic group and at 10^{-6}-10^{-4} M ($p<0.05$–0.001) concentrations in the early pregnant group (Fig. 2C') compared to the pre-treatment period. The decrease was significantly ($p<0.05$) lower in the cyclic group after treatment at the 10^{-5} M concentration compared to the early pregnant group.

Effect of butoxamine pre-treatment on salbutamol and BRL 37344 activity

Butoxamine alone did not cause significant changes in any parameter in either group (Fig. 3) compared to the pre-treatment period.

Salbutamol administered after butoxamine did not affect the tension in either cyclic or early pregnant groups (Fig. 3A) although it significantly ($p<0.01$–0.001) decreased the contraction frequency at 10^{-6}-10^{-4} M and 10^{-5}-10^{-4} M concentrations in the cyclic and early pregnant group (Fig. 3B), respectively, and the amplitude at the 10^{-4} M concentration in both of the examined groups (Fig. 3C) compared to the pre-treatment period.

BRL 37344 administered after butoxamine did not affect the tension in the cyclic group but caused a significant ($p<0.05$–0.001) decrease in 10^{-6}-10^{-4} M concentrations in the early pregnant group (Fig. 3A') compared to the pre-treatment period. In the early pregnant group, the tension was signifi -cantly ($p<0.05$–0.001) lower after treatment at 10^{-6}-10^{-4} M concentrations compared to the cyclic group. In both groups, the contraction frequency decreased significantly after BRL 37344 administration at 10^{-6} M ($p<0.05$) and 10^{-5} and 10^{-4} M ($p<0.001$) (Fig. 3B') concentrations compared to the pre-treatment period. The contraction amplitude significantly decreased after an agonist administration at 10^{-5} M ($p<0.05$) and 10^{-4} M ($p<0.001$) concentrations in the cyclic group and 10^{-6} M ($p<0.05$) and 10^{-5}-10^{-4} M ($p<0.001$) concentrations in the early pregnant group (Fig. 3C') compared to the pre-treatment period.

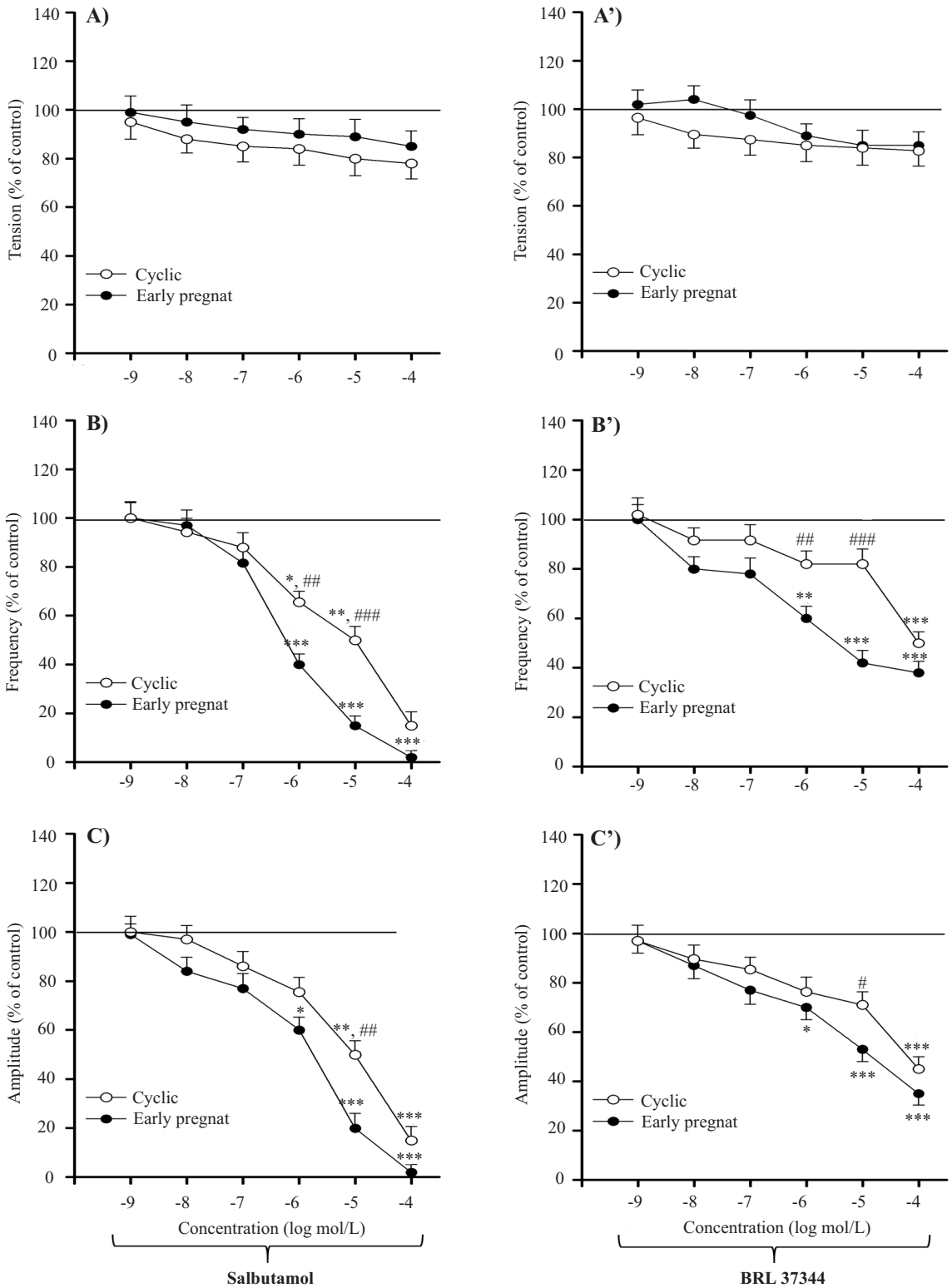

Fig. 2. The effect of increasing (10^{-9}-10^{-4} M) concentrations of salbutamol, a selective agonist of β_2-adrenoceptors and BRL 37344, a selective agonist of β_3-adrenoceptors on the tension (A, A'), frequency (B, B') and amplitude (C, C') of contractions of the porcine myometrial strips collected on days 10-14 of the oestrous cycle (-o- – Cyclic; n=10) and on days 3-5 of early pregnancy (-●- – Early pregnant; n=6). The results calculated for a 10 min period after treatments were expressed as a percentage (mean ± SD) of the tension, amplitude and frequency determined for a 10 min period before agonist administration.
*p<0.05, **p<0.01, ***p<0.001 – indicate significant differences compared to a 10 min pre-treatment period; #p<0.05, ##p<0.01, ###p<0.001 – indicate significant differences between agonist used in the cyclic and early pregnant groups at the same concentrations.

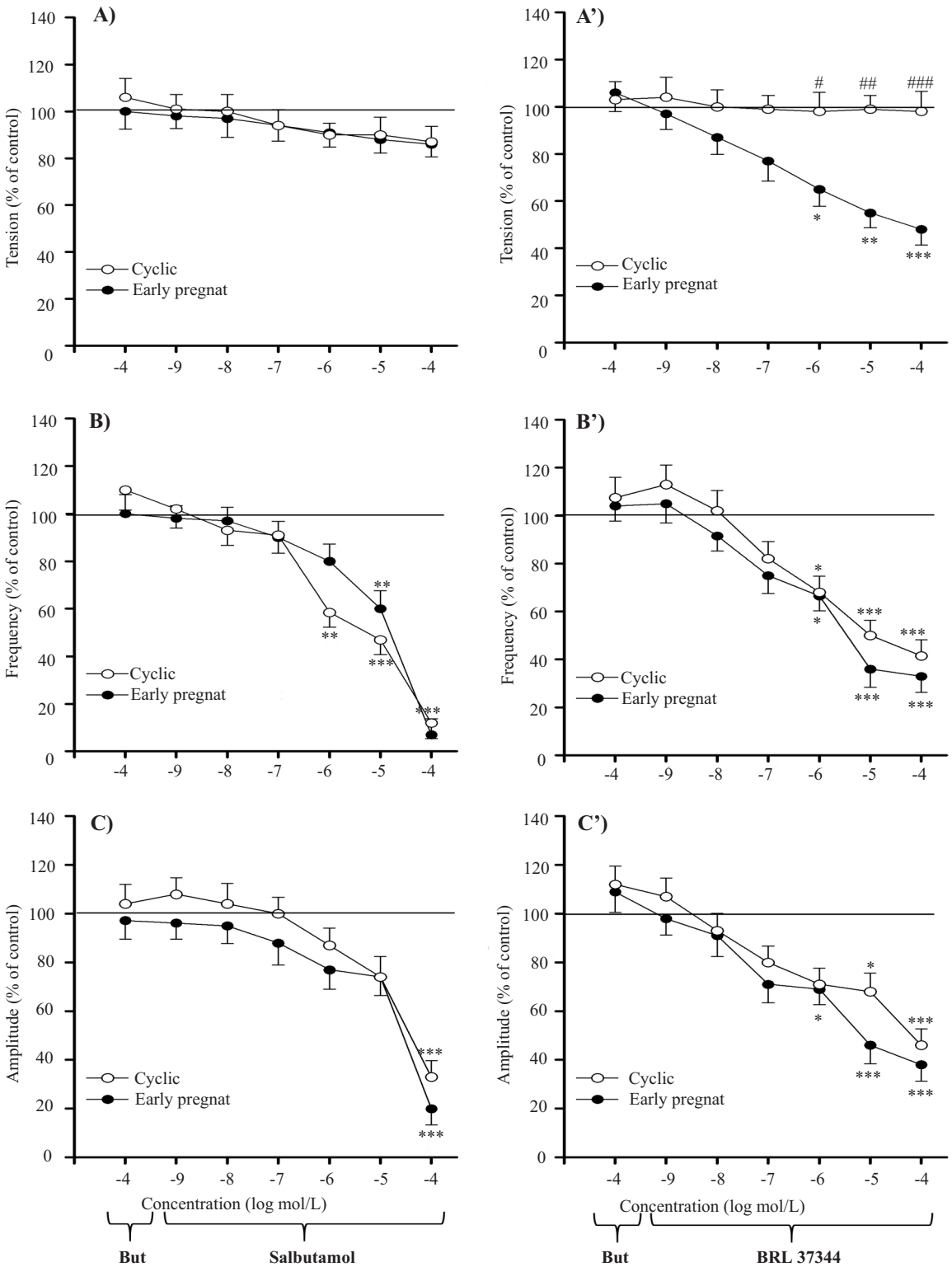

Fig. 3. The influence of butoxamine (But), a selective antagonist of β_2-adrenoceptors, on changes in the tension (A, A'), frequency (B, B') and amplitude (C, C') induced by increasing (10^{-9}-10^{-4} M) concentrations of salbutamol, a selective agonist of β_2-adrenoceptors and BRL 37344, a selective agonist of β_3-adrenoceptors, in the porcine myometrial strips collected on days 10-14 of the oestrous cycle (-o- – Cyclic; n=10) and on days 3-5 of early pregnancy (-●- – Early pregnant; n=6). The results calculated for a 10 min period after treatments were expressed as a percentage (mean ± SD) of the tension, amplitude and frequency determined for a 10 min period before agonist administration.

*p<0.05, **p<0.01, ***p<0.001 – indicate significant differences compared to a 10 min pre-treatment period; #p<0.05, ##p<0.01, ###p<0.001 – indicate significant differences between agonist used in cyclic and early pregnant group at the same concentrations.

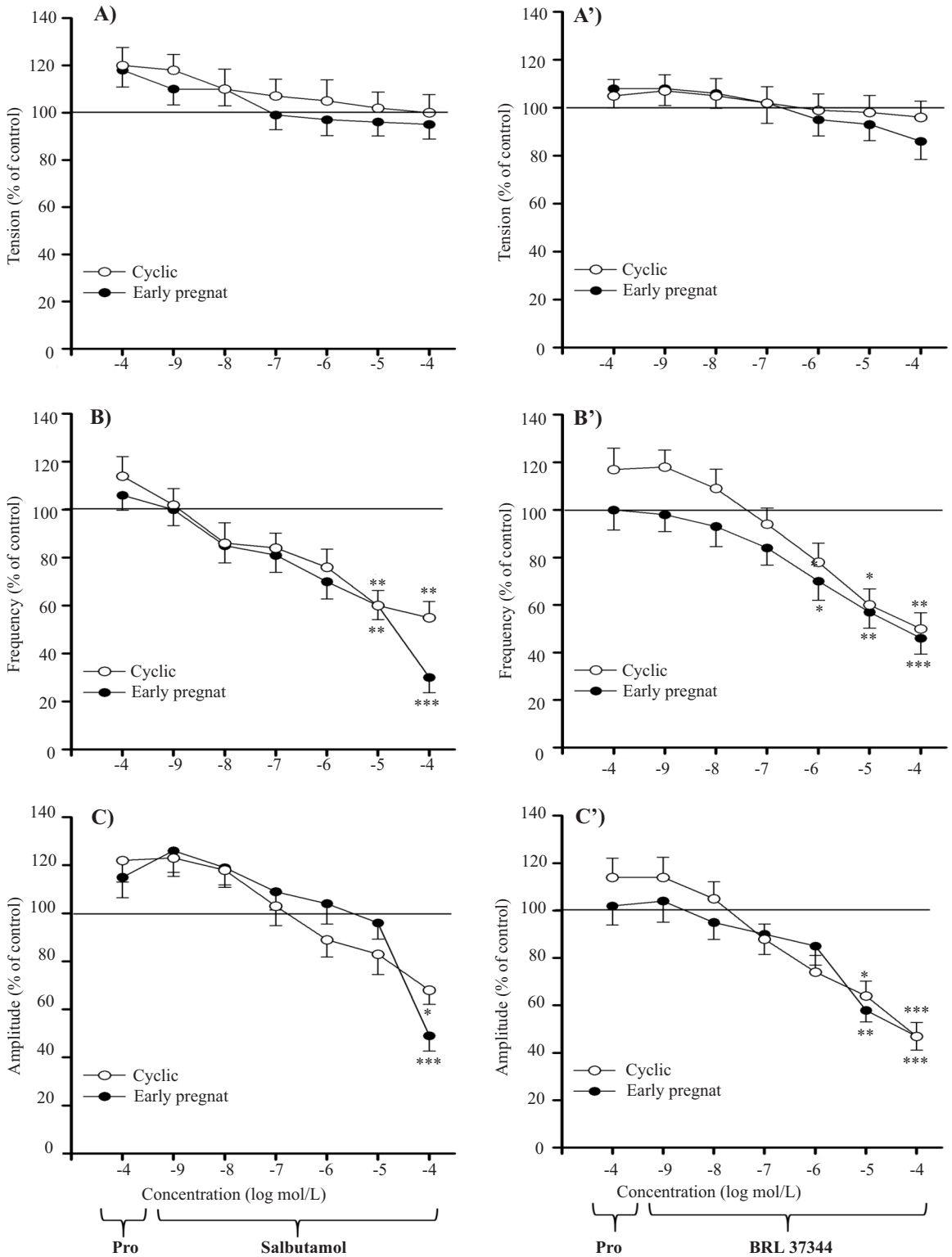

Fig. 4. The influence of propranolol (Pro), an antagonist of β_1- and β_2-adrenoceptors on changes in the tension (A, A'), frequency (B, B') and amplitude (C, C') induced by increasing (10^{-9}-10^{-4} M) concentrations of salbutamol, a selective agonist of β_2-adrenoceptors and BRL 37344, a selective agonist of β_3-adrenoceptors in the porcine myometrial strips collected on days 10-14 of the oestrous cycle (-o- – Cyclic; n=10) and on days 3-5 of early pregnancy (-●- – Early pregnant; n=6). The results calculated for a 10 min period after treatments were expressed as a percentage (mean ± SD) of the tension, amplitude and frequency determined for a 10 min period before agonist administration.
*p<0.05, **p<0.01, ***p<0.001 – indicate significant differences compared to a 10 min pre-treatment period.

Effect of propranolol pre-treatment on salbutamol and BRL 37344 activity

Propranolol did not affect contractile activity in either of the examined groups (Fig. 4).

The administration of salbutamol after propranolol did not cause significant changes in the tension (Fig. 4A), but caused a significant decrease in the contraction frequency at concentration 10^{-5} M ($p<0.01$) in both of the examined groups and 10^{-4} M ($p<0.01$) in the cyclic and the early pregnant ($p<0.001$) group (Fig. 4B) and in the contraction amplitude at the 10^{-4} M concentration in the cyclic ($p<0.05$) and the early pregnant ($p<0.001$) group (Fig. 4C) compared to the pre-treatment period.

BRL 37344 administered after propranolol did not cause significant changes in the tension in either group (Fig. 4A') compared to the pre-treatment period. A significant decrease in the frequency of contractions was observed after the administration of the agonist at 10^{-5} and 10^{-4} M ($p<0.05$ – 0.01) concentrations in the cyclic group and at 10^{-6}-10^{-4} M ($p<0.05$ – 0.001) concentrations in the early pregnant group (Fig. 4B') compared to the pre-treatment period. The amplitude of contractions decreased significantly ($p<0.05$ – 0.001) after agonist administration at 10^{-5} and 10^{-4} M concentrations in both groups (Fig. 4C').

Effect of bupranolol pre-treatment on salbutamol and BRL 37344 activity

Bupranolol did not change the spontaneous contractile activity in either group (Fig. 5).

Salbutamol administered after bupranolol caused a significant increase in the tension at 10^{-9} and 10^{-8} M ($p<0.01$) and 10^{-7} M ($p<0.05$) concentrations in the cyclic group but did not affect this parameter in the early pregnant group (Fig. 5A) compared to the pre-treatment period. The contraction frequency was significantly ($p<0.01$–0.001) decreased after salbutamol administration at 10^{-5} and 10^{-4} M and 10^{-6}-10^{-4} M concentrations in the cyclic and early pregnant groups, respectively (Fig. 5B) compared to the pre-treatment period. The decrease in the cyclic group was significantly lower after the agonist treatment at the 10^{-5} M ($p<0.01$) and 10^{-4} M ($p<0.05$) concentrations compared to the early pregnant group. The amplitude significantly decreased after salbutamol treatment at the 10^{-4} M ($p<0.05$) concentration in the cyclic group and at 10^{-6}-10^{-4} M ($p<0.01$–0.001) concentrations in the early pregnant group (Fig. 5C) compared to the pre-treatment period. The decrease in the early pregnant group was significantly ($p<0.001$) higher after treatment at 10^{-6}-10^{-4} M concentrations compared to the cyclic group.

In both examined groups, BRL 37344 administered after bupranolol did not cause significant changes in the tension (Fig. 5A') or contraction frequency (Fig. 5B') compared to the pre-treatment period. The amplitude significantly increased after agonist administration at 10^{-9}-10^{-7} M ($p<0.05$) concentrations in the cyclic group and 10^{-9}-10^{-5} M ($p<0.05$–0.01) concentrations in the early pregnant group (Fig. 5C') compared to the pre-treatment period. In the cyclic group, this parameter was significantly ($p<0.05$) lower after treatment at the 10^{-4} M concentration compared to the early pregnant group.

Discussion

Our data indicate that neither salbutamol nor BRL 37344 caused changes in the tension, but at the highest concentrations they decreased the frequency and amplitude of contractions. However, these changes were more evident after salbutamol treatment and in the early pregnant group than in cyclic ones. This suggests that in the post-conception period, the representation and/or reactivity of β_2-adrenoceptors in the porcine myometrium is higher than β_3-adrenoceptors. Our results are similar to the data obtained by Kitazawa et al. (2001) who showed that inhibition of porcine uterine contractility by catecholamines in the proestrous is mediated mainly via β_2-adrenoceptors. The authors also showed that in cyclic gilts, clenbuterol (a selective β_2-adrenoceptor agonist) was more potent in inhibiting uterine contractility than xamoterol (a selective β_1-adrenoceptor agonist) and BRL 37344 (a selective β_3-adrenoceptor agonist). Moreover, inhibition of spontaneous contractions by isoprenaline increased in pregnant pigs (25-60 gestation days) compared to proestrous pigs (Kitazawa et al. 2001). Our previous findings also indicated that activation of the β_2-adrenoceptors in the peri-implantation period triggers relaxation of the myometrium to a greater extent than the activation of the β_3-adrenoceptors (Markiewicz and Jaroszewski 2016). These findings confirm the suggestion that in the porcine uterus, β_2-adrenoceptors play a predominant role and their activity increases during the course of pregnancy.

Our data also indicate that blockade of β_2-adrenoceptors with butoxamine did not change the activity of salbutamol but induced a decrease in tension after BRL 37344 treatment in the early pregnant gilts. These data are in contrast with our previous observation from the peri-implantation period (Markiewicz and Jaroszewski 2016) when the activity of salbutamol

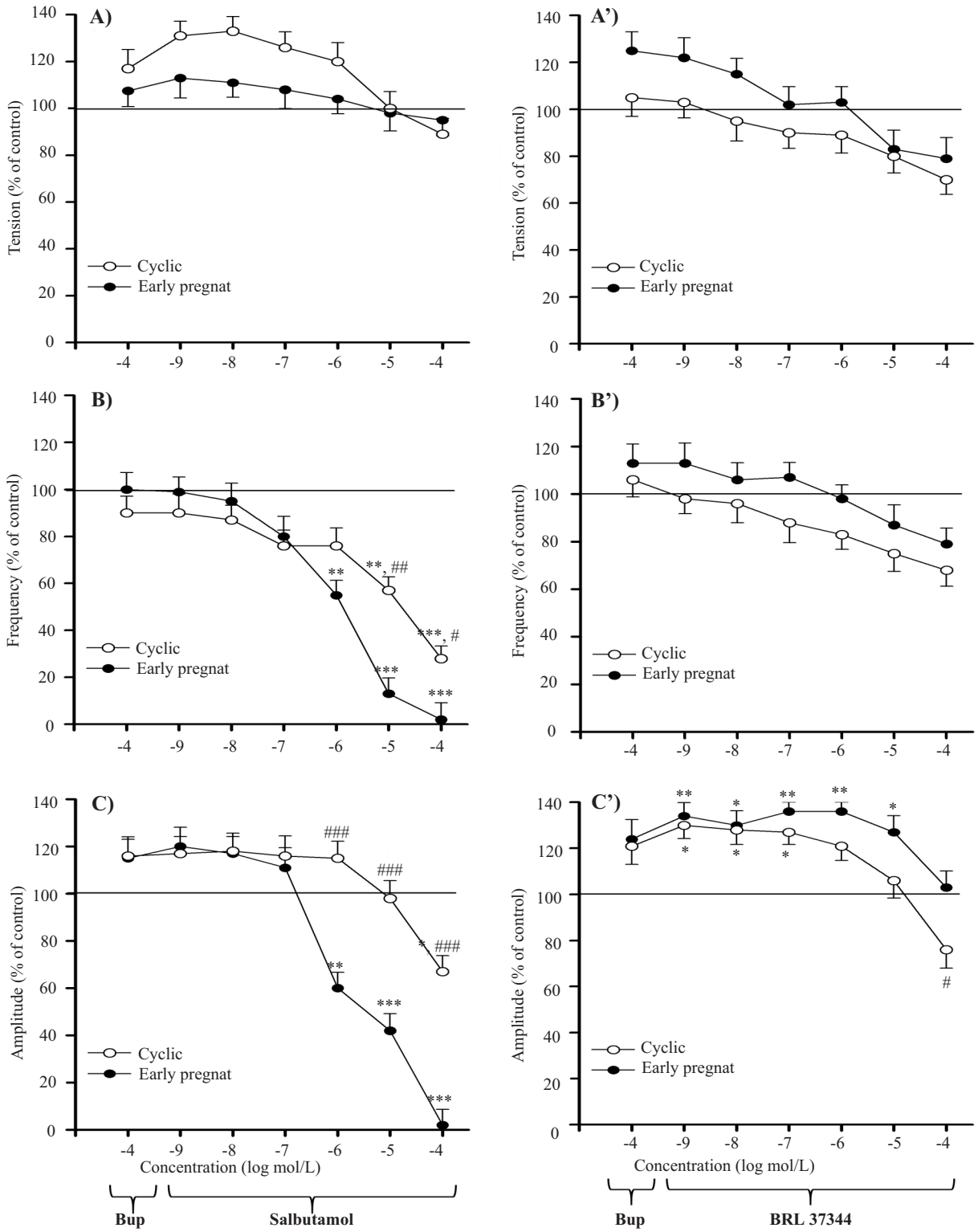

Fig. 5. The influence of bupranolol (Bup), an antagonist of β_1-, β_2- and β_3- adrenoceptors on changes in the tension (A, A'), frequency (B, B') and amplitude (C, C') induced by increasing (10^{-9}-10^{-4} M) concentrations of salbutamol, a selective agonist of β_2-adrenoceptors and BRL 37344, a selective agonist of β_3-adrenoceptors in the porcine myometrial strips collected on days 10-14 of the oestrous cycle (-o- – Cyclic; n=10) and on days 3-5 of early pregnancy (-●- – Early pregnant; n=6). The results calculated for a 10 min period after treatments were expressed as a percentage (mean ± SD) of the tension, amplitude and frequency determined for a 10 min period before agonist administration.
*p<0.05, **p<0.01, ***p<0.001 – indicate significant differences compared to a 10 min pre-treatment period; $^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001 – indicate significant differences between agonist used in cyclic and early pregnant group at the same concentrations.

was inhibited by a β_2-adrenoceptor antagonist. Such differences were not observed when the administration of agonists was preceded by propranolol treatment. Our results may indicate that the response of β_2-adrenoceptors to their stimulation/inhibition depends on the exact stage of pregnancy and the final contractile effect also depends on the activity of β_1- and β_3-adrenoceptors. A study comparing the effect of isoprenaline and two selective β_2-adrenoceptor agonists (salbutamol and ritodrine) in strips from the pregnant and non-pregnant myometrium of the goat and from the pregnant myometrium of the cow showed that isoprenaline caused a reduction in the spontaneous contractions of the pregnant myometrium, but neither salbutamol nor ritodrine caused a reduction in the spontaneous contractions in the non-pregnant myometrium (Larsen 1979). Moreover, Kitazawa et al. (2003) showed that the inhibition of contractility caused by isoprenaline was decreased by propranolol. The above data indicate that all β-adrenoceptors are involved in the regulation of the myometrium contractility and the predominance of one of them may be dependent on the physiological status of the uterus and animal species.

Rouget et al. (2005) provided the first evidence that not only are β_3-receptors present, but that they are also the predominant subtype compared to β_2-receptors, both in human non-pregnant and pregnant myometrium. More recently, Dennedy et al. (2002) showed that BRL 37344 induced relaxation of human myometrial strips from biopsies obtained from caesarean sections with a similar potency to ritodrine. Pędzińska-Bietuk et al. 2008, using another agonist (CL 316243), also confirmed the participation of β_3-adrenoceptors in the inhibition of spontaneous contractile activity of human non-pregnant myometrium. In our study, the administration of bupranolol before salbutamol treatment caused an increase in the tension and reduction of the decrease in the frequency in the cyclic group. Moreover, bupranolol abolished a decrease in the frequency and induced an increase in amplitude caused by BRL 37344 in both groups and these changes were more evident in the early pregnant group. A similar antagonistic impact of bupranolol on the effect of BRL 37344 and ritodrine was observed in human non-pregnant myometrium (Pędzińska-Bietuk et al. 2011). The results of our study indicate that participation of β_3-adrenoceptors in the regulation of the porcine myometrium contractility increased during the first days of pregnancy. Moreover, the data confirmed the involvement of both β_2- and β_3-adrenoceptors in the regulation of the porcine myometrium contractility in the estrous cycle and post-conception period.

Summarizing, the present study provides evidence that both β_2- and β_3-adenoreceptors are involved in the regulation of the myometrium contractility in cyclic and early pregnant gilts, but the changes in the contractile activity after agonist and antagonist treatment are more evident in the early pregnant myometrium. In the future, pharmacological modulation of uterine β_3-adrenoceptors may be used to reduce excessive contractile activity function during embryo transfer. However, some discrepancies in the results obtained from different models of study indicate that a precise explanation of the role of β_3-adrenoceptors in the uterine contractile activity needs further scientific analysis.

Acknowledgments

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