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ORIGINAL RESEARCH ARTICLE

Combined uterorelaxant effect of magnesium sulfate and terbutaline: Studies on late pregnant rat uteri in vitro and in vivo

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Abstract

Introduction: Preterm delivery and its complications are among the biggest challenges and health risks in obstetrical practice. Several tocolytic agents are used in clinical practice, although the efficacy and side effect profiles of these drugs are not satisfying. The aim of this study was to investigate the uterus relaxant effect of the coadministration of β_2-mimetic terbutaline and magnesium sulfate ($MgSO_4$) in an isolated organ bath and to perform in vivo smooth muscle electromyographic (SMEMG) studies in pregnant rats. In addition, we also investigated whether the tachycardia-inducing effect of terbutaline can be reduced by the presence of magnesium, due to the opposite heart rate modifying effects of the two agents.

Material and methods: In the isolated organ bath studies, rhythmic contractions of 22-day- pregnant Sprague–Dawley rats were stimulated with KCl, and cumulative dose–response curves were constructed in the presence of $MgSO_4$ or terbutaline. The uterus-relaxing effects of terbutaline were also investigated in the presence of $MgSO_4$ in both normal buffer and Ca^{2+}-poor buffer. The in vivo SMEMG studies were carried out under anesthesia with the subcutaneous implantation of an electrode pair. The animals were treated with $MgSO_4$ or terbutaline alone or in combination in a cumulative bolus injection. The implanted electrode pair also detected the heart rate.

Results: Both $MgSO_4$ and terbutaline reduced uterine contractions in vitro and in vivo, furthermore, the administration of a small dose of $MgSO_4$ significantly enhanced the relaxant effect of terbutaline, especially in the lower range. However, in Ca^{2+}-poor environment, $MgSO_4$ was not able to increase the effect of terbutaline, indicating the role of $MgSO_4$ as a Ca^{2+} channel blocker. In the cardiovascular studies, $MgSO_4$ significantly decreased the tachycardia-inducing effect of terbutaline in late pregnant rats.

Abbreviations: AUC, area under the curve; EC_{50}, half maximal effective concentration; E_{max}, maximal inhibitory effect; SMEMG, smooth muscle electromyography.

Conclusions: The combined application of $MgSO_4$ and terbutaline may have clinical significance in tocolysis, which must be confirmed in clinical trials. Furthermore, $MgSO_4$ could substantially reduce the tachycardia-inducing side effect of terbutaline.

KEYWORDS
magnesium sulfate, pregnancy, tocolysis, uterine contractility, β_2-adrenoreceptor agonists

1 | INTRODUCTION

Preterm birth is defined by the World Health Organization as childbirth between 20 and 37 weeks of gestation, which is one of the biggest challenges and health risks in obstetrical practice. Preterm delivery and its complications are the leading cause of mortality and a variety of health and developmental problems, such as cerebral palsy, intellectual disabilities, and vision or hearing impairments all over the world.[1,2] Several mechanisms of diseases implicated in spontaneous preterm labor are known nowadays. Infections, vascular or cervical diseases, decidual senescence, uterine overdistension, breakdown of maternal-fetal tolerance and other genetic or environmental factors may contribute to the process.[3] A wide range of drugs (tocolytics) are applied to inhibit myometrial contractions, including β-adrenergic receptor agonists (betamimetics), calcium channel blockers, prostaglandin inhibitors, oxytocin receptor antagonists, nitric oxide donors and magnesium sulfate ($MgSO_4$). The main goal of using these tocolytic drugs is to delay delivery long enough to allow for the administration of prophylactic corticosteroids to decrease the severity of lung disease of prematurity, prolong gestation to achieve fetal maturation and allow time to transfer the mother to a high-level health care facility.[4] Although the currently available tocolytic agents are used in clinical practice, the efficacy and side effect profiles of these drugs are not satisfying.[5]

It is known that β_2-agonist terbutaline had been considered for first-line clinical use; however, the applied high doses and the presence of β-adrenergic receptors in the cardiovascular system cause a number of severe maternal side effects, such as reflex tachycardia, which compensate for the hypotension caused by vasodilation. Moreover, other adverse effects such as headache, tremor, dyspnea or pulmonary oedema are responsible for its limited use.[6] Its smooth muscle relaxant effect is linked to the increased intracellular level of cyclic adenosine monophosphate (cAMP) as myosin light-chain kinase activity is inhibited.[7]

$MgSO_4$ was first described as a tocolytic agent, but nowadays it is mostly used in the treatment of eclampsia and for fetal neuroprotection.[8,9] However, the exact mechanism of action of $MgSO_4$ has not been completely defined. It is suggested that magnesium acts both intra- and extracellularly. It is able to inhibit the transport of Ca^{2+} through the voltage-gated calcium channels and to decrease Ca^{2+} release from the sarcoplasmic reticulum.[10] The therapeutic use of $MgSO_4$ is controversial regarding the benefits and maternal and fetal adverse effects. Common maternal side effects such as bradycardia, flushing, nausea, headache, and hypothermia, as well as fetal side effects like lethargy, hypotonia, hypocalcemia, and respiratory depression limit the applicability of $MgSO_4$.[7,11] In spite of these unfavorable side effects, magnesium can be used successfully in cardiac arrhythmias due to its important role in cardiac metabolism and its electrophysiological properties.[12]

Key message

$MgSO_4$ significantly enhanced the uterorelaxant effect of terbutaline, while the tachycardia-inducing adverse effect of terbutaline was reduced. The combined application of $MgSO_4$ and terbutaline may have clinical significance in tocolysis.

There is an increased need for tocolytic therapy with better efficacy, which may involve the combination of already applied drugs. Earlier we proved that the addition of a β_2-agonist to a Ca^{2+} channel blocker enhanced the effect of the Ca^{2+} antagonist on pregnant rat myometrium in vitro and in vivo.[13] As a further combination with terbutaline, our aims were to investigate the uterus relaxant effect of the coadministration of β_2-mimetic terbutaline and $MgSO_4$ in an isolated organ bath and to perform in vivo smooth muscle electromyographic (SMEMG) studies in pregnant rats. In addition, we also investigated whether the tachycardia-inducing effect of terbutaline can be reduced by the presence of magnesium, due to the opposite heart rate modifying effects of the two agents.

2 | MATERIAL AND METHODS

2.1 | Housing and handling

The animals were housed in rooms with controlled temperature (22 ± 3°C), humidity (30%–70%), and light (12 h light/dark cycle), with tap water and standard rodent pellet (Animalab Hungary Ltd, Vác, Hungary) available ad libitum.

2.2 | Mating of the animals

Male (240–260 g) and female (180–200 g in the estrus phase) Sprague–Dawley rats were mated in a special mating cage. Copulation was confirmed by the presence of a copulation plug or sperm in the

vaginal smears. After the successful copulation, female rats were separated and were regarded as first-day pregnant animals.

2.3 | Isolated organ studies

2.3.1 | Uterus preparation

The animals were terminated by inhalation of carbon dioxide. Uterine samples were removed from 22-day-pregnant rats (250–350 g). After the horns of uteri were excised, 5-mm-long muscle rings were sliced (4 rings from 1 animal), cleaned of fat and connective tissue, and mounted vertically in an organ bath containing 10 mL of de Jongh solution (composition: 137 mM NaCl, 3 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 12 mM $NaHCO_3$, 4 mM NaH_2PO_4, 6 mM glucose, pH = 7.4). The organ bath was maintained at 37°C and carbogen (95% O_2+ 5% CO_2) was bubbled through the buffer. Before carrying out the experiments, the rings were equilibrated for about 1 h, with a solution change every 15 min. The initial tension of the uterus samples was set to about 1.5 g, which was measured with a gauge transducer (SG-02; MDE GmbH.) and recorded and analyzed with a SPEL Advanced ISOSYS Data Acquisition System (MDE GmbH).

2.3.2 | Magnesium sulfate studies

The uteri were placed in the organ bath as described above. Equilibrated contractions were elicited with 25 mM KCl (7–10 min), and cumulative concentration–response curves were constructed in each experiment in the presence of $MgSO_4$ (10^{-8} – 10^{-2} M) (Molar Chemicals Kft.). Recording was performed for 5 min after each concentration of $MgSO_4$. Concentration–response curves were fitted, and the areas under the curves (AUCs) were evaluated and analyzed statistically. From the AUC values, the maximal inhibitory effect (Emax) of $MgSO_4$ and the concentration of $MgSO_4$ eliciting 50% of the maximal inhibition of uterine contraction (EC_{50}) were calculated.

2.3.3 | Magnesium sulfate combination with terbutaline

The drug combination studies were carried out by using the method described above, and the contractions were induced by KCl. The cumulative-concentration response curves were elicited in the presence of $MgSO_4$ in combination with terbutaline (Sigma-Aldrich, Budapest, Hungary). After one dose of $MgSO_4$ (10^{-7} M), terbutaline (10^{-9}–10^{-5} M) was administered every 5 min. The uterus-relaxing effects of terbutaline were also investigated alone.

The uterus relaxant effects of the combination of $MgSO_4$ and terbutaline were also investigated in Ca^{2+}-reduced buffer in vitro. As opposed to the normal 1 mM Ca^{2+}-containing buffer, a solution containing 0.1 mM Ca^{2+} was used to induce a low Ca^{2+} environment. During the incubation time, normal De Jongh solution was used for 1 h, and after this equilibration period, the buffer was changed to the low Ca^{2+}-containing buffer.

2.4 | Smooth muscle electromyographic studies

Twenty-two-day-pregnant rats were used for the SMEMG measurements. Anesthesia was induced by intraperitoneal (i.p.) injection of ketamine (36 mg/kg)-xylazine (4 mg/kg) and maintained by the inhalation of isoflurane (0.5%–1%) (R550 multioutput Animal Anesthesia Machine, Animalab Hungary Ltd.). The jugular vein was cannulated for intravenous drug administration, and a bipolar disk electrode (SEN-15-2; MDE GmbH) was inserted subcutaneously above the uterus to detect the myoelectric signals of contractions in the pregnant uterus (the distance between the two electrodes was 20 mm). Control myoelectric signals were registered for 45 min, and a 1: 100 mixture of heparin-Na and physiological saline was injected into the jugular vein every 15 min to prevent coagulation. The animals were treated with $MgSO_4$ or terbutaline alone in a cumulative way every 15 min. The effect of the coadministration of $MgSO_4$-terbutaline was also registered. In each dose, the animals were treated with constant intravenous $MgSO_4$ (0.3 mg/kg) while increasing doses of terbutaline (from 0.05 to 50 μg/kg every 15 min) were added in a cumulative manner. The myoelectric signals of the pregnant uterus, representing the strength of contractions,[14] were detected by an online computer system (SPEL Advanced ISOSYS Data Acquisition System). Uterine contractility was evaluated by fast Fourier transformation (FFT). The spectrum of the SMEMG activity was characterized in the frequency range of 1–3 cycles per minute, and the power spectrum density maximum (PsD_{max}) was calculated.

2.5 | Heart rate measurements

A bipolar disk electrode (SEN-15-2; MDE GmbH) was placed subcutaneously on the surface of the abdominal wall to detect the heart rate signals of rats on day 22 of pregnancy under anesthesia as described above (Figure 1). After control signals were measured (15 min), terbutaline (50 μg/kg or 500 μg/kg) was injected into the cannulated jugular vein to detect the changes in frequency for 15 min. The combination of terbutaline (50 μg/kg or 500 μg/kg) with $MgSO_4$ (2.1 mg/kg, which is equivalent to 7 doses of $MgSO_4$ used during the SMEMG experiments) was also registered. Heart rate signals were detected with an SMEMG/HR/BT Holter system (MSB-MET Ltd.).

2.6 | Statistical analyses

All data were analyzed using Prism version 5.01 (GraphPad Software) computer program. The values were statistically evaluated with an

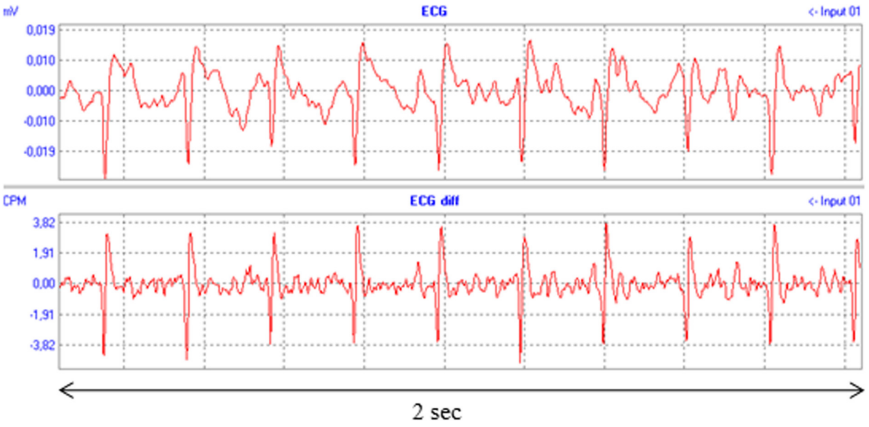

FIGURE 1 Heart rate signals of the pregnant rat detected with a bipolar disk electrode, which was positioned on the abdomen under anesthesia. For easier readability, we used the differential of the electrocardiogram signal (ECG diff) for analysis.

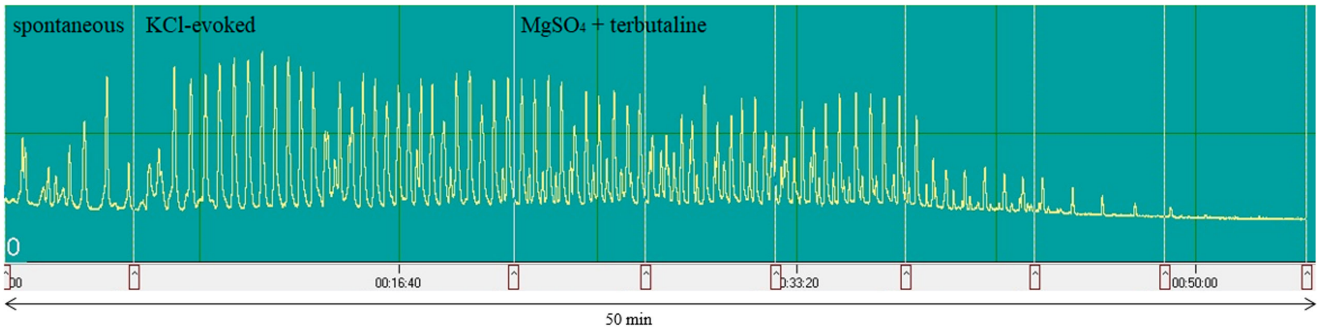

FIGURE 2 Recorded signals of the 22-day-pregnant uterus in vitro: spontaneous contractions, KCl-evoked contractions and contractions in the presence of $MgSO_4$ and terbutaline.

unpaired *t*-test. Shapiro–Wilk test was used to assess normality of distribution (p-value = 0.743).

2.7 | Ethics statement

The animals were treated in accordance with the European Communities Council Directive (2010/63/EU) and the Hungarian Act for the Protection of Animals in Research (Article 32 of Act XXVIII). All experiments involving animal subjects were carried out with the approval of the National Scientific Ethical Committee on Animal Experimentation (registration number: XIII./72/2020, February 25, 2020–February 25, 2023).

3 | RESULTS

3.1 | In vitro contractility studies

Myometrial activity was determined by the AUC of the concentration-response curves of 22-day-pregnant Sprague–Dawley rat uterine strips (Figure 2). Both $MgSO_4$ and terbutaline inhibited the KCl-evoked (25 mM) contractions in a concentration-dependent manner. The maximal inhibitory effect (E_{max}) of $MgSO_4$ reached almost 100% in the range of 10^{-8}–10^{-1} M (Figure 3A; Table 1). The E_{max} of terbutaline alone was also over 90% in the range of 10^{-10}–10^{-4} M. Pre-treatment with $MgSO_4$ (10^{-7} M) significantly enhanced the relaxant effect of terbutaline, especially in the lower range ($p < 0.01$); however, it could not improve the E_{max} of terbutaline (Figure 2, 3B). The maximal uterus relaxant effect (E_{max}) and the EC_{50} of terbutaline compared with the combination ($MgSO_4$ pre-treatment (10^{-7} M + terbutaline)) were not significant in reduced Ca^{2+} buffer (0.1 mM Ca^{2+}) (Figure 3C; Table 1).

3.2 | In vivo contractility studies

Both $MgSO_4$ and terbutaline caused dose-dependent myometrial relaxation on 22-day-pregnant rats in vivo. The E_{max} of $MgSO_4$ was about 70% relaxation in the range of 0.1–30 mg/kg (Figure 5A), while the relaxing E_{max} of terbutaline (94.3% ± 1.8%) was similar to the in vitro results in the range of 0.05–50 μg/kg. The maximal inhibition of the coadministration was not statistically different from the administration of terbutaline alone; however, the curve was shifted to the left (Figure 4, 5B; Table 2).

3.3 | Heart rate studies

Both the lower dose (50 μg/kg) and the higher dose (500 μg/kg) of terbutaline alone increased heart rate, especially at the beginning of the experiment. In the case of the lower dose of terbutaline

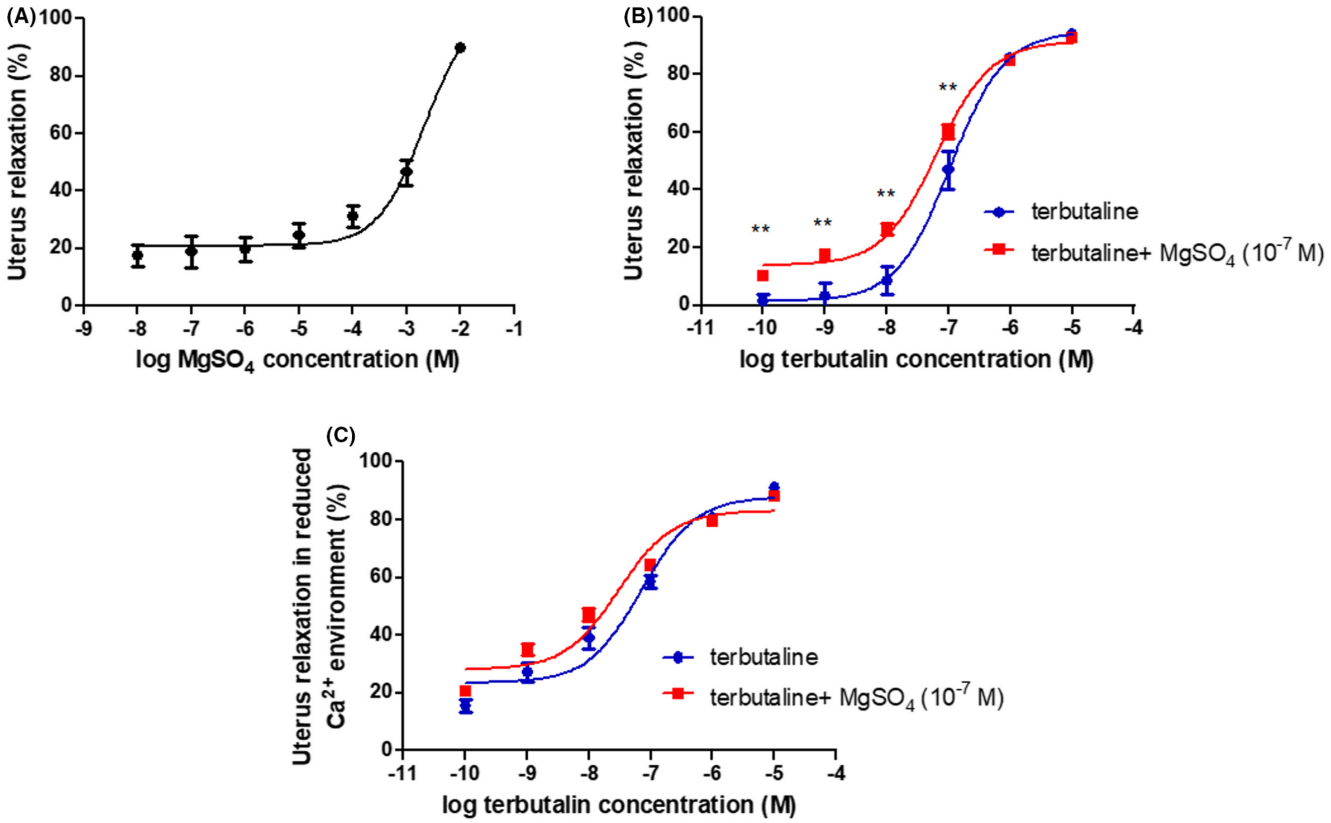

FIGURE 3 Inhibitory effect of $MgSO_4$ alone (A), terbutaline alone (B) and in combination with $MgSO_4$ (10^{-7} M) (B) in normal Ca^{2+}-containing buffer. Also, inhibitory effect of terbutaline alone (C) and in combination with $MgSO_4$ (C) in reduced Ca^{2+} environment on contractions evoked by 25 mM KCl on pregnancy day 22. $^{**}p < 0.01$.

TABLE 1 EC_{50} and E_{max} values of curves of uterine relaxation induced by $MgSO_4$ (A), terbutaline (10^{-10}–10^{-5} M) alone or in the presence of $MgSO_4$ (10^{-7} M) at 1 mM (B) or 0.1 mM (C) Ca^{2+} level-containing buffer. The level of significance is related to the comparison with the values of terbutaline

	EC_{50} (M ± SEM)	*p*-value	E_{max} (% ± SEM)	*p*-value
(A)				
$MgSO_4$	$1.6 \pm 0.7 \times 10^{-3}$	–	89.8 ± 1.1	–
(B)				
terbutaline	$1.3 \pm 0.6 \times 10^{-7}$		95.9 ± 2.3	
terbutaline + $MgSO_4$	$7.2 \pm 3.1 \times 10^{-8}$*	0.022	92.0 ± 4.9	0.089
(C)				
terbutaline	$7.4 \pm 5.4 \times 10^{-8}$		87.5 ± 4.6	
terbutaline + $MgSO_4$	$3.6 \pm 2.7 \times 10^{-8}$*	0.041	83.2 ± 3.3	0.056

Abbreviation: SEM, standard error of the mean.
*$p < 0.05$.

(Figure 6A), the changes in cardiac frequency were below 10% in each minute; however, in the presence of $MgSO_4$ (2.1 mg/kg), the heart rate-increasing effect of terbutaline was significantly decreased between the first and fifth minute ($^{*}p < 0.05$, $^{**}p < 0.01$). Similarly to the lower dose, the higher dose of terbutaline also increased the heart rate (Figure 6B). From the second minute, the changes in cardiac frequency were over 10%. In combination with $MgSO_4$, the heart rate was significantly reduced ($^{*}p < 0.05$, $^{**}p < 0.01$), especially from the third minute. In both cases, there were no changes in cardiac frequency after the fifth minute.

4 | DISCUSSION

In view of the efficiency of the currently used tocolytic therapy, combinations of different smooth muscle relaxant agents should be considered as an option to decrease adverse maternal and fetal events and enhance efficacy. Progestogen treatment was previously found to enhance the tocolytic effect of salmeterol in hormone-induced preterm labor in rats in vivo, and the addition of terbutaline to nifedipin also increased the uterorelaxant effect of nifedipin on pregnant rat myometrium in vitro and in vivo.[13,15]

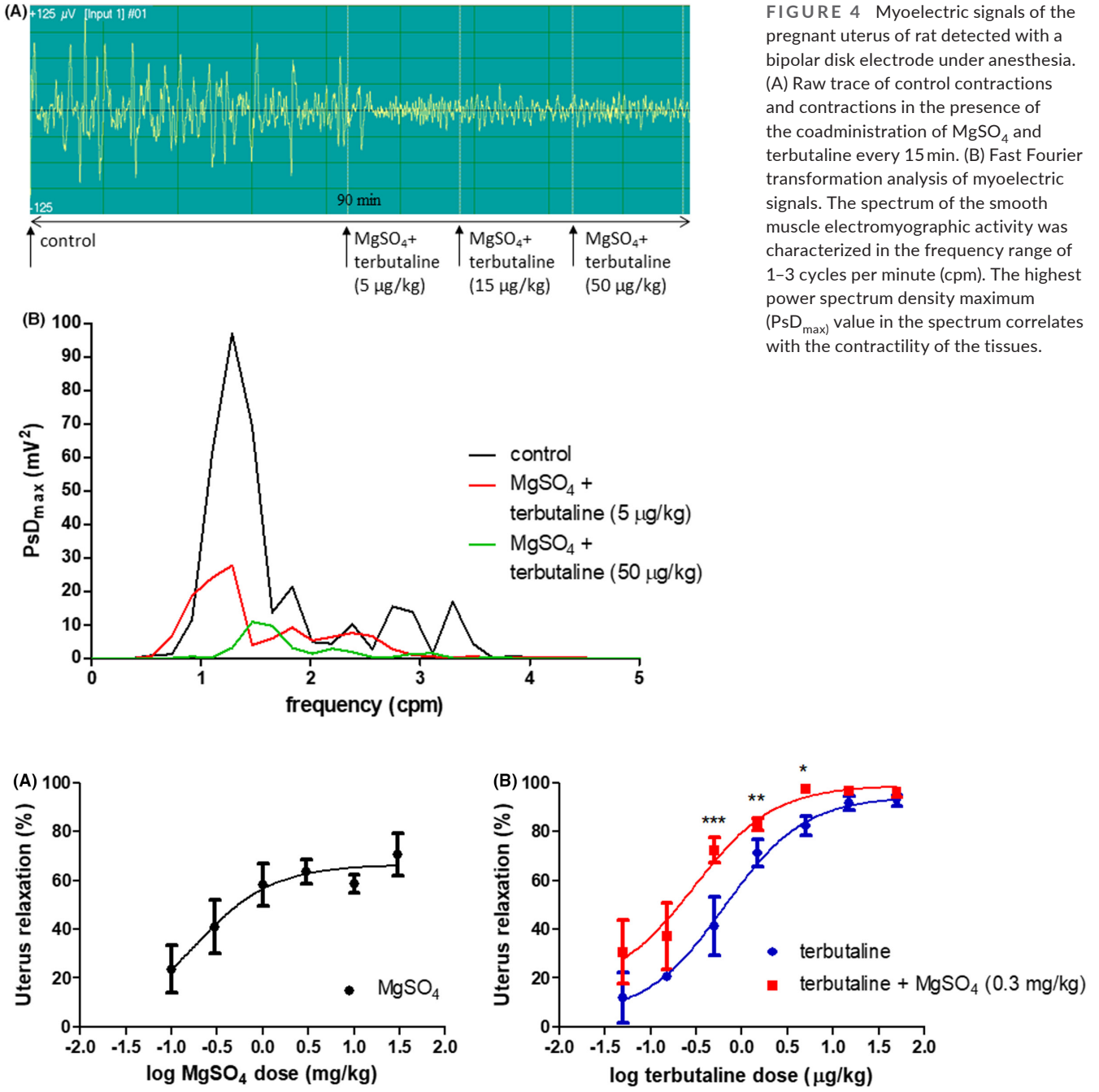

FIGURE 4 Myoelectric signals of the pregnant uterus of rat detected with a bipolar disk electrode under anesthesia. (A) Raw trace of control contractions and contractions in the presence of the coadministration of $MgSO_4$ and terbutaline every 15 min. (B) Fast Fourier transformation analysis of myoelectric signals. The spectrum of the smooth muscle electromyographic activity was characterized in the frequency range of 1–3 cycles per minute (cpm). The highest power spectrum density maximum (PsD_{max}) value in the spectrum correlates with the contractility of the tissues.

FIGURE 5 Inhibitory effect of $MgSO_4$ alone (A), terbutaline alone (B) and in combination with $MgSO_4$ (0.3 mg/kg) (B) on pregnancy day 22 in vivo. $^*p<0.05$; $^{**}p<0.01$, $^{***}p<0.001$

Since terbutaline and $MgSO_4$ are widely used tocolytic agents, even though their efficacy and side effect profiles are not completely satisfying, our main goal was to investigate the uterus relaxant effect of the combination of these drugs. In our study, we have successfully demonstrated that both the in vitro and in vivo combinations of the two compounds elicited a uterorelaxant effect stronger than that of the compounds alone.

In the isolated organ bath studies, we found synergism in the uterorelaxant effect of terbutaline and $MgSO_4$, although $MgSO_4$ was not able to enhance the maximal inhibitory effect of terbutaline. However, we observed a significant potentiating effect at lower concentrations, which may have importance in the reduction of adverse effects. We also proved that Ca^{2+} plays a significant role in this process. It is known that the entry of Ca^{2+} into the cells through the voltage-dependent Ca^{2+} channels has a crucial influence on smooth muscle contraction. One possible mechanism of action of $MgSO_4$ is the blockade of the voltage-dependent Ca^{2+} channel, which ability can be blocked in Ca^{2+}-poor environment.[10] Hence, the coadministration of the two agents was also investigated in a buffer containing Ca^{2+} reduced by 90% in order to verify the above-mentioned hypothesis. In a Ca^{2+}-poor buffer, $MgSO_4$ was not able to enhance the effect of terbutaline. These results led us to conclude that $MgSO_4$

TABLE 2 ED_{50} and E_{max} values of curves of uterine relaxation induced by $MgSO_4$, terbutaline (10^{-10}–10^{-5} M) alone or in the presence of $MgSO_4$ (0.3 mg/kg) in vivo. The level of significance is related to the comparison with the values for terbutaline

	ED_{50} (± SEM)	*p*-value	E_{max} (% ± SEM)	*p*-value
(A) $MgSO_4$	0.20 ± 0.08 mg/kg	—	69.9 ± 12.2	—
(B) terbutaline	0.65 ± 0.19 μg/kg		94.3 ± 1.8	
terbutaline + $MgSO_4$	0.30 ± 0.10* μg/kg	0.036	98.7 ± 2.2	0.106

Abbreviation: SEM, standard error of the mean.

*$p < 0.05$.

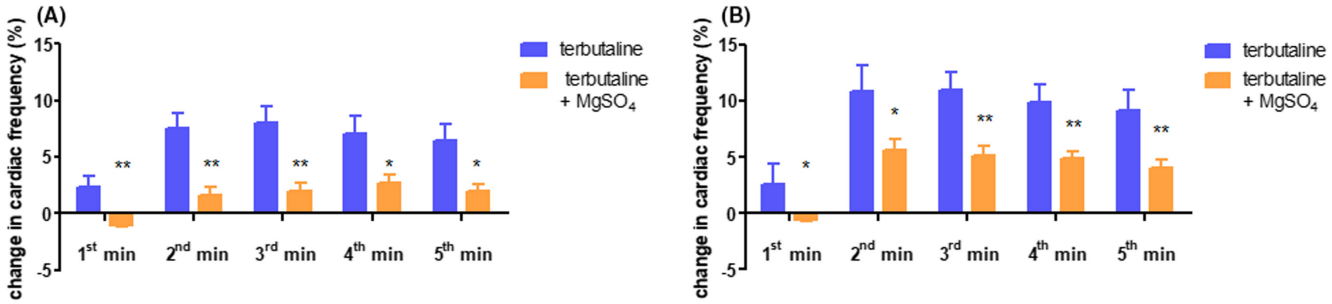

FIGURE 6 Changes in cardiac frequency during treatment with 50 μg/kg (A) or 500 μg/kg (B) terbutaline alone or in combination with $MgSO_4$ on pregnancy day 22. *$p < 0.05$

potentiates the uterorelaxant effect of terbutaline via the inhibition of voltage-dependent Ca^{2+} channels.

In the second series of our experiments, we proved that the synergistic combination of $MgSO_4$ and terbutaline also works in vivo. The relaxing effect of the combination was maintained successfully with the applied repeated administrations. Although $MgSO_4$ did not increase the maximal effect of terbutaline again, it shifted the dose–response curve to the left, which means that a beneficial effect can be expected when using the combination in the lower dose range of terbutaline. It is known that β_2-adrenergic receptor desensitization could worsen the efficacy of β_2-mimetics during tocolytic therapy.[16] Consequently, a lower dose of terbutaline with the potentiation of $MgSO_4$ could reduce the desensitization of β_2-adrenergic receptors, additionally contributing to the potential advantages of this combination during tocolytic therapy.

It is known that the cardiac effects of $MgSO_4$ and terbutaline are the opposite. Due to the unfavorable tachycardia-inducing effect of terbutaline, we also wanted to examine how this kind of combination affects the heart rate. Low and high doses of terbutaline increased cardiac frequency in rats, but in both cases the tachycardia-causing effect of terbutaline was minimized or reduced by the coadministration of $MgSO_4$. This means that in addition to the improved uterorelaxant activity, $MgSO_4$ may significantly reduce the main cardiovascular side effect of terbutaline during tocolysis.

As to the strengths of this study, we successfully proved the potentiating effect of low concentration of $MgSO_4$ on terbutaline effect both in vitro and in vivo. $MgSO_4$ was also able to decrease the heart rate enhancing effect of terbutaline. The applied dose of $MgSO_4$ during our in vivo studies was hundredfold less than that of its concentration eliciting the maximum effect, therefore we have a high chance to reduce or even eliminate the potential side effects and to maintain the cardiac benefit. Nevertheless, the study also had some limitations. As it is known, $MgSO_4$ has several maternal and fetal side effects. Unfortunately, a rat model was not suitable to check the side effects of hot flushes or burning sensations, thus only a clinical trial can clarify this question. The fetal cardiovascular effect of the combination has also not been measured. Another limitation of this study is that the blood pressure modulating effect of the combination was not nvestigated.

It is known that β-mimetic drugs cause hypertension in high doses; however, $MgSO_4$ also has the potential to decrease the enhanced blood pressure as it was seen in the heart rate. Therefore, one of our aims in the future is also to investigate the blood pressure modifying effect of the $MgSO_4$ + terbutaline combination. Additionally, among future research, the in vitro examination of the combination in cases of full-term and preterm human uteri tissues from cesarean section also should be considered.

5 | CONCLUSION

In the light of our results, we can conclude that the combined administration of β_2-agonist terbutaline with $MgSO_4$ has potential therapeutic importance in the inhibition of uterine contractions, especially in the lower concentration range. Moreover, this combination may reduce the unfavorable tachycardia-inducing effect of terbutaline. We hypothesize that if the dose of $MgSO_4$ is substantially reduced, the side effect both of terbutaline and $MgSO_4$ should be more tolerable with an enhanced clinical effect, that may give the clinical importance of this combination. The coadministration of these compounds can be efficacious and safe for tocolysis, but its applicability should be confirmed in well-designed clinical trials.

AUTHOR CONTRIBUTIONS

TB investigation: performed in vitro and in vivo studies, contributed to sample preparation; formal analysis of the results of contractility measurements; writing - original draft. KFS investigation: designed and performed in vivo contractility studies; formal analysis of the results. AS investigation: performed in vitro contractility studies; formal analysis: aided in interpreting the results. MM investigation: performed in vitro contractility studies. JH-T conceptualization; investigation: performed in vitro contractility studies; formal analysis: aided in interpreting the results. RG conceptualization; methodology; writing - review & editing: provided critical feedback; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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