K_{ATP} channels are involved in the tocolytic effect of ß$_2$ agonists in pregnant rat.

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INTRODUCTION

Preterm birth defined as childbirth between 20 and 37 weeks of gestation by WHO, is a major determinant of neonatal mortality and morbidity and has long term adverse consequences for health. In the USA, the preterm delivery rate is 12-13%, in Europe and other developed country, reported rates are generally 5-9%. The exact causes and aetiologies of preterm birth are not known. The incidence of preterm birth has not decreased over the years despite major improvements in medical, especially perinatal care facilities and extensive medical research. In the view to decreasing the potentially maternal and foetal adverse events and improving the perinatal outcome, it is a pharmacological challenge to find new therapeutic strategies, mechanisms or combinations. In the clinical practice the most frequently used tocolytic agents are the ß$_2$-adrenoceptor (ß$_2$-AR) agonist (e.g. terbutaline, fenoterol, hexoprenaline,).

Present study unravels the functional presence of ATP-sensitive potassium channel (K_{ATP} channel) and its involvement in mediating ß$_2$-AR agonist-induced myometrial relaxation in rat myometrium at 6 and 22 days of gestation.

MATERIALS AND METHODS

- Animals: non-pregnant and 6-, 8-, 10-, 12-, 14-, 15-, 18-, 20-, 21-, 22-day pregnant SPRD rats.
- Quantative real-time PCR (ABI, Step One) and Western blot analysis were used to demonstrate the expressions of SUR1 gene and protein expressions in the pregnant and non-pregnant uterus, respectively.
- In vitro contractility study: the uterus-relaxant effect of the ß2-AR agonists (terbutaline, ritodrine and salmaterol) (10^{-10}-10^{-5} M) were investigated on spontaneous rhythmic contractions cumulatively alone, and in the presence of K_{ATP} channel blocker glibenclamide (10^{-6} M) and K_{ATP} channel opener pinacidil (10^{-9}-10^{-7} M) after 5 minutes pre-incubation. For statistical evaluations, data were analysed by the ANOVA Neuman–Keuls test.

RESULTS

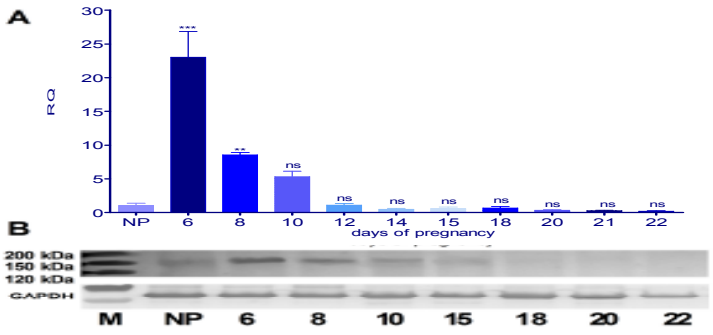

Figure 1 A Changes in expression of SUR1 mRNA during pregnancy in the rat myometrium. RQ (Relative Quantity) values on different days of pregnancy were compared with those in non-pregnant rats. ns: non-significant, ** denotes p< 0.01, *** p<0.001. Each bar indicates the mean ± S.E.M, n = 5. **B** Representative Western blot of SUR1 protein expression in the non-pregnant (NP) and the pregnant rat myometrium and GAPDH as endogenous control.

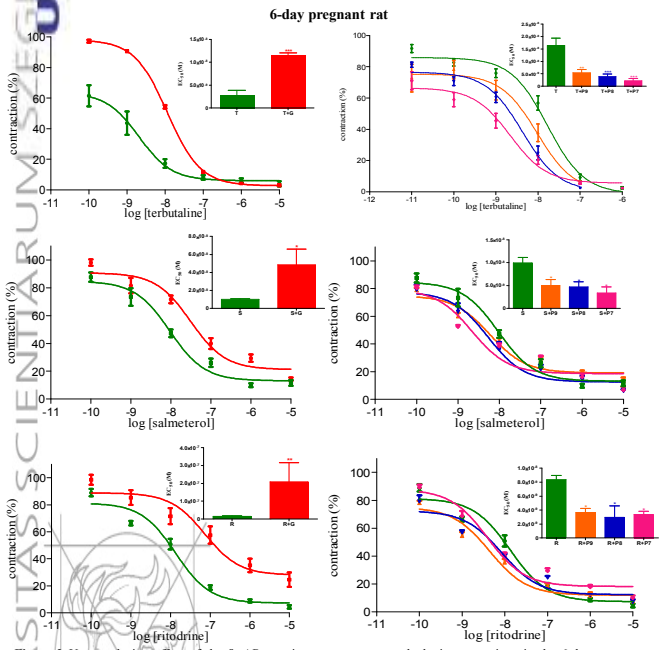

Figure 2 Uterus-relaxing effect of the ß$_2$-AR agonists on spontaneous rhythmic contractions in the 6-day-pregnant rat myometrium (green), reversal by glibenclamide (10^{-6} M) (red) and in the presence of pinacidil; 10^{-9}M (orange), 10^{-8}M (blue) and 10^{-7}M (pink). Inserts: changes in IC_{50} values of the ß$_2$-AR agonists on spontaneous rhythmic contractions in the 6-day-pregnant rat. * p ≤0.05, ** p< 0.01 and *** p < 0.001. Each value denotes the mean ± S.E.M, n = 6.

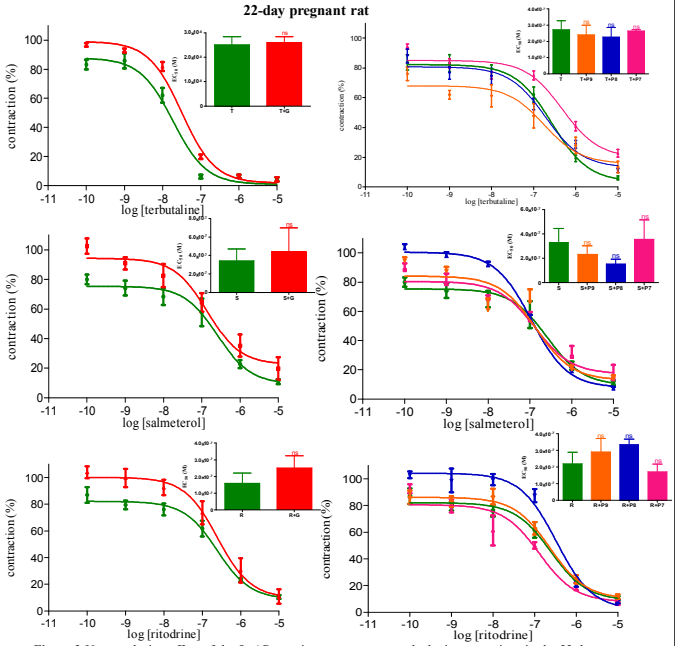

Figure 3 Uterus-relaxing effect of the ß$_2$-AR agonists on spontaneous rhythmic contractions in the 22-day-pregnant rat myometrium (green), reversal by glibenclamide (10^{-6} M) (red) and in the presence of pinacidil; 10^{-9}M (orange), 10^{-8}M (blue) and 10^{-7}M (pink). Inserts: changes in IC_{50} values of the ß$_2$-AR agonists on spontaneous rhythmic contractions in the 22-day-pregnant rat, ns: non significant. Each value denotes the mean ± S.E.M, n = 6.

CONCLUSIONS

- Results of our study evidently suggest the functional presence of K_{ATP} channel in the pregnant rat myometrium and its role in ß$_2$-adrenoceptor agonists induced myometrial relaxation at early stage of pregnancy.
- K_{ATP} channels are not involved in the tocolytic effect of the ß$_2$-adrenoceptor agonists at term. According to the clinical observation the tocolytic effect of the ß-mimetics decrease at term. The reason of this phenomenon can be explained with the down-regulated K_{ATP} channels near delivery.
- Based on these findings, it may not be suggest that the therapeutic application of both the ß$_2$-adrenoceptor agonist and specific K_{ATP} channel opener as promising tocolytic agent. However, it may be used for treatment of habitual abortion.

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