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MK 571, a multidrug resistance protein inhibitor, reduces uterus smooth muscle contractility in rats.

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Abstract

Polycystic ovary syndrome (PCOS) is a genetic condition highly associated with infertility in women. The increased uterine smooth muscle contractility plays a role in the PCOS pathogenesis. Studies have demonstrated the inhibitory effect of MK 571, a multidrug resistance protein inhibitor in the prostate, bladder and urethra contractility. However, no previous study has focused on the effects of MK 571 in the uterine contractions. Therefore, the aim of the present study is to evaluate the in vitro effects of MK 571 on uterine smooth muscle contractility in female rats. We have shown for the first time that MK 571 (20 µM) associated with isoproterenol (a non-selective β-adrenoceptor agonist, 10 µM) produced an inhibitory effect on uterine tissue contractility. More experimental and clinical studies are needed to elucidate the mechanism of action, as well as the safety and efficacy of MK 571 under pathological conditions in animals and humans.

Key words: *Polycystic ovary syndrome, cAMP, cGMP.*

Introduction

Polycystic ovary syndrome (PCOS) is a complex genetic condition, characterized by increased serum androgen levels along with uterine morphometric abnormalities. Infertility is frequently associated with PCOS and studies have been demonstrated that uterine hypercontractility contributes to spontaneous abortion due to impaired embryo nesting.

MK 571 is an multidrug resistance protein (MRP) inhibitor, acting selectively on MRP4 and MRP5. Studies have been demonstrated that MK 571 reduces the smooth muscle contractility in mice prostate, bladder and urethra by increasing the intracellular levels of cyclic nucleotides levels. Considering that MRP has been reported in the uterine tissue, we hypothesized that MK 571 could reduce the uterus smooth muscle contractility by increasing cAMP and/or cGMP intracellular levels. Therefore, the aim of the present study is to evaluate the uterus smooth muscle contractility in presence of MK 571.

Results and Discussion

To achieve the goal proposed, we have employed 6-month old female Sprague Dawley rats (CEUA no 4421-1). To avoid the hormone interference due to the reproductive cycle, vaginal smears were performed. The cells were fixed in a slide, stained with violet crystal (1%) and the analyzed using a Nikon microscope under 40x magnification. The determination of the reproductive cycle phase was based on the proportion among three different types of cells: epithelial, cornified and leukocytes cells (Figure 1). The cycle phase of chosen was estrus due to lower serum levels of estrogen.

For the functional protocols, the animals were killed, uterine tissue was removed and cleaned from fat tissue. The right uterus was divided in two segments and the distal part to the ovary was used. Concentration-response curves to carbacol (a non-selective muscarinic receptor agonist, 100 pM – 100 µM) were performed in the presence and absence of isoproterenol (a non-selective β-adrenoceptor agonist, 10 µM) and MK 571 (20 µM).

As shown in the figure 2, carbacol produced a concentration-dependent uterine smooth muscle contraction. The *in vitro* incubation with MK 571 (20 µM, 20 min) followed by isoproterenol (10 µM, 20 min) produced a reduction in the maximal response by 32% and a rightward shift in the potency by 9 times.

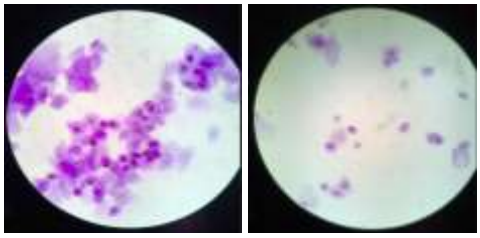

Figure 1: Vaginal smear of female Sprague Dawley rats showing the estrus phase.

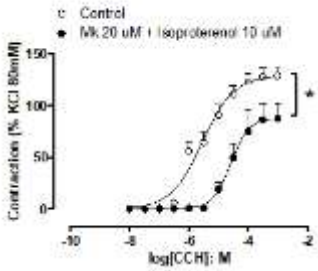

Figure 2: Effect of MK 571 (20 µM) and isoproterenol (10 µM) on the uterine contraction of Sprague Dawley rats.

Conclusions

Drugs that reduce uterine contractility may be a valuable therapeutic tool to overcome the PCOS-induced infertility. We report here that MK 571 associated with isoproterenol account for uterine hypocontractility. More experimental and clinical studies are needed to elucidate the mechanism of action, as well as the safety and efficacy in humans.

Acknowledgement

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