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Freire M P F[1], Ludwig L L[1], Lorenzetti F[1], van Koeveringe G[2], van Kerrebroeck P[2], Dambros M D[1]
1. *Federal University Of Sao Paulo,* ***2.*** *University of Maastrich*

ROLE OF A SPECIFIC 1,4,5 INOSITOL TRIPHOSPHATE BLOCKER ON THE BLADDER SMOOTH MUSCLE CONTRACTIONS – RESULTS FROM IN VITRO AND IN VIVO STUDIES.

Hypothesis / aims of study

Xestospongine C is a marine natural product extracted from Pacific sponges. It blocks the calcium-releasing action of 1,4,5 inositol triphosphate (IP3) at the receptor level of the sarcoplasmatic reticulum, inhibiting the increase in intracellular calcium in vascular smooth muscle cells.
In order to evaluate the effects of this IP3 receptor blocker in the bladder smooth muscle, we studied its role on *in vitro* and *in vivo* experiments.

Study design, materials and methods

In vitro experiment: we studied the xestospongine C effect on detrusor muscle in organ baths. We evaluated the detrusor contractility through electrical field stimulation (EFS) and through exposures to solutions of carbachol (10μM/l), ATP (10μM/l) and KCl (80μM/l) before and after exposure to xestospongine C solution (1μM/l). *In vivo* experiment: partial obstruction (PBO) was created in 12 young animals using a jeweler´s jump ring (2.2 mm i.d.). 2 animals were sham operated. After 3 and 5 weeks of obstruction, we studied the filling and emptying characteristics of the bladders under anesthesia (urethane 1mg/kg). At the moment overactivity was observed during urodynamic evaluation, we instillated Xestonpongine C and performed 2 filling / emptying cycles. A last filling cycle with saline solution were performed. The amplitude and number of contractions were analysed.

Results

In vitro study: Detrusor contractions were significantly inhibited after the exposure of xestongine C. After xestospongina C, muscle fiber´s contractions decreased from 28 mN to 5 mN (82%) under the EFS ($p<0,01$), from 23 mN to 3 mN (86%) ($p<0,01$) under carbachol stimulation; from 11mN to 9mN (19%) ($p<0,01$) under the ATP stimulation; and from 15 mN to 5 mN (66,7%) ($p<0,01$) under KCl stimulation.
In vivo study: 4 animals developed overactive contractions after 3 weeks of PBO and 3 animals developed such contractions after 5 weeks. Instillations of Xestospongine C lead to a decrease of 86% on the frequency of contractions. Voiding pressures decreased 58% after xestospongine C. In the last saline cycle, micturition was observed with voiding pressure of 77% and 68% of the initial voiding pressures in the 3 and 5 week group, respectively.

Interpretation of results

Xestospongine C is a potent *in vitro* and *in vivo* inhibitor of detrusor muscle contractions. Adequate voiding pressures were obtained in the animals after the exposure to this blocker.

Concluding message

This results points to new pathways on the development of drugs for the treatment of overactive bladder.

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Commite for Ethics and Research of the Federal University of Sao Paulo**