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EFFECTS OF 138-355, A BETA3-ADRENOCEPTOR SELECTIVE AGONIST, ON RELAXATION OF THE HUMAN DETRUSOR MUSCLE IN VITRO

Hypothesis / aims of study

Beta-adrenoceptors have been demonstrated in the bladder and urethra of several species including human [1,2]. Beta-adrenoceptors are predominantly present in the bladder dome. It has been reported that beta-adrenoceptors mediate relaxation of these smooth muscles in several species, and this relaxation may be mediated via $beta_1$-, $beta_2$- or $beta_3$-receptor or a mixture of these subtypes. Recently, mRNA encoding for the $beta_3$-adrenoceptor has been found in the human detrusor along with that encoding for both the $beta_1$ and $beta_2$-adrenoceptors, and $beta_3$-adrenoceptors have been suggested to have a role in mediating relaxation of detrusor muscles of the human and pig [3].

This study investigates the effects of 138-355, active-matabolite of TT-138 and a $beta_3$-adrenoceptor selective agonist, on relaxation of the human detrusor muscle in vitro.

Study design, materials and methods

Tissue samples of human bladder muscle from 15 patients undergoing total cystectomy due to bladder cancer were obtained, and the mucosa and serosa were removed. Tissues were mounted in 5 or 10ml organ baths containing Krebs solution, which was gassed with 95%O2 and 5% CO2. Resting tension of 1g was obtained. When the contraction had stabilized, increasing concentrations of beta-adrenoceptor agonists (non-selective, isoprenaline; $beta_2$-selective, clenbuterol; $beta_3$-selective, 138-355 and BRL37344) and propiverine (a non-selective anti-muscarinic antagonist) were added cumulatively and concentration-relaxation curves (CRCs) were obtained. CRCs to 138-355 were obtained in the absence and presence of SR59230A, a $beta_3$-selective antagonist, and antagonist affinity values (pA_2) were calculated from the Schild plot. The study has been conducted in accord with the Helsinki Declaration. The procedures have been approved by the local ethics committee, and written informed consent was obtained from each patient before entry into the study.

Results

Isoproterenol, clenbuterol, 138-355 and BRL37344 concentration-dependently relaxed isolated human urinary bladder strips with pD_2 (-log EC_{50} value) being 6.8±0.2, 5.2±0.2, 5.8±0.3 and 5.9±0.3, respectively. On the other hand, propiverine had no relaxation effect.

Following antagonist assay revealed that concentration-relaxation curves to 138-355 was competitively antagonized by beta3 adrenoceptor antagonist, SR59230A with a pA_2 value of 7.0±0.5 and with a Schild slope of 0.7±0.1.

Interpretation of results

Both $beta_2$-agonist (clenbuterol) and $beta_3$-agonists (138-355 and BRL37344)relaxed human bladder smooth muscles. But the potency of $beta_3$-agonist was greater than that of $beta_2$-agonist. SR59230A, a $beta_3$-antagonist, antagonized CRCs to 138-355 competitively with a pA_2 value of 7.0±0.5, indicating that relaxation response of 138-355 may be via $beta_3$-adrenoceptors.

Concluding message

138-355, active-matabolite of TT-138 relaxed urinary bladder via not beta1/beta2 but $beta_3$-adrenoceptor stimuli.

References

1. Identification of β-adrenoceptor subtypes in lower urinary tract of the female pig. J. Urol. 168, 2706-2710, 2003.

2. The role of ß-adrenoceptor subtypes in mediating relaxation of the pig bladder trigonal muscle in vitro. Neurourol. Urodyn. 22,338-342.

3. The role of β_3-Adrenoceptors in mediating relaxation of porcine detrusor muscle. Br. J. Pharmacol. 135,129-134.

Fig.1. CRCs to beta antagonists and propiverine

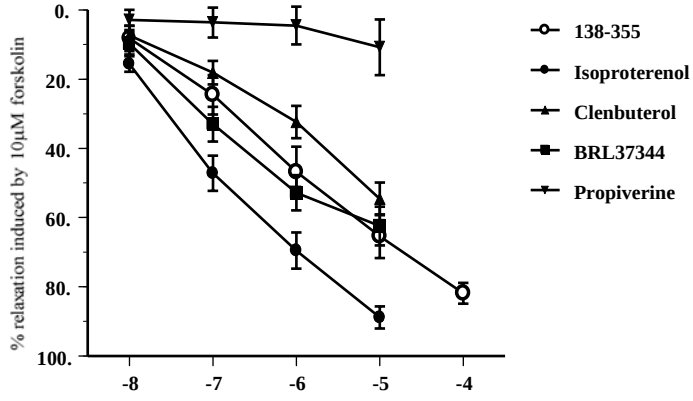
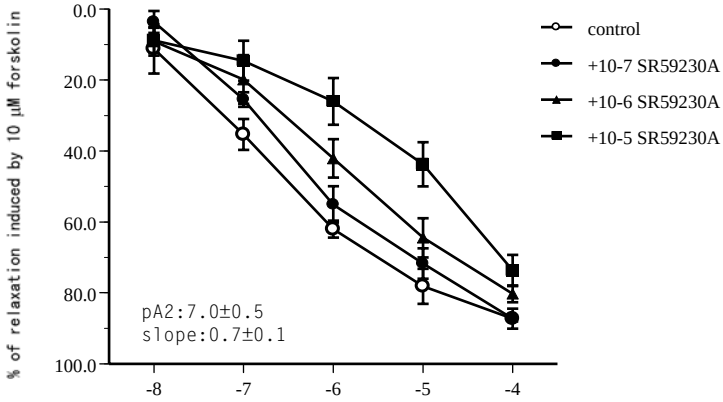


Fig.2. Effects of SR59230A on CRCs to 138-355



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