

FUNCTIONAL INVESTIGATION OF BETA-ADRENOCEPTORS IN ISOLATED HUMAN DETRUSOR – USING THE NOVEL SELECTIVE BETA3-ADRENOCEPTOR AGONIST, KUC-7322

Aims of Study

It is well known that the activation of the sympathetic nervous system contributes to urine storage by relaxing the detrusor via activation of beta-adrenoceptors (beta-ARs). It has been demonstrated that the relaxation of human detrusor, including the neurogenic detrusor, is mediated mainly via beta3-ARs [1-3]. However, the beta3-AR agonists previously used, such as BRL37344A, CL316243 and CGP12177A, showed only a partial relaxing effect on human detrusor, though isoproterenol, a non-selective beta-AR agonist, completely relaxes it. In the present study, we investigated whether a novel selective beta3-AR agonist, KUC-7322, exhibits full agonistic activity on human detrusor. The effects of this beta3-AR agonist and other bladder relaxants on the contractile response induced by carbachol were also studied.

Methods

Bladder tissue was obtained from the anterior or posterior wall of the bladder body in 15 bladder carcinoma patients (11 men and 4 women; 43 to 86 years old, mean age 68.3±3.0) with neurologically normal bladder function undergoing radical cystectomy. After the mucosa and adventitia had been removed, detrusor preparations (approximately 10X5X3 mm) were isolated. Each preparation was suspended in a 10 ml organ bath containing Krebs solution; this was maintained at 37°C and continuously gassed with a mixture of 95% oxygen and 5% carbon dioxide. One end of the preparation was connected to a force-displacement transducer and changes in muscle tension were measured on a pen-writing oscillograph. The preparation was gradually stretched until a stable tension of 10 mN was obtained. Concentration-response curves for each drug were obtained. The relaxing effect of each drug was expressed as a percentage of the maximal relaxation induced by 1×10^{-5} M forskolin, a reference drug. To test the effect of beta-AR agonists or anti-muscarinic drugs against the carbachol-induced contractile response, stable concentration-response curves for carbachol were obtained. Then, each drug was added to the bath 30 min before the carbachol-induced concentration-response curve was repeated.

Results

Isoproterenol relaxed detrusor preparations in a concentration-dependent manner. Neither clenbuterol (beta2-AR agonist) nor tolterodine (anti-muscarinic drug) produced any significant relaxation at concentration up to 1×10^{-4} M. On the other hand, KUC-7322 significantly relaxed human detrusor in a concentration-dependent manner. The EC₅₀ values of isoproterenol and KUC-7322 were $(5.8 \pm 2.1) \times 10^{-7}$ M and $(1.9 \pm 0.55) \times 10^{-6}$ M, respectively. The maximal relaxation obtained by isoproterenol, KUC-7322, clenbuterol and tolterodine were 86.4±3.5%, 87.1±2.3%, 38.1±6.6% and 20.0±3.6%, respectively (Fig.1). Carbachol (3×10^{-8} to 3×10^{-5} M) produced concentration-dependent contractions of human detrusor with EC₅₀ value of $(1.8 \pm 0.31) \times 10^{-6}$ M. Oxybutynin (1×10^{-6} M), tolterodine (1×10^{-6} M) and atropine (1×10^{-7} M) caused rightward shifts of the concentration-response curve for carbachol. Forskolin (1×10^{-5} M) slightly inhibited the maximal response of contraction. On the other hand, neither isoproterenol (1×10^{-8} to 1×10^{-4} M) nor KUC-7322 (1×10^{-8} to 1×10^{-4} M) affected the carbachol-induced bladder contraction.

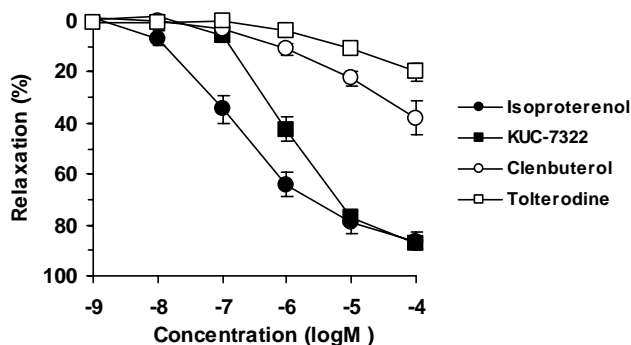


Fig. 1 Effects of isoproterenol, KUC-7322, clenbuterol and tolterodine on isolated human detrusor.

Conclusions

KUC-7322, a selective beta3-AR agonist, showed full agonistic activity on human detrusor. Moreover, beta-AR agonists, including KUC-7322, did not affect the carbachol-induced contraction of human detrusor. These results suggest that novel selective beta3-AR agonists, such as KUC-7322, may be used for treatment of overactive bladder in patients, possibly without negative effects on voiding function.

References

1. Acta Physiol. Scand. 164: 117, 1998
2. Br. J. Pharmacol. 126: 819, 1999
3. J. Urol. 165: 240, 2001