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THE EFFECTS OF TOLTERODINE ON CARBACHOL-INDUCED CONTRACTION IN HUMAN BLADDER SMOOTH MUSCLES IN NORMAL STATE AND IN DETRUSOR OVERACTIVITY ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA

Hypothesis / aims of study

Detrusor overactivity is noted in 50-70% of benign prostatic hyperplasia (BPH). It has been reported that tolterodine is effective for the treatment of overactive bladder symptom associated with BPH[1)]. It has been reported that M3 muscarinic receptor (MR) subtypes mainly mediate contraction in normal bladder. It has also been reported that M2-receptors participate in the contractile response under pathologic conditions in both rat and human detrusor smooth muscles. M2-receptors have been reported to mediate contraction in the rat with pelvic nerve denervation or spinal cord transaction, and in patients with neurogenic bladder dysfunction[2,3)]. The aim of the present study is to compare the antagonist affinities of tolterodine against carbachol-induced contraction in human detrusor muscles between normal state and detrusor overactivity due to BPH.

Study design, materials and methods

Tissue samples of human bladder muscles were obtained from patients undergoing total cystectomy due to bladder cancer (normal bladder, n=6), and those undergoing prostatectomy due to benign prostatic hyperplasia (BPH, n=5). All of the patients with BPH had detrusor overactivity in video-urodynamic studies or ambulatory urodynamics before the surgery. Tissues were mounted in 10 ml organ baths containing Krebs solution, and concentration-response curves (CRCs) to carbachol were obtained. After incubation for 30 minutes, a second CRC to carbachol was constructed in the continued presence of antagonist or vehicle. In this way, 4 CRCs to carbachol were obtained from the same strip, three in the presence of increasing concentrations of tolterodine (3, 10, 30nM) or in the presence of vehicle. 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

Carbachol produced concentration-dependent contraction with mean pEC_{50} values and maximum responses of 5.57±0.04 and 10.03±2.9 g, respectively, in the normal bladder. Carbachol produced concentration-dependent contraction of the human urinary bladder with BPH with mean pEC50 values and maximum responses of 6.24±0.11 and 10.96±3.38 g, respectively. Tolterodine produced parallel, rightward displacement of the CRCs to carbachol without affecting maximum responses. Schild plot Mean (±SEM) pA_2 values in normal bladder and BPH, respectively, were 9.11±0.17 and 8.70±0.16.

Interpretation of results

Tolterodine, a non-selective muscarinic receptor antagonist antagonized CRCs to carbachol with high affinities. Antagonist affinities of tolterodine did not change in bladder smooth muscle with BPH.

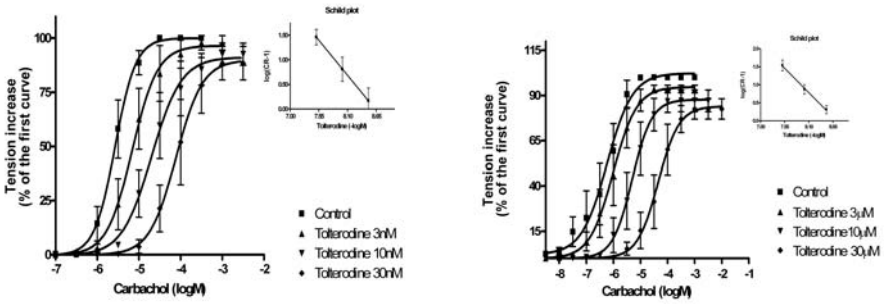
Concluding message

Tolterodine inhibits bladder smooth muscle contraction induced by muscarinic receptor stimulation both in the normal state and in overactive bladder associated with BPH.

References

1. Abrams et al., Expert Opin Pharmacother,2:1685,2001
2. Braverman, A. S. et al. Am. J. Physiol. 275 5 Pt 2 R1654, 1998
3. Braverman, A. S. et al. J. Urol. 165 5 Suppl. 36, 2001

Figure: Effects of tolterodine on CRCs to carbachol in normal bladder (left) and BPH (right)



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