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ANTIMUSCARINIC DRUG COMPENSATES FOR DETRUSOR DYSFUNCTION BY DECREASING URETHRAL RESISTANCE VIA AN EFFECT ON THE L-TYPE VOLTAGE-OPERATED CALCIUM CHANNEL

Hypothesis / aims of study

Antimuscarinic drugs increase bladder capacity without prominent side effects such as urinary retention when administered to women or even to men with overactive bladder and bladder outlet obstruction (BOO) [1]. Some mechanisms might exist in the urethra to compensate for the emptying dysfunction of the detrusor after the administration of antimuscarinic drugs. Antimuscarinic drugs have the possibility to reduce urethral resistance by decreasing prostate muscle tonus. Nevertheless, no reports could be found addressing the influences of antimuscarinics on the urethral smooth muscle. We investigated the influences of an antimuscarinic drug, propiverine, on urethral function.

Study design, materials and methods

All surgical and urodynamic procedures were performed under urethane anesthesia. To eliminate the influence of bladder activity and to monitor urethral baseline pressure, the isovolumetric pressure of the urethra was recorded after cystectomy and ligation of the external urethral meatus. The effects of propiverine (2x10 to $2x10^3$ nM/kg) on urethral baseline pressure were compared between the urethra filled with prostaglandin (PG) E_2 or 0.1 M phosphate buffer (vehicle). As in vitro functional study, circular smooth muscle strips (width 1.5 mm, length 4 mm) were prepared from the middle part of the urethra. The contractile responses to electrical field stimulation (EFS) were examined in the presence of propiverine, tamsulosin (α_1-blocker), verapamil (an inhibitor of L-type voltage-operated calcium channels), ω-conotoxin (an inhibitor of N-type voltage-operated calcium channels), and atropine. The negative logarithm of the drug concentration eliciting half maximum inhibition (IC_{50}) was determined by linear regression analysis.□□□□

Results

Urethral baseline pressure was compared between the urethra filled with PGE_2 or 0.1 M phosphate buffer. A slight but significant decrease in urethral baseline pressure was found after $2x10^3$ nM/kg propiverine administration ($p < 0.05$). EFS induced contractions in the urethral circular smooth muscle at resting tension. A small tetorodotoxin ($1x10^{-6}$ mol/L) abolished EFS-induced contraction (Fig.). These contractions were significantly inhibited by propiverine (IC_{50} = 1.16 x 10^{-5} mol/L) and verapamil (IC_{50} = 1.43 x 10^{-5} mol/L), but not by tamsulosin, atropine or ω-conotoxin.

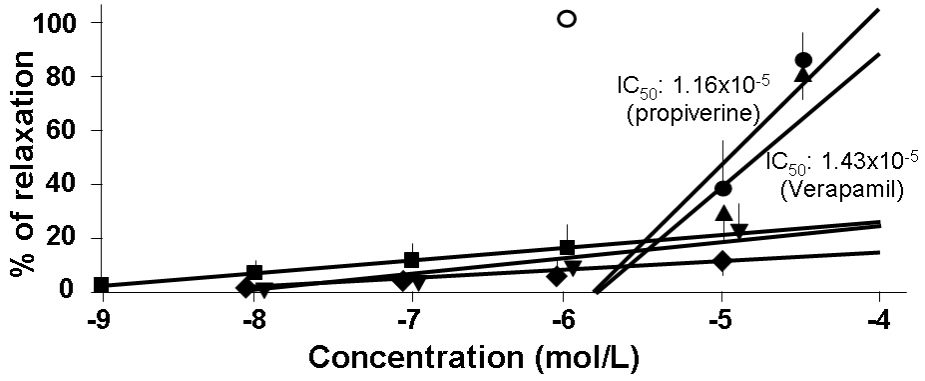

Figure Effects of compounds on the EFS-induced contraction of the urethral circular smooth muscle. This contraction was abolished by 1 μM tetrodotoxin (open circle). Note that propiverine (circles) and verapamil (triangles) inhibited contractions to EFS, but tamsulosin (inverted triangles), ω-conotoxin (squares) and atropine (diamonds) did not.

Interpretation of results

The circular layer of the urethra is not continuous with the detrusor. It was suggested to be important for maintaining urethral closure and to be less sensitive to acetylcholine [2]. In the present study of the rat urethra contraction response of the circular muscle to EFS was not inhibited by atropine□ or tamsulosin, meaning non-adrenergic and non-cholinergic contractions. Furthermore, the contraction response to EFS was not suppressed by ω-conotoxin, but was inhibited by propiverine and verapamil. The fact that, in the present study, propiverine inhibited the EFS-induced contractions of the circular muscle of the rat urethra may be explained by the blocking effect on the L-type voltage-operated calcium channel. An antimuscarinic drug, propiverine, has an effect on the L-type voltage-operated calcium channel [3], and may compensate for detrusor dysfunction by decreasing urethral resistance in the voiding phase.

Concluding message

Antimuscarinic drugs have the possibility to reduce urethral resistance by decreasing prostatic and urethral muscle tonus. This effect might diminish incomplete emptying by decreasing urethral resistance in patients with BOO.

References

1. J Urol **175**: 999, 2006
2. J Urol **168**: 308, 2002
3. Br J Pharmacol **145**: 608, 2005

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