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# COMPARISON OF EFFECTS OF VARIOUS ANTIMUSCARINIC DRUGS ON NORADRENALINE RELEASE FROM HUMAN ISOLATED URETHRA

## Aims of Study

Several antimuscarinic drugs are clinically used, and clinical trials of newly synthesized antimuscarinic drugs for the treatment of overactive bladder are now going. Pharmacological studies have demonstrated the affinity and selectivity for muscarinic receptor subtype, and selectivity for the bladder over other organs. It is well known that muscarinic receptors exist on bladder smooth muscles, and prejunctional site of cholinergic nerve endings in bladder. Muscarinic receptors on cholinergic nerve endings regulate the acetylcholine release from the nerve (1). In addition, several reports (2) have suggested that there are muscarinic receptors on prejunctional site of adrenergic nerve ending, which may regulate noradrenaline releases from the nerves, and have the effects on urethral tones. Therefore, the present study was designed to compare the effects of various antimuscarinic drugs (atropine, pirenzepine, methoctoramine, 4-DAMP, oxybutynin, propiverine and tolterodine) on noradrenaline release in human isolated proximal urethral smooth muscles, using microdialysis method (3).

## Methods

Human urethras (20 male and 2 female: mean age 68.4 years) were obtained from patients undergoing radical cysto-urethrectomy due to bladder carcinoma. Smooth muscle strips were dissected from the proximal urethra of each patient. Microdialysis probe was inserted into each strip, and Ringer solution was perfused into the probe. Each strip with microdialysis probe, which was suspended in an organ bath filled with oxygenated Krebs-Henseleit solution, was connected to an isometric force displacement transducer, and an isometric tension development was recorded. The effects of pretreatment with various antimuscarinic drugs on the contractile responses induced by electrical field stimulation (EFS: supramaximum voltage, 0.5 msec duration, 2-60 Hz and 3 sec train) were evaluated. Furthermore, in noradrenaline release experiments, the dialysate during EFS (supramaximum voltage, 0.5 msec duration, 40 Hz and 3 sec train at 1 min interval for 10 min) was collected, and the amount of noradrenaline released in the dialysate was measured by HPLC with ECD.

## Results

Carbachol (0.01 μM – 1.0 mM) did not cause significant contractile responses, but EFS caused frequency-dependent contractile responses in human isolated proximal urethral smooth muscles. Pretreatment with pirenzepine (M1 selective drug) at 1.0 μM significantly decreased the EFS-induced contractile response and noradrenaline release ($p<0.01$), although the compound at 0.01 and 0.1 μM had no effects on both contractile response and noradrenaline release. In contrast, methoctoramine (M2 selective drug) (0.01 - 1.0 μM) showed significant and concentration-depended increases in EFS-induced contractile response and noradrenaline release ($p<0.01$). Pretreatment with 4-DUMP (M3 selective drug), propiverine, oxybutynin and atropine at the concentration up to 1.0 μM had no significant effect on the EFS-induced contractile responses and noradrenaline releases. However, pretreatment with tolterodine (0.01 - 1.0 μM) caused concentration-dependent increases in EFS-induced contractile response and noradrenaline release in human urethral smooth muscles.

## Conclusions

The present data demonstrate that excitatory M1 receptor and inhibitory M2 receptor subtypes exist on prejunctional site of adrenergic nerve endings in human proximal urethral smooth muscles, and that pharmacological effects of various antimuscarinic drugs on human urethral smooth muscles are different. Some drugs may have prejunctional inhibiting or excitatory action of noradrenaline releases from adrenergic nerve endings, which may have effect on the human proximal urethral tone.

Table - Effects of various antimuscarinic drugs (1.0 μM) on EFS-induced contractile responses and noradrenaline releases in human proximal urethral smooth muscles

| Antimuscarinic drug | Contractile response, % | Noradrenaline release % |
|---|---|---|
| Atropine (n=8) | 102.0±3.8 | 103.5±2.4 |
| Pirenzepine (n=8) | 86.6±3.5* | 87.6±3.1* |
| Methoctoramine (n=8) | 129.6±3.6* | 132.5±3.5* |
| 4-DAMP (n=8) | 105.2±2.8 | 103.9±2.2 |
| Oxybutynin (n=10) | 100.3±4.4 | 105.1±3.3 |
| Propiverine (n=10) | 108.2±4.0 | 111.6±3.6 |
| Tolterodine (n=10) | 126.5±3.7* | 128.6±4.0* |

Value is represented as % of control value in each parameter. Control values are EFS-induced contractile responses and noradrenaline releases without drug treatment. EFS conditions are supramaximum voltage, 0.5 msec duration, 40 Hz and 3 sec train at 1 min interval for 10 min.

* $P < 0.05$; significantly different from control values

**References**


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