

## PHARMACOLOGICAL EFFECTS OF SOLIFENACIN (YM905) ON HUMAN ISOLATED URINARY BLADDER

### Aims of Study

Solifenacin (YM905) is a new antimuscarinic drug, and clinical trials for the treatment of overactive bladder with symptoms of frequency, urgency and urge incontinence have been successfully completed. Pharmacological studies have demonstrated that solifenacin (YM905) has selectivity for urinary bladder smooth muscles in vitro and vivo animal experiments. However, there are few reports about the effects of solifenacin (YM905) on human smooth muscles of urinary bladder. Therefore, the present study was performed to evaluate the effects of solifenacin (YM905) on human detrusor smooth muscles, using muscle bath technique.

### Methods

Specimens of human urinary bladder were obtained from 27 patients (19 males and eight females) who underwent total cystectomy due to malignant bladder tumor. Smooth muscle strips were dissected from the normal part of body of urinary bladder. We obtained permission for using human bladder tissue from the ethics committee at Kumamoto University School of Medicine. All patients did not receive preoperative local radiotherapy and/or chemotherapy.

After surgical removal of the bladder, The serosal and mucosal layers were dissected and detrusor strips were cut (approximately 4 mm wide and 15 mm long) from the intact part of the dome region of the bladder. Each detrusor strip was suspended in a 20-ml bath filled modified Krebs-Henseleit solution, gassed with 5%CO<sub>2</sub> 95%O<sub>2</sub>, and was connected to a force displacement transducer and isometric force was recorded and monitored on an ink-writing recorder. After each strip was stretched until optimal force developed (about 1.5g resting tension), the strip was washed with modified Krebs-Henseleit solution several times and allowed to equilibrate for 90 min before the start of the experiments. We investigated the effects of solifenacin (YM905) and atropine on the contractions induced by carbachol (CCh), 80 mM KCl, 5 mM CaCl<sub>2</sub> and electrical field stimulation (supramaximum voltage, 0.3 msec duration, 2-60 Hz, 3 sec train) in the detrusor strips.

### Results

Carbachol ( $10^{-7}$  M~ $10^{-2}$  M) caused concentration-dependent contractions of human detrusor smooth muscles. solifenacin (YM905) ( $10^{-8}$  M~ $10^{-5}$  M) and atropine ( $10^{-9}$  M~ $10^{-6}$  M) caused parallel shifts to the right of the concentration-response curves to carbachol. All slopes of the regression line of Schild plots were close to unity, and the pA<sub>2</sub> values and slopes of the Schild plots for these drugs tested, are shown in Table. These drugs did not inhibit the maximum contractions to carbachol and the KCl- and CaCl<sub>2</sub>-induced contractions. Electrical field stimulation caused frequency-dependent contractions of human detrusor smooth muscles, and which were inhibited by atropine and solifenacin (YM905) in a concentration-dependent manner. In the presence of atropine ( $10^{-6}$  M), solifenacin (YM905) did not significantly inhibit the residual atropine resistant contractions induced by electrical field stimulation.

### Conclusions

The present results suggest that solifenacin (YM905) inhibits the contractions of human detrusor smooth muscles mainly by the antimuscarinic action. This finding supports the usefulness of solifenacin (YM905) as a therapeutic drug for overactive bladder with symptoms of frequency, urgency and urge incontinence.