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PHARMACOLOGICAL EFFECTS OF KRP-197 ON HUMAN ISOLATED URINARY BLADDER

Aims of Study

KRP-197, 4-(2-methylimidazol-l-yl)-2,2-diphenylbutyramide, is a newly synthesized antimuscarinic drug developed for the treatment of pollakisuria and urinary incontinence. Pharmacological studies have demonstrated that this compound has no calcium antagonistic actions, and that this exhibits favorable selectivity for the bladder over the salivary glands in vivo experiments. It is suggested that KRP-197 blocks not only postjunctional receptors, but also prejunctional receptors to modulate acetylcholine releases in parasympathetic nerve endings in detrusor smooth muscle. Therefore, we investigated the effects of KRP-197 on prejunctional and postjunctional muscarinic receptors of the isolate human detrusor smooth muscle, compared with the effects of atropine,oxybutynin and propiverine.

Methods

Specimens of human urinary bladder were obtained from 43 patients (34 male and 9 female, mean age 65.4 years old) undergoing radical cystectomy for bladder carcinoma.Smooth muscle strips were dissected from the body of urinary bladder of each patient. Each strip, 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. Using this muscle bath technique, we investigated the effects of various antimuscarinic drugs (KRP-197, atropine, oxybutynin, propiverine) on the contractions induced by carbachol, KCl, $CaCl_2$ and electrical field stimulation (supramaximal voltage, 0.3 msec duration, 2 - 60 Hz and 3 sec train). Furthermore, using microdialysis technique, we collected the dialysate obtained from microdialysis probe inserted into the muscle strips during electrical field stimulation, and measured the amount of acetylcholine in the dialysate fraction by high performance liquid chromatography with electro-chemical detection.

Results

Carbachol (10^{-8}-10^{-2} M) induced dose - dependent contractions in the human detrusor smooth muscles. Pretreatment with various antimuscarinic drugs caused parallel shifts to the right in the carbachol-induced dose-response curves. The pA_2 value of KRP-197 was 9.23 ± 0.06, which was similar to that of atropine. The rank order of pA_2 value was KRP-197 ≥ atropine > oxybutynin > propiverine (table). Atropine and KRP-197 did not cause significant inhibitions of KCl (80 mM) and $CaCl_2$ (5 mM) - induced contractions. All drugs caused dose-dependent inhibitions in contractions induced by electrical field stimulation. Pretreatment with propiverine and atropine did not cause significant changes in electrical field stimulation-induced acetylcholine release. Pretreatment with atropine decreased electrical field stimulation-induced acetylcholine release, not significantly. However, KRP-197 and oxybutynin significantly decreased electrical field stimulation-induced acetylcholine release in human detrusor smooth muscles.

Conclusions

The present study demonstrated that KRP-197 blocks not only postjunctional receptors, but also prejunctional receptors to modulate acetylcholine releases in cholinergic nerve endings of human detrusor smooth muscle. These findings support the usefulness of KRP-197 as a therapeutic drug for urinary dysfunction such as pollakisuria and urinary incontinence.

References

1. Urol. Int., 61: 135-141, 1998.
2. Bioorg. Med. Chem., 7: 1151-1161, 1999.

Drugs	pA_2	Slope
KRP-197	**9.23±0.06**	**1.14±0.01**
Atropine	**9.02±0.12**	**1.08±0.04**
Oxybutynin	**7.96±0.09**	**1.04±0.08**
Propiverine	**6.88±0.15**	**0.83±0.01**