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CAN MUSCARINIC RECEPTOR ANTAGONISTS INCREASE URINE STORING FUNCTION WITHOUT REDUCING VOIDING FUNCTION ?

Hypothesis / aims of study

Muscarinic receptor antagonists, used as therapeutic drugs for overactive bladder, are concerned about their potential of reducing voiding function and provoking residual urine despite their efficacy for urine storage. In spinal cord-injured rats, increased atropine resistance has been reported because of purine receptor- and C-fiber-mediated enhancement of the sensory system (1,2). In this study, we examined the involvement of atropine resistance and the actions of muscarinic receptor antagonists at the onset of overactive bladder and investigated their potential of improving pollakiuria without developing residual urine.

Study design, materials and methods

1. Spinal cord-injured rats [female SD rats whose spinal cord was transected at the T6-8 levels] were prepared and were then used in this study at week 4 after surgery when pollakiuria developed. An isolated urinary bladder contraction study compared intact rats with spinal cord-injured rats in terms of contractions induced by carbachol and by
α, β-Methylene-ATP.
2. Cystometry in anesthetized, spinal cord-injured rats examined the actions of muscarinic receptor antagonists on dysuria through the measurement of micturition interval, micturition volume, micturition pressure, and residual urine volume.
3. Acetic acid-induced pollakiuria model dogs were used to examine whether muscarinic receptor antagonists (oxybutynin, tolterodine, darifenacine, solifenacin, and propiverine) have pollakiuria-improving activity by measuring the number of micturitions, micturition duration, micturition interval, and intravesical pressure.
4. The affinity of the above muscarinic receptor antagonists for muscarinic receptor subtypes was examined. Furthermore, the affinity of propiverine for calcium receptors was examined.

Results

1. Spinal cord injury increased urinary bladder weight, thus verifying its hypertrophy. Furthermore, spinal cord-injured rats showed enhanced responsiveness to carbachol, as well as to α, β-Methylene-ATP compared to intact rats, especially with marked responsiveness in bladder body.
2. Thoracic vertebral injury provoked increases in static intracystic pressure and micturition pressure. Consequently, a significant increase in residual urine volume, along with shortening of micturition interval and a decrease in single micturition volume, were verified. On the contrary, propiverine prolonged micturition interval without affecting micturition pressure and residual urine volume and also increased single micturition volume.
3. Continuous intracystic injection of 0.3% acetic acid reduced voided volume and micturition interval, and this action was inhibited by capsaicin desensitization. The actions of muscarinic receptor antagonists on acetic acid-induced pollakiuria were examined. Consequently, only propiverine significantly improved pollakiuria.
4. The affinity of muscarinic receptor antagonists for muscarinic receptor subtypes was high in the following decreasing order: darifenacine > oxybutynin > tolterodine = solifenacin > propiverine. Darifenacine showed high affinity, especially for M3. However, propiverine exhibited no selectivity to muscarinic receptor subtypes. Furthermore, propiverine showed high affinity for L-type calcium receptors.

Interpretation of results

The urinary bladder of spinal cord-injured rats showed enhancement of the purine nervous system and of the cholinergic nervous system. In spinal cord-injured rats, propiverine increased single micturition volume without increasing residual urine volume. In acetic acid-induced pollakiuria model rats in which C-fibers were enhanced, furthermore, only propiverine significantly improved pollakiuria. Propiverine showed low antimuscarinic activity compared to other muscarinic receptor antagonists and exhibited no selectivity to muscarinic receptor subtypes. However, propiverine was found to inhibit C-fibers in addition to having calcium antagonistic activity.

Concluding message

The development of muscarinic receptor antagonists has targeted at enhancement of their selectivity to and activity on the subtype M3. However, the relevant approach was accompanied by the development of adverse reactions, e.g., residual urine and thirst. On the other hand, the involvement of atropine resistance mediated by purine receptors, C-fibers, and others increased in the urinary bladder of spinal cord-injured rats. Consequently, uninhibited contractions were considered to be enhanced. The above results led us to consider that, to enhance urine-storing function without deteriorating voiding function, the prescription of an anticholinergic agent which currently has atropine resistance-inhibitory activity is recommended rather than strengthening selectivity to and activity on muscarinic receptor subtypes.

References

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2. Neurochem Int., 45, 987-993, 2004

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