Antimuscarinic Drugs in Detrusor Overactivity and Overactive Bladder Syndrome: Motor or Sensory Actions?

Yao-Chi Chuang, M.D

Department of Urology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung,Taiwan

ABSTRACT

Traditionally, antimuscarinic agents are thought to exert their inhibitory effects on detrusor muscle contractions and have therapeutic benefits on detrusor overactivity and overactive bladder. However, recent studies have demonstrated that the major mechanisms of antimuscarinic agents are on the regulation of afferent activity during the storage phase of micturition, instead of efferent activity during the voiding phase. Key words: muscarinic receptor, overactive bladder, urinary incontience

INTRODUCTION

Overactive bladder (OAB) is a syndrome characterized by symptoms of "urgency with or without urge incontinence, usually with frequency and nocturia" [1]. OAB is estimated to affect 17% of the adult population in the United States as well as Taiwan, and is ranked among the 10 most common chronic conditions [1-3]. Worldwide, the drug treatment for OAB includes antimuscarinic agents [2], which clinically act to increase bladder capacity and decrease urgency during the storage phase when there is normally no activity in the parasympathetic nerves [4]. Traditionally, antimuscarinic agents have been thought to inhibit detrusor muscle contractions, mainly through suppression of the muscarinic M_3 receptor subtype [5]. However, recent studies have demonstrated that the mechanisms of antimuscarinic agents are on the regulation of afferent activity during the storage phase of micturition, instead of efferent activity during the voiding phase of micturition [6].

BLADDER AND MUSCARINIC RECEPTORS

A previous study using radioligand-binding studies with [^{3}H] quinuclidinyl benzylate ([^{3}H]QNB) demonstrated that mAChR (muscarinic acetylcholine receptor) density in the human bladder mucosa was equal to that in the detrusor (7). Furthermore, mRNA for all mAChR subtypes in the human bladder has been shown to have a predominant expression of M_2 and M_3 receptors [8]. In addition, Tyagi et al found a receptor population of 71%, 22% and 7% for M_2, M_3 and M_1 receptors in detrusor muscle, and 75%, and 25% for M_2 and M_3/M_5 in the mucosa by using a competitive-binding assay in the human bladder [9].

Received: July 21, 2008 Accepted: July 22, 2008
Address correspondence to: Dr. Yao-Chi Chuang, Department of Urology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, 123, Ta-Pei Road, Niao-Sung Hsiang, Kaohsiung, 83301, Taiwan
E-mail: chuang82@ms26.hinet.net

ANTIMUSCARINIC MECHANISMS OF ACTION

The urothelium has been considered a simple inert barrier to prevent the leakage of urine, which causes irritative voiding symptoms by stimulating the submucosal nerves or detrusor, when it passed the barrier. However, the urothelium is metabolically active, and recent studies have reported that it acts as an important regulator of bladder contractility and/or sensation [10]. It has also been reported that bladder urothelium can release acetylcholine (Ach), and mAChRs are located on the urothelium [9]. The non-neuronal Ach can activate mAChRs on nearby bladder nerves, smooth muscle and myofibroblasts as well as autocrine/paracine function to activate cholinergic receptors on the urothelial cell surface. The basal release of Ach from the urothelium increases with age and stretch [11]. In the case of OAB, the release of Ach from the urothelium during the storage phase of micturition can activate the muscarinic receptors in the urothelium, which trigger the release of urothelium ATP and nitric oxide and lead to activation of afferent pathways [12]. Thus, blocking the urothelial muscarinic receptors could act indirectly to reduce afferent nerve activation and therefore decrease OAB symptoms. A recent study revealed that intravenous administration of darifenacin, an M_3 selective muscarinic antagonist, reduced bladder afferent activity [13]. Thus it appears that the beneficial therapeutic effects of antimuscarinic drugs may be partially mediated by their actions on sensory nerves.

Kim et al demonstrated that intravesical antimuscarinic agents suppressed a carbachol -induced intercontraction interval reduction, but had no effect on normal bladder storage and contractile function [14], thus separating the local inhibitory effects of antimuscarinic agents during the storage phase from a reduction in voiding pressure.

After oral administration, differences in the structure of the antimuscarinics result in varying degrees of inactive and active metabolites of antimuscarinic agents in the urine [15]. Ingestion of trospium results in excretion of 60% of an active metabolite into the urine, which has shown a significant inhibitory effect over tolterodine LA and oxybutynin in a rat model of detrusor overactivity [16]. Solifenacin succinate has approximately 15% of active compound excreted into the urine compared with 3% and <1% with darifenacin and tolterodine LA, respectively [15,17]. Not surprisingly, a previous study showed that urine collected after taking solifenacin suppressed carbachol -induced detrusor overactivity, but this effect was not seen in the darifenacin and tolterodine groups [17]. Taken together, these results suggest that antimuscarinic agents excreted into the urine might have different degrees of local inhibitory effects on muscarinic receptors in the urothelium and suburothelial sensory fibers and suppress bladder overactivity.

EVIDENCE FROM CLINICAL STUDIES

Finney et al analyzed 14 original articles which contained cystometric data on both the filling and voiding phases in patients with OAB before and after antimuscarinic treatment [18]. They found that after antimuscarinic treatment, variables associated with storage, such as the first desire to void and the maximum cystometric capacity, were significantly improved in the vast majority of studies, and variables associated with voiding, e. g. the detrusor pressure at maximal flow rate (PdetQmax) and Qmax, were not significantly changed. They suggested that the beneficial effects of antimuscarinics are due to improvements in bladder sensory function.

CONCLUSION

Recent studies have demonstrated that the major mechanisms of antimuscarinic agents are on the regulation of afferent activity during the storage phase of micturition, instead of efferent activity during the voiding phase.

REFERENCES

1. Abrams P, Cardozo L, Fall M, et al: The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002; **21**:167-178.
2. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ: How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001; **87**:760-766.
3. Yu HJ, Liu CY, Lee KL, Lee WC, Chen TH: Overactive bladder syndrome among community-dwelling adults in Taiwan: Prevalence, correlates, perception, and treatment seeking. Urol Int 2006; **77**: 327-333.
4. De Groat WC, Booth AM, Yoshimura N: Neurophysiology of micturition and its modifications in animal models of human disease, in Maggi CA (Ed): The autonomic nervous system; Nervous control of the urogenital system. London, Harwood, 1993, vol. 6, pp 227-289.
5. Hegde SS, Eglen RM: Muscarinic receptor subtypes mudulating smooth muscle contractility in the urinary bladder. Life Sci 1999; **64**:419-428.
6. Andersson KE, Yoshida M: Antimuscarinic and the overactive detrusor-which is the main mechanism of action? Eur Urol 2003; **43**:1-5.
7. Mansfield KJ, Liu L, Mitchelson FJ, Moore KH, Millard RJ, Burcher E: Muscarnic receptor subtypes in human bladder and mucosa, studied by radioligand binding and quantitative competitive RT-PCR: Changes in ageing. Br J Pharmacol 2005; **144**:1089-1099.
8. Yamaguchi O, Shishido K, Tamura K, Ogawa T, Fujimura T, Ohtsuka M: Evaluation of mRNAs encoding muscarinic receptor subtypes in human detrusor muscle. J Urol 1996; **156**:1208-1213.
9. Tyagi S, Le TSV, Thomas CA, et al: Qualitative and quantitative expression profile of muscarinic receptors in human urothelium and detrusor. J Urol 2006; **176**:1673-1678.
10. Fry CH, Ikeda Y, Harvey R, Wu C, Sui GP: Control of bladder function by peripheral nerves: Avenues for novel drug targets. Urology 2004; **63(Suppl 1)**:24-31.
11. Yoshida M, Miyamae K, Iwashita H, Otani M, Inadome A: Management of detrusor dysfunction in the elderly: Changes in acetylcholine and adenosine triphosphate release during aging. Urology 2004; **63(3 Suppl 1)**:17-23.
12. Hanna-Mitchell AT, Beckel JM, Barbadora S, Kanai AJ, de Groat WC, Birder LA: Non-neuronal acetylcholine and urinary bladder urothelium. Life Sci 2007; **80**:2298-2302.
13. Iijima K, De Wachter S, Wyndaele JJ: Effects of the M_3 receptor selective muscarinic antagonist darifenacin on bladder afferent activity of the rat pelvic nerve. Eur Urol 2007; **52**:842-847.
14. Kim Y, Yoshimura N, Masuda H, de Miguel F, Chancellor MB: Antimuscarinic agents exhibit local inhibitory effects on muscarinic receptors in bladder-afferent pathways. Urology 2005; **65**:238-242.
15. Michel MC, Hegde SS: Treatment of the overactive bladder syndrome with muscarinic receptor antagonists: A matter of metabolites? Naunyn Schmiedebergs Arch Pharmacol 2006: **374**:79-85.
16. Kim Y, Yoshimura N, Masuda H, De Miguel F, Chancellor MB: Intravesical instillation of human urine after oral administration of trospium, tolterodine and oxybutynin in a rat model of detrusor overactivity. BJU Int 2005; **97**:400-403.
17. Chuang YC, Thomas CA, Tyagi T, Yoshimura N, Tyagi P, Chancellor MB: Human Urine With Solifenacin Intake but not tolterodine or darifenacin intake, blocks detrusor overactivity. Int Urogynecol J Pelvic Floor Dysfunct 2008; **19**:1353-1357.
18. Finney SM, Andersson KE, Gillespie JI, Stewart LH: Antimuscarinic drugs in detrusor overactivity and the overactive bladder syndrome: Motor or sensory actions? BJU Int 2006; **98**:503-507.