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Selective Inhibitory Effect of Imidafenacin and 5-Hydroxymethyl Tolterodine on Capsaicin Sensitive C Fibers of the Primary Bladder Mechanosensitive Afferent Nerves in the Rat

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Purpose: Imidafenacin and fesoterodine are used to treat overactive bladder. Imidafenacin, fesoterodine and its active metabolite 5-hydroxymethyl tolterodine are muscarinic receptor antagonists. It is believed that these agents act on afferent nerves in addition to smooth muscle. We investigated the effects of imidafenacin and 5-hydroxymethyl tolterodine on single unit afferent activity of mechanosensitive capsaicin sensitive and insensitive primary bladder afferent nerve fibers in rats.

Materials and Methods: Female Sprague Dawley® rats were anesthetized. Single unit afferent activity was recorded from the L6 dorsal roots and classified by conduction velocity as that of Aδ or C fibers. After measuring control single afferent activity during constant filling cystometry the procedure was repeated with intravenous administration of imidafenacin (0.3 to 30 μg/kg) or 5-hydroxymethyl tolterodine (0.01 to 1 mg/kg) at cumulative doses with or without intravesical capsaicin or oxotremorine-M instillation.

Results: A total of 116 single unit afferent fibers were isolated from 91 rats, including 19 Aδ and 97 C fibers. Neither imidafenacin nor 5-hydroxymethyl tolterodine significantly affected the overall single unit afferent activity of Aδ or C fibers. Based on capsaicin sensitivity C fibers were divided into capsaicin sensitive and insensitive groups. Each antimuscarinic inhibited the single unit afferent activity of capsaicin sensitive C fibers but not of capsaicin insensitive C fibers at the highest dose. Moreover, oxotremorine-M facilitated single unit afferent activity in a proportion of C fibers. The facilitated single unit afferent activity was significantly attenuated by the highest dose of imidafenacin.

Conclusions: These findings demonstrate that imidafenacin and 5-hydroxymethyl tolterodine can selectively inhibit capsaicin sensitive C fibers among mechanosensitive bladder afferents by antagonizing bladder muscarinic receptors.

Key Words: urinary bladder; neurons, afferent; capsaicin; imidafenacin; 5-hydroxymethyl tolterodine

Abbreviations and Acronyms

5-HMT = 5-hydroxymethyl tolterodine

ATP = adenosine triphosphate

CAP = capsaicin

mAChR = muscarinic acetylcholine receptor

OAB = overactive bladder

Oxo-M = oxotremorine-M

RTX = resiniferatoxin

SAA = single unit afferent activity

TRPV = transient receptor potential vanilloid

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ANTIMUSCARINIC agents such as imidafenacin and fesoterodine have been used as first line pharmacological treatment of OAB.[1] Imidafenacin has higher affinity for the M1 and M3 subtypes than for the M2 receptor subtype[2] with organ selectivity for the bladder.[3] Fesoterodine and its

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active metabolite 5-HMT (previously named SPM 7605) block all mAChR subtypes in the human bladder.[4]

The pharmacological action of antimuscarinics is presumed to be the suppression of detrusor contractions.[1] However, recent observations indicated that oxybutynin and darifenacin, which are nonselective and M3 receptor subtype selective antimuscarinic agents, respectively, inhibited the activity of mechanosensitive primary bladder afferent nerves in rats.[5,6] RTX and CAP can activate TRPV1, which is expressed on urothelial cells and bladder primary afferent fibers that run suburothelially.[7] Our previous studies demonstrated that approximately a third and two-thirds of mechanosensitive bladder C-fiber afferents can be classified as CAP sensitive and insensitive, respectively, and TRPV4 agonists and exogenous ATP activated only CAP insensitive C fibers.[8,9] Recent animal studies revealed that imidafenacin and tolterodine, of which the effects are mediated by the active metabolite 5-HMT, improved cerebral infarction induced detrusor overactivity in rats by suppressing RTX sensitive C fibers.[10,11] The antidiuretic effect of imidafenacin but not of atropine occurs through the activation of RTX sensitive C fibers in the rat bladder.[12] These results suggest that imidafenacin and 5-HMT act on bladder afferent function through RTX sensitive C fibers and possibly TRPV1 mediated C fibers.

We investigated the direct effect of imidafenacin and 5-HMT on the SAA of primary mechanosensitive bladder afferent nerves and determined the relationship with CAP sensitivity in urethane anesthetized rats.

METHODS

Animals

We used 111 adult female Sprague Dawley rats at ages 9 to 11 weeks weighing 180 to 250 gm. Rats were maintained under standard laboratory conditions with a 12:12-hour light-dark cycle and free access to food and water. The protocol was approved by the University of Tokyo institutional animal care and use committee and conformed to NIH (National Institutes of Health) guidelines for the care and use of experimental animals.

Afferent Measurement Experimental Procedure

Rats were anesthetized with urethane (1.2 gm/kg intraperitoneally). Body temperature was maintained at 38C by a heated blanket. Single afferent fiber measurements were made as previously described.[8,9] Briefly, the left pelvic nerve was dissected from the surrounding tissue proximal to the major pelvic ganglion. A pair of silver electrodes was placed around the pelvic nerve. A PE-50 catheter (Clay-Adams®) was inserted in the bladder. The 2 L6 dorsal roots were cut near the entrance to the spinal cord after laminectomy. Fine filaments were dissected from the left L6 dorsal root and placed across shielded bipolar silver electrodes. Clearly different unitary action potentials of afferent fibers originating from the bladder were identified by electrical stimulation of the left pelvic nerve and bladder distension with saline using the Spike2 (http://ced.co.uk/) impulse shape recognition program. Action potentials of a maximum of 3 fibers were investigated at the same time during a single bladder filling. Conduction velocity of the identified action potential was calculated from the latency of the response to electrical stimulation and the conduction distance between stimulation and recording sites, which was based on our anatomical data. Fibers were grouped based on conduction velocity. Those with a conduction velocity of less than 2.5 m per second and 2.5 or greater were considered to correspond to unmyelinated C and myelinated Aδ fibers, respectively.[13]

To facilitate CAP permeability after intravesical instillation protamine sulfate solution (10 mg/ml, 0.3 ml) was intravesically instilled and kept in the bladder for 60 minutes just before measurement. Our previous studies demonstrated that this does not lead to any significant difference in bladder compliance or SAA before or after protamine sulfate exposure.[9] In contrast, a study showed that the intravesical Oxo-M sites of action are likely the muscarinic receptors near the lumen based on the fast onset of action of intravesical Oxo-M on cystometry and the known properties of Oxo-M, a quaternary structure and hydrophilic properties.[14] Considering this information, we did not use protamine sulfate to facilitate Oxo-M permeability. SAA was recorded during constant filling cystometry using saline at a rate of 0.08 ml per minute. Filling continued until 30 cm H_2O intravesical pressure was attained. Bladder compliance was calculated between the start and end of bladder filling. The afferent activity caused by pelvic nerve stimulation was also recorded before and after bladder filling, and confirmed to correspond to that caused by bladder filling.

At the beginning of the experiments recording was repeated 3 consecutive times at 5-minute intervals to evaluate reproducibility. The third recording served as the control (before drug administration) value. Five experimental protocols were subsequently performed in separate rats. 1) Imidafenacin (0.3, 3 and 30 μg/kg cumulatively) or 5-HMT (0.01, 0.1 and 1 mg/kg cumulatively) was administered intravenously. Three minutes after each administration the 3 cycle recordings were performed to evaluate the dose dependence of the immediate drug effect during each 5-minute interval (fig. 1, *A*). [F1] 2) Imidafenacin was administered only at the highest dose (30 μg/kg intravenously). At 20 minutes after administration recording was performed to evaluate time dependence (fig. 1, *B*). 3) Higher doses of imidafenacin (cumulatively 3 and 30 μg/kg intravenously) or 5-HMT (cumulatively 0.1 and 1 mg/kg intravenously) were administered. Three minutes after each dose 2 cycle recordings were performed. CAP (10^{-5} M) was then instilled in the bladder to evaluate the relationship to CAP sensitivity (fig. 1, *C*). 4) Oxo-M (25 μM) was instilled in the bladder at 0.04 ml per minute for 8 minutes to evaluate whether imidafenacin would antagonize mAChR

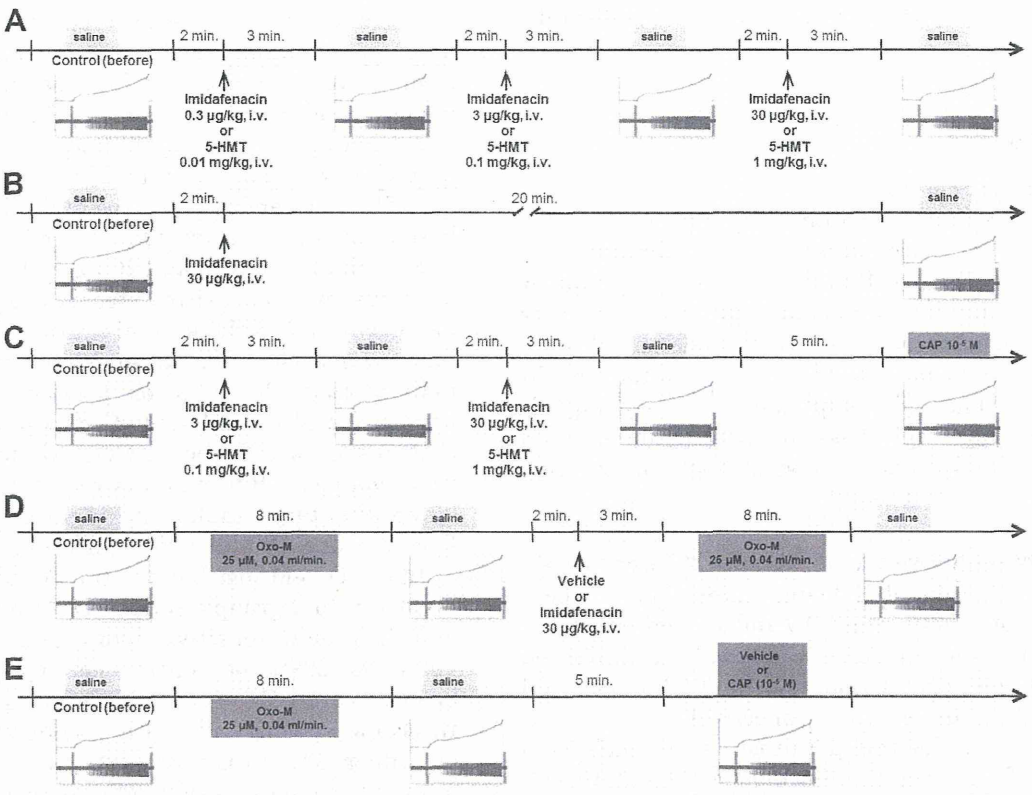

Figure 1. Experimental model and procedures, including cumulative drug with 5 minutes between each recording (*A*), single imidafenacin administration with measurement repeated 20 minutes later (*B*), drug and CAP with 5 minutes between each recording (*C*), Oxo-M and vehicle or imidafenacin (*D*), and Oxo-M and subsequent vehicle or CAP (*E*). *i.v.*, intravenously.

activation by Oxo-M. After Oxo-M instillation if C-fiber SAA was facilitated compared to that before instillation this fiber was defined as Oxo-M sensitive. Vehicle or imidafenacin (30 µg/kg) was administered intravenously 3 minutes before the second Oxo-M instillation (fig. 1, *D*). 5) To address whether Oxo-M facilitates distension evoked firing of CAP sensitive and CAP insensitive afferents Oxo-M (25 µM) was instilled in the bladder at 0.04 ml per minute for 8 minutes. After Oxo-M instillation if C-fiber SAA was facilitated compared to the control (before instillation), this fiber was defined as Oxo-M sensitive. Five minutes later vehicle or CAP (10^{-5} M) was instilled intravesically to evaluate the effect of CAP on Oxo-M sensitive or insensitive C-fiber activity (fig. 1, *E*).

The relationship of nerve activity to pressure was established by comparing nerve activity and intravesical pressure at 1-second intervals. These values were subsequently averaged at a 5 cm H_2O pressure interval during the filling phase. Average total unitary activity was calculated as a function of intravesical pressure. Afferent nerve activity is shown in Hz and a percent of control activity based on pressure integrated for the whole filling phase.

C fibers were classified as CAP sensitive or insensitive based on SAA increases over those of controls at CAP instillation with 150% considered the minimum threshold for sensitivity.[8,9] Classification as Oxo-M sensitive or insensitive was defined the same way.

Drugs

We used protamine sulfate, CAP (Sigma-Aldrich®), Oxo-M (Tocris Bioscience, Bristol, United Kingdom), imidafenacin (4-(2-methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide) and 5-HMT (R-enantiomer: 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl)phenol). Protamine sulfate was dissolved in distilled water. CAP was dissolved in absolute ethanol as a stock solution (10^{-3} M) and stored at −80C. Drugs were subsequently diluted on the day of the experiment using saline. Oxo-M was dissolved in saline. Imidafenacin was dissolved in saline with 1 M hydrochloric acid, subsequently neutralized with 1 M sodium hydroxide and serially diluted to desired concentrations. We dissolved 5-HMT (10 mg/ml) in 10% *N,N*-dimethylacetamide, 10% Cremophor® and 80% saline. Subsequent dilutions were made in saline. Doses were chosen according to previous studies in rats.[4,8,9,15–17]

Statistical Analysis

All data are shown as the mean ± SEM. Results of comparisons between 2 groups were analyzed using the paired or unpaired Student t-test. Results of multiple comparisons with the control (before drug administration) were analyzed by 1-way ANOVA followed by the Dunnett (repeated measures) or Friedman test followed by the Tukey test. Results of multiple comparisons between groups were analyzed by 2-way ANOVA followed by

the Tukey test with $p < 0.05$ considered statistically significant.

RESULTS

Bladder Compliance

Bladder compliance significantly increased after moderate and high doses of imidafenacin and [T1] 5-HMT as well as CAP (table 1). However, bladder compliance did not significantly change 20 minutes after single administration of the highest dose of imidafenacin (table 1). In addition, after Oxo-M instillation bladder compliance did not significantly change regardless of pretreatment with vehicle or imidafenacin, or subsequent instillation [T2] of vehicle or CAP (table 2).

Primary Mechanosensitive Bladder Afferent SAA

We isolated a total of 139 single unit afferent fibers from 111 rats. Of the units 19 and 120 corresponded to the criteria for myelinated Aδ and unmyelinated C fibers (mean conduction velocity 4.23 ± 0.40 and 1.71 ± 0.04 m per second, respectively).

Neither cumulatively administered imidafenacin nor 5-HMT significantly affected the SAA of Aδ or C fibers even at the highest dose when evaluated 3 minutes after each dose (supplementary table, http://jurology.com/, and fig. 2, *A* and *B*). In addition, 20 minutes after the highest dose of imidafenacin was administered neither Aδ nor C-fibers SAA was significantly changed (supplementary table, http://jurology.com/, and fig. 2, *C*). [F2]

C-fiber afferent activity was divided into 2 groups based on CAP sensitivity. Of 45 discriminated C-fiber single units 19 and 26 were classified as CAP sensitive and insensitive, respectively. Upon imidafenacin or 5-HMT administration CAP sensitive fiber sensitivity decreased significantly at the highest dose (30 μg/kg or 1 mg/kg, respectively, figs. 3, *A* and *C*, and 4, *A*, *C*, *D* and *F*). However, [F3] CAP insensitive C-fiber activity showed no significant changes after administration of either drug [F4] (supplementary table, http://jurology.com/, and figs. 3, *B* and *D*, and 4, *B*, *C*, *E* and *F*).

In the Oxo-M instillation study C fibers were also divided into 2 groups, that is 15 Oxo-M insensitive and 32 Oxo-M sensitive fibers (100% vs 94% and 100% vs 209% of control activity, respectively, before vs after Oxo-M instillation) (fig. 1, *D* and *E*). In Oxo-M sensitive fibers the facilitatory responses of C-fiber SAA to Oxo-M rather slightly increased after intravenous vehicle administration (figs. 5, *A* [F5] and 6, *A* and *C*). In contrast, the SAA response [F6] significantly decreased after the highest dose of imidafenacin (30 μg/kg intravenously) (supplementary table, http://jurology.com/, and figs. 5, *B*, and 6, *B* and *D*).

In Oxo-M sensitive C fibers the facilitated afferent activities induced by Oxo-M were significantly decreased upon the second measurement after vehicle instillation at a 5-minute interval (fig. 7, *A* and *C*). Seven of 9 Oxo-M sensitive C fibers [F7] were further facilitated by CAP instillation. However, another 2 fibers were not facilitated and the overall response was significantly increased (supplementary table, http://jurology.com/, and fig. 7, *B* and *D*). In contrast, intravesical instillation of CAP did not significantly increase Oxo-M insensitive C-fiber activity (supplementary table, http://jurology.com/, and fig. 8). [F8]

Table 1. *Bladder compliance before and after drug and CAP administration*

	Imidafenacin	5-HMT
Cumulative administration + measurement at 5-min intervals		
No. rats	14	9
Dose:		
Low	0.3 μg/kg	0.01 mg/kg
Middle	3 μg/kg	0.1 mg/kg
High	30 μg/kg	1 mg/kg
Mean ± SEM bladder compliance (ml/cm H_2O):		
Control	0.0214 ± 0.0010	0.0146 ± 0.0012
Low dose	0.0227 ± 0.0011	0.0160 ± 0.0014
Middle dose	0.0243 ± 0.0014*	0.0173 ± 0.0016†
High dose†	0.0257 ± 0.0015	0.0180 ± 0.0015
Bolus + measurement 20 mins after administration		
No. rats	14	—
Dose	30 μg/kg	—
Mean ± SEM bladder compliance (ml/cm H_2O):		—
Control	0.0218 ± 0.0009	
Dose	0.0233 ± 0.0010	
Higher doses, CAP (10^{-5} M) + measurement at 5-min intervals		
No. rats	18	15
Dose:		
Middle	3 μg/kg	0.1 mg/kg
High	30 μg/kg	1 mg/kg
Mean ± SEM bladder compliance (ml/cm H_2O):		
Control	0.0157 ± 0.0006	0.0142 ± 0.0006
Middle dose	0.0167 ± 0.0006*	0.0152 ± 0.0007
High dose†	0.0174 ± 0.0006	0.0156 ± 0.0007
CAP†	0.0181 ± 0.0010	0.0174 ± 0.0008

* Significantly different vs control (Friedman and Tukey tests $p < 0.05$).
† Significantly different vs control (Friedman and Tukey tests $p < 0.01$).

DISCUSSION

It was suggested that during the storage phase there is ongoing acetylcholine release from nerves and/or urothelium, acting on mAChRs located on afferent nerves, which may initiate the micturition reflex and contribute to OAB symptoms.[18,19] Previous studies in an experimental model similar to that in the current study showed that intravenous administration of the antimuscarinic agents oxybutynin and darifenacin could inhibit Aδ and C-afferent fiber SAA.[5,6]

Table 2. *Bladder compliance before and after drug and Oxo-M administration*

Oxo-M*	No. Rats	Mean ± SEM Bladder Compliance (ml/cm H_2O)		
		Control	After Oxo-M	After Oxo-M + Vehicle or Imidafenacin
+ Highest imidafenacin dose:				
Vehicle	8	0.0155 ± 0.0005	0.0171 ± 0.0008	0.0178 ± 0.0010
Imidafenacin (30 μg/kg)	8	0.0158 ± 0.0013	0.0165 ± 0.0012	0.0179 ± 0.0012
+ CAP:				
Vehicle	6	0.0115 ± 0.0008	0.0125 ± 0.0010	0.0121 ± 0.0009
CAP (10^{-5})	14	0.0143 ± 0.0007	0.0127 ± 0.0008	0.0139 ± 0.0009

*Dose 25 μM at 0.04 ml per minute for 8 minutes.

Therefore, we hypothesized that imidafenacin and 5-HMT would have an inhibitory effect on the SAA of Aδ and C fibers of the mechanosensitive primary bladder afferent nerves. However, our results revealed that neither imidafenacin nor 5-HMT inhibited the SAA of either type of afferent fiber. The great discrepancy between this and previous[5,6] studies may be attributable to the difference of agents or time points after drug administration. In the previous studies changes were assessed 30, 60, 90 and 120 minutes after drug administration but we analyzed changes 3 minutes after drug administration. We further investigated the change in SAA 20 minutes after administering the highest imidafenacin dose (30 μg/kg). The result clearly showed that imidafenacin did not change the SAA of either type of afferent fiber (fig. 2, *C*). Again this was inconsistent with previous findings in studies of oxybutynin and darifenacin.[5,6] Imidafenacin has higher affinity for the M1 and M3 receptor subtypes than for the M2 receptor subtype, darifenacin has higher affinity only for the M3 receptor subtype, and oxybutynin and 5-HMT have affinity for the M1 to M3 subtypes.[2,4] Therefore, mAChR subtype selectivity may not reasonably explain the discrepancy.

Mechanosensitive bladder afferents consist of various nerve types with different response properties to CAP, K^+ and menthol.[20–22] We previously noted that mechanosensitive bladder C-fiber afferents can be classified as CAP sensitive and insensitive with the latter more prevalent and activated by TRPV4 agonists and intravesical ATP instillation.[8,9] Imidafenacin and 5-HMT can inhibit detrusor overactivity through RTX sensitive C fibers in

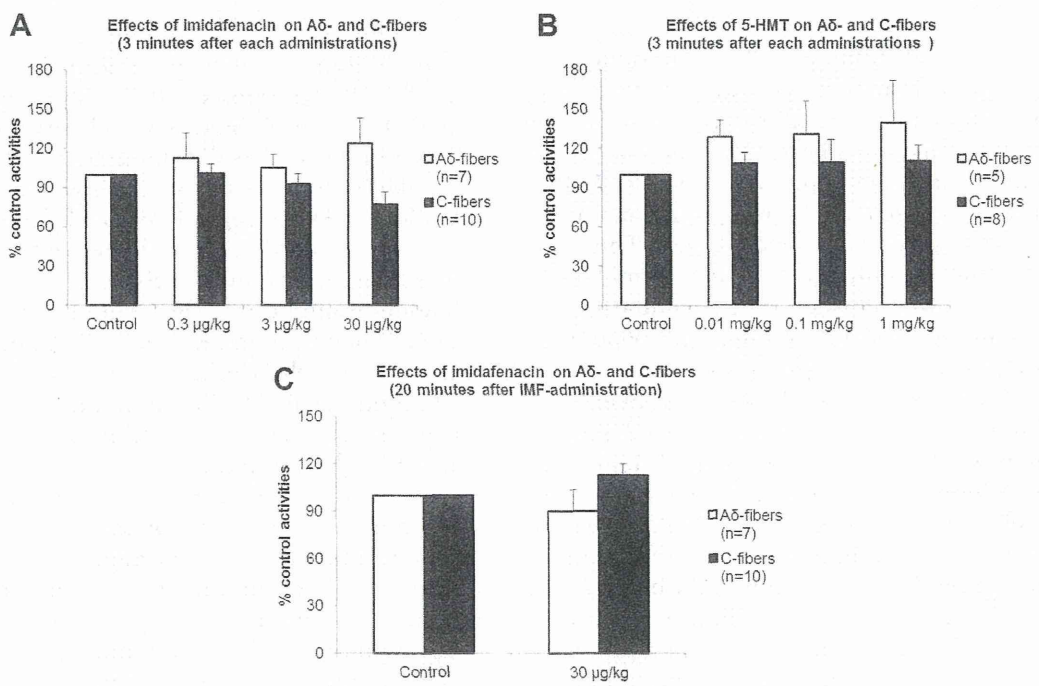

Figure 2. Mean ± SEM responses before and after cumulative intravenous drug administration shown as percent of control activity (*A* to *C*). *IMF*, imidafenacin. No significant difference between control and drug responses (1-way ANOVA and Dunnett test or paired Student t-test).

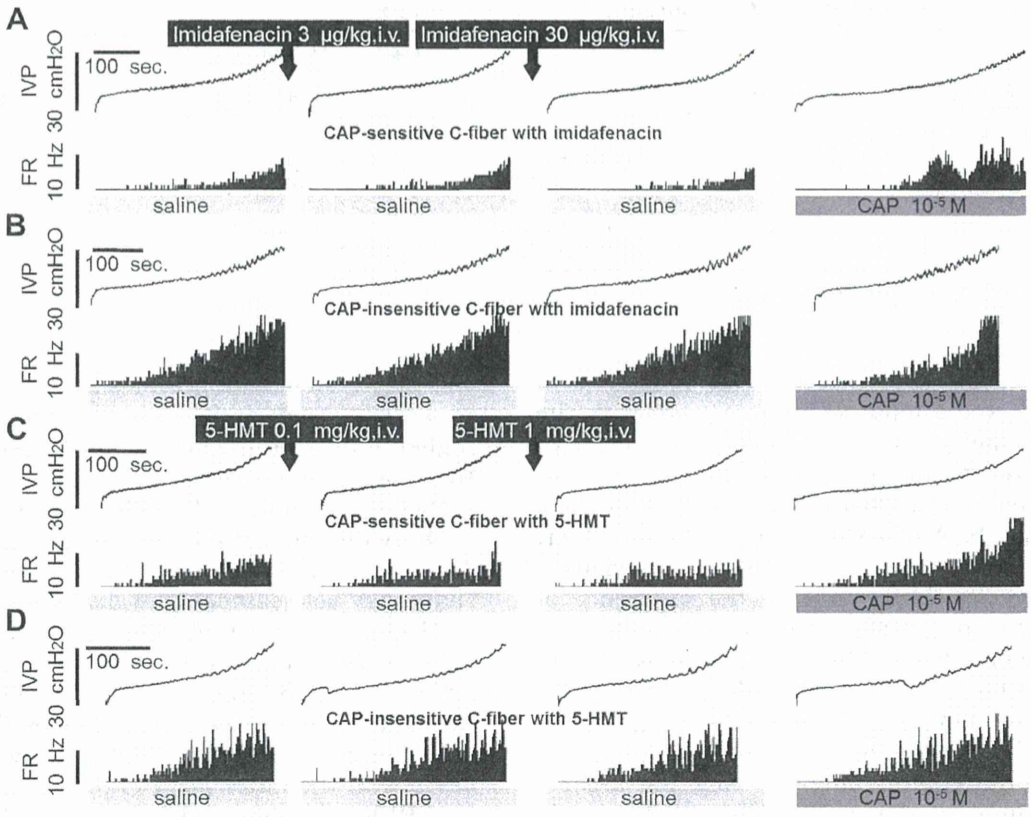

Figure 3. Representative traces show intravesical pressure (*IVP*) and firing rate (*FR*) of mechanosensitive afferent nerve activity by imidafenacin and 5-HMT in CAP sensitive and insensitive C fibers (*A* to *D*). *i.v.*, intravenously.

rats with cerebral infarction.[10,11] Therefore, we postulated that imidafenacin and 5-HMT may contribute to mechano-afferent transduction through CAP sensitive fibers. The results of this study clearly show that imidafenacin and 5-HMT significantly decreased the SAA of CAP sensitive C fibers but not of CAP insensitive C fibers. Thus, it is conceivable that the inhibitory action of imidafenacin and 5-HMT was masked when evaluating the overall C-fiber SAA because of the larger population of the CAP insensitive subgroup.

Selective inhibition on CAP sensitive fibers was observed only at the highest doses of imidafenacin and 5-HMT. To determine whether such high drug doses act on mAChRs or on other effectors located near the bladder lumen, the ie urothelium and/or suburothelial afferent nerves, we further studied intravesical instillation of the mAChR agonist Oxo-M.[14,17,23] As a result, the facilitatory responses of the C-fiber SAA to intravesical Oxo-M was suppressed by the same dose of intravenous imidafenacin. This strongly suggests that the doses of imidafenacin used acted on bladder mAChRs located near the bladder lumen. In terms of overall responses the C fibers that responded to intravesical Oxo-M were significantly activated by intravesical CAP, although some did not respond well to CAP. In contrast, Oxo-M insensitive C fibers did not respond to CAP. These results suggest that CAP sensitive C fibers are mostly responsive to activation of bladder mAChRs by intravesical Oxo-M.

Higher doses of imidafenacin and 5-HMT administered cumulatively significantly increased bladder compliance. However, the highest dose of imidafenacin induced no significant change in bladder compliance 20 minutes after single administration (table 1). This may have been due to the number of cystometry cycles rather than to the pharmacological effects of the agents. Our previous studies using a similar experimental protocol showed a tendency toward increased bladder compliance during repeat measurements even after saline administration, which supports this speculation.[8,24] A previous study using cystometrogram measurements in urethane anesthetized rats demonstrated that imidafenacin at a lower dose (3 μg/kg intravenously) increased bladder capacity without a change in micturition pressure or postvoid residual volume while a dose of 10 μg/kg intravenously decreased micturition pressure and

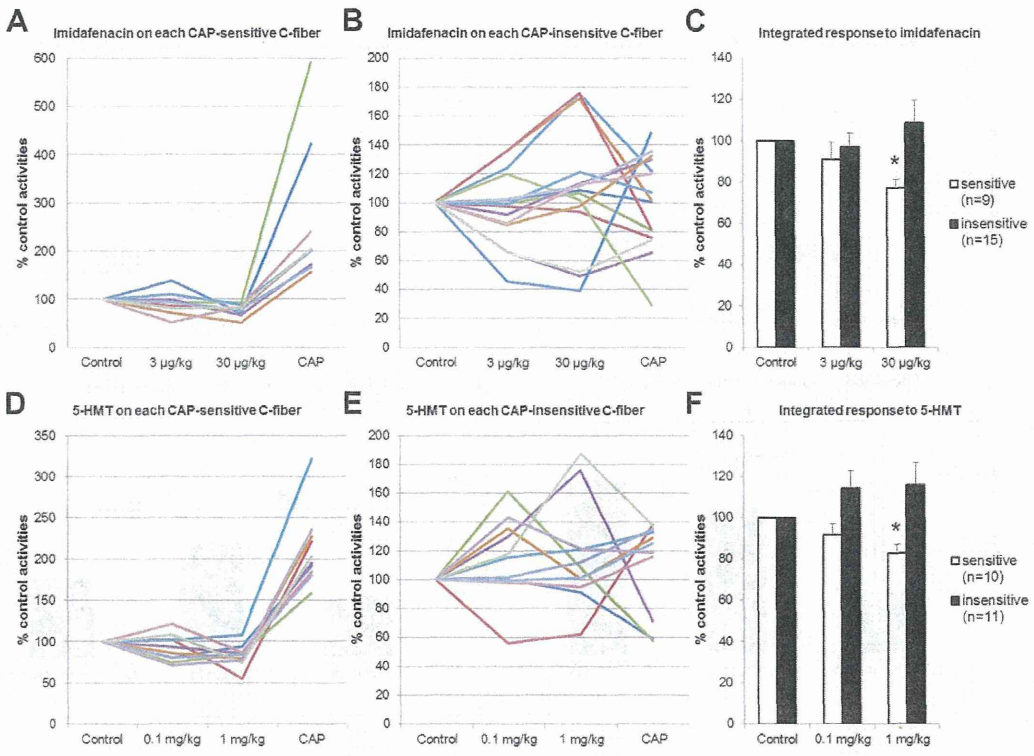

Figure 4. Responses to imidafenacin and 5-HMT on individual CAP sensitive and insensitive C fibers (*A* to *D*), and summarized imidafenacin and 5-HMT results (*C* and *F*). Values are shown as mean ± SEM percent of control activity. Asterisk indicates significantly different vs control (1-way ANOVA and repeated measures Dunnett test $p < 0.05$).

increased post-void residual volume.[15] In contrast, only a higher dose of imidafenacin (30 μg/kg intravenously) showed a significant inhibitory effect on CAP sensitive C-fiber afferent activity in the current study. The effective dose to increase bladder capacity in the previous study and the dose to

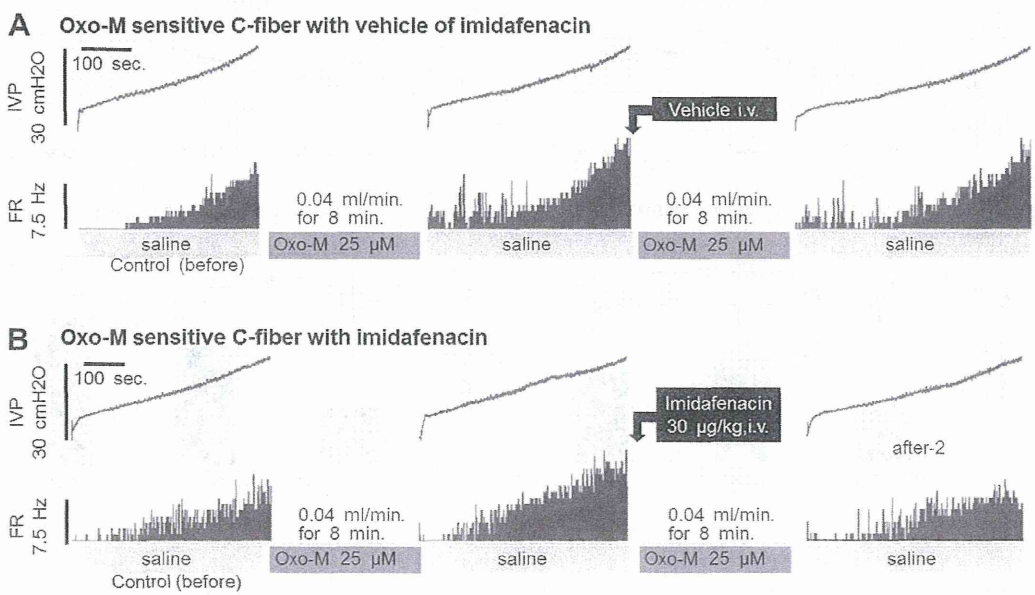

Figure 5. Representative traces show mechanosensitive afferent nerve activity intravesical pressure (*IVP*) and firing rate (*FR*) of Oxo-M sensitive C fibers after vehicle or imidafenacin (*A* and *B*). *i.v.*, intravenously.

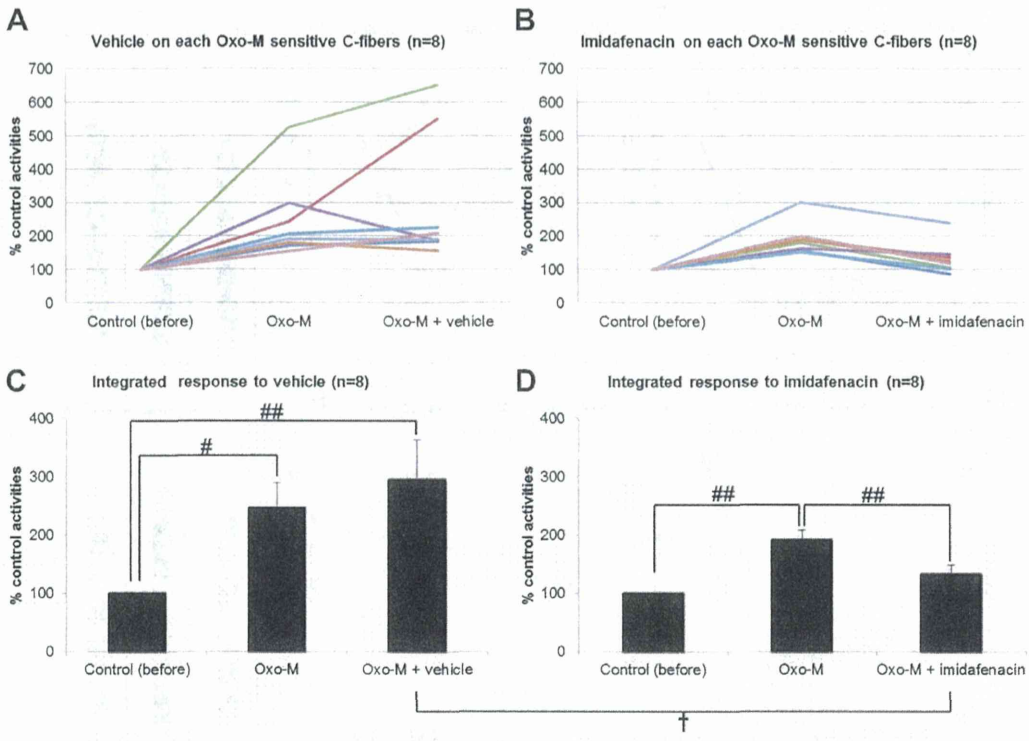

Figure 6. Oxo-M sensitive C fiber (*A* and *B*), and integrated Oxo-M sensitive C-fiber responses to vehicle and imidafenacin during whole filling phase after Oxo-M alone and in presence of vehicle (*C* and *D*) in 8 nerve fibers each. Values are shown as mean ± SEM percent of control activity. Single pound sign indicates significantly different (2-way ANOVA and Tukey test $p < 0.05$). Double pound signs indicate significantly different (2-way ANOVA and Tukey test $p < 0.01$). Dagger indicates significantly different (unpaired Student t test $p < 0.05$).

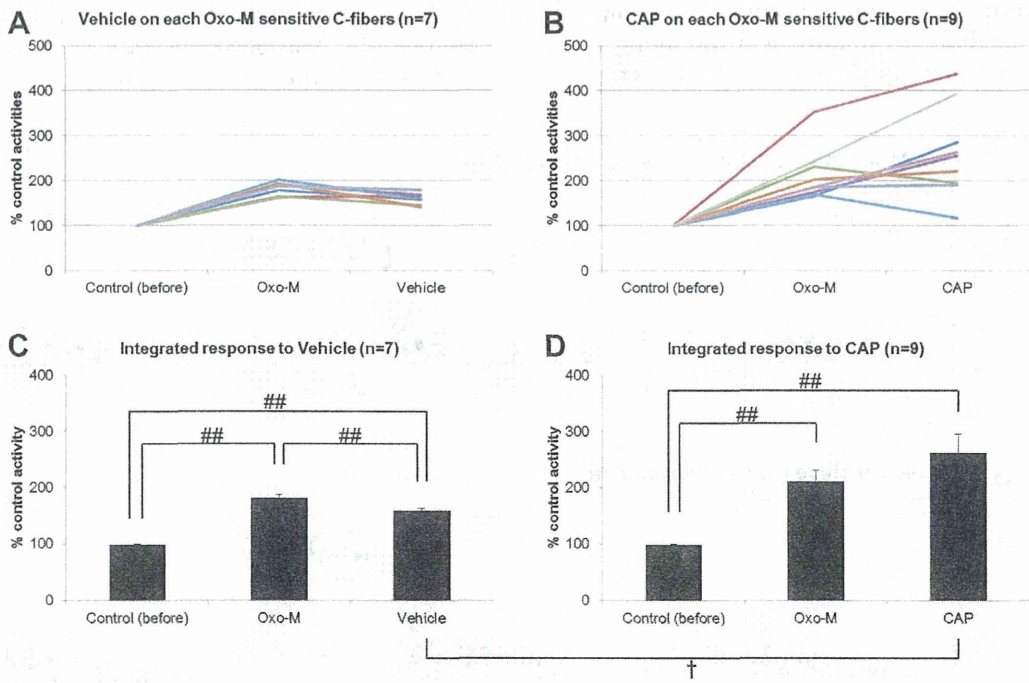

Figure 7. Responses to vehicle and CAP in individual Oxo-M sensitive C fibers (*A* and *B*) and integrated Oxo-M sensitive C-fiber responses during whole filling phase after Oxo-M and vehicle or CAP (*C* and *D*) in 7 or 9 nerve fibers each. Values are shown as mean ± SEM percent of control activity. Pound signs indicate significantly different (2-way ANOVA and Tukey test $p < 0.01$). Dagger indicates significantly different (unpaired Student t test $p < 0.05$).

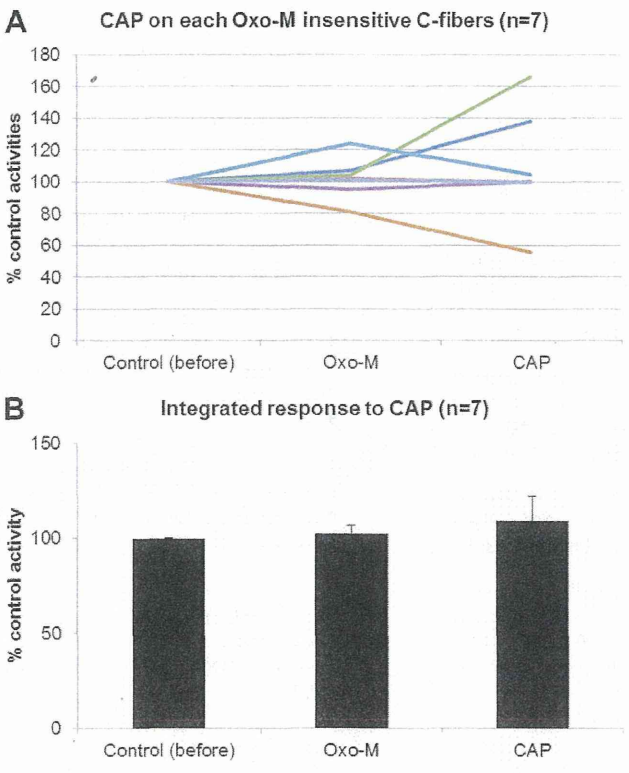

Figure 8. Responses of 7 individual Oxo-M insensitive and integrated Oxo-M insensitive C fibers each during whole filling phase after Oxo-M and CAP (*A* and *B*). Values are shown as mean ± SEM percent of control activity. No significant difference between groups (2-way ANOVA and Tukey test).

suppress mechanosensitive bladder afferent fibers in the current study appear discrepant, which may have been due to the different experimental setups, such as transection of the bilateral L6 roots in the current series.

In this study we did not investigate the effect of the drug on bladder capacity or micturition pressure. However, since single bolus administration of imidafenacin at the dose (30 μg/kg intravenously) that suppressed CAP sensitive C-fiber afferent activity did not significantly increase bladder compliance, imidafenacin may not act on the tonus of the detrusor smooth muscle at the dose that suppresses CAP sensitive C-fiber afferent activity. Taken together the current results indicate that imidafenacin can suppress the afferent activity of CAP sensitive C fibers selectively by inhibiting bladder mAChRs through an action other than decreasing detrusor smooth muscle tonus, at least under the special experimental conditions of the current study.

We acknowledge the controversy about the effect of antimuscarinic agents on mechanosensitive Aδ-fiber afferent activity.[5,6] The effects of atropine on bladder afferent function differ from those of other antimuscarinic agents.[12,25] Further investigation is required to explore the possibility of different mechanisms of action by antimuscarinic agents.

CONCLUSIONS

To our knowledge the current series demonstrates for the first time that imidafenacin and 5-HMT can selectively inhibit the mechanosensitive bladder afferent activity of CAP sensitive C fibers but not Aδ fibers or CAP insensitive C fibers. These effects are mediated by the antagonism of bladder muscarinic receptors in urethane anesthetized rats. The findings suggest a possible additional action of antimuscarinics, eg inhibitory action on bladder sensory function in pathophysiological conditions, as therapeutic agents for OAB or other bladder sensory disorders.

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