

DIRECT EVIDENCE FOR CONTRIBUTION OF MUSCARINIC RECEPTORS TO THE FACILITATION OF PRIMARY BLADDER MECHANOSENSITIVE C-FIBER AFFERENTS IN THE RAT

Hypothesis / aims of study

It has been reported that bladder muscarinic receptor (mAChR) may have a physiological role in the bladder afferent functions, especially in the C-fibers (1). In addition, a previous study demonstrated that bladder mechanosensitive C-fibers can be classified as capsaicin-sensitive and capsaicin-insensitive, and imidafenacin (IMF), a mAChR antagonist, selectively inhibited the capsaicin-sensitive subgroup of these C-fibers (2). Moreover in clinical observation, a considerable part of the patients with overactive bladder (OAB) do not respond to the treatment of antimuscarinic agents (3).

Therefore, we hypothesized that bladder mechanosensitive C-fiber afferent nerves have various sensitivities to the mAChR stimulation. In this study, we investigated the relationship between the afferent activities and oxotremorine-M (Oxo-M, a mAChR agonist)-sensitivity in the normal urethane-anesthetized rat by using the single-unit afferent activities (SAAs) measurement.

Study design, materials and methods

Female Sprague-Dawley rats were anesthetized and SAAs recorded from the L6 dorsal roots were classified by conduction velocity as C-fibers by electro-stimulation of the left pelvic nerve and by bladder-filling with saline. After measuring the baselines of SAA during constant filling cystometry, Oxo-M (25 μ M) was instilled into the bladder (0.04 ml/minute for 8 minutes), and, if SAA was facilitated more than 150% compared with baseline, this fiber was defined as Oxo-M-sensitive. In the Oxo-M-sensitive fibers, to evaluate whether the facilitated SAAs by Oxo-M-instillation mediated through the mAChRs, vehicle or IMF (30 μ g/kg) was administrated intravenously 3 minutes prior to the further (second) Oxo-M instillation (Figure 1).

Results

Twenty-four single-unit afferent C-fibers were isolated (CV: 1.79 ± 0.09 m/second) from 20 rats, and were divided into two groups by the sensitivities for Oxo-M; Oxo-M-insensitive (n=8, base: 100%, after Oxo-M instillation: 87%) and Oxo-M-sensitive (n=16, base: 100%, after Oxo-M instillation: 219%).

In the Oxo-M-sensitive fibers, in the vehicle-pretreated group, the second Oxo-M instillation also significantly increased SAAs similar as the first instillation did (Figures 2AC). On the other hand, in the IMF-pretreated group, the second Oxo-M instillation did not affect SAAs (Figures 2BD).

Interpretation of results

In the present study, intravesical instillation of the mAChRs agonist, Oxo-M, facilitated a subpopulation of bladder mechanosensitive C-fiber's SAAs. This facilitatory effect of Oxo-M was counteracted by the pretreatment with the mAChR antagonist, IMF. These findings indicate involvement of mAChRs in the bladder wall, probably located on the urothelial cells and/or afferent C-fibers in the suburothelial layer. Moreover, a previous study demonstrated that IMF can selectively inhibit SAAs of capsaicin-sensitive C-fibers in the bladder (2). Taken together, these findings support the view that antimuscarinic agents (mAChR antagonists) can act through the inhibition of capsaicin-sensitive C-fibers involved in the bladder urothelial afferent transduction. Such selectivity of antimuscarinic agents for inhibiting mechanoafferent fibers may be related to their refractoriness in the OAB treatment.

Concluding message

The results of the present study suggest the presence of different types of mechanosensitive bladder afferent C-fibers in response to mAChR stimulation. Such observation may link to the clinical observation that a part of the patients with OAB do not respond to the treatment of antimuscarinic agents.

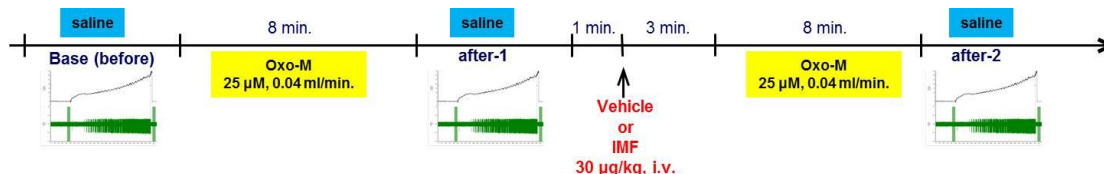


Figure 1. Experimental protocol of Oxo-M instillation with vehicle- or IMF-administration

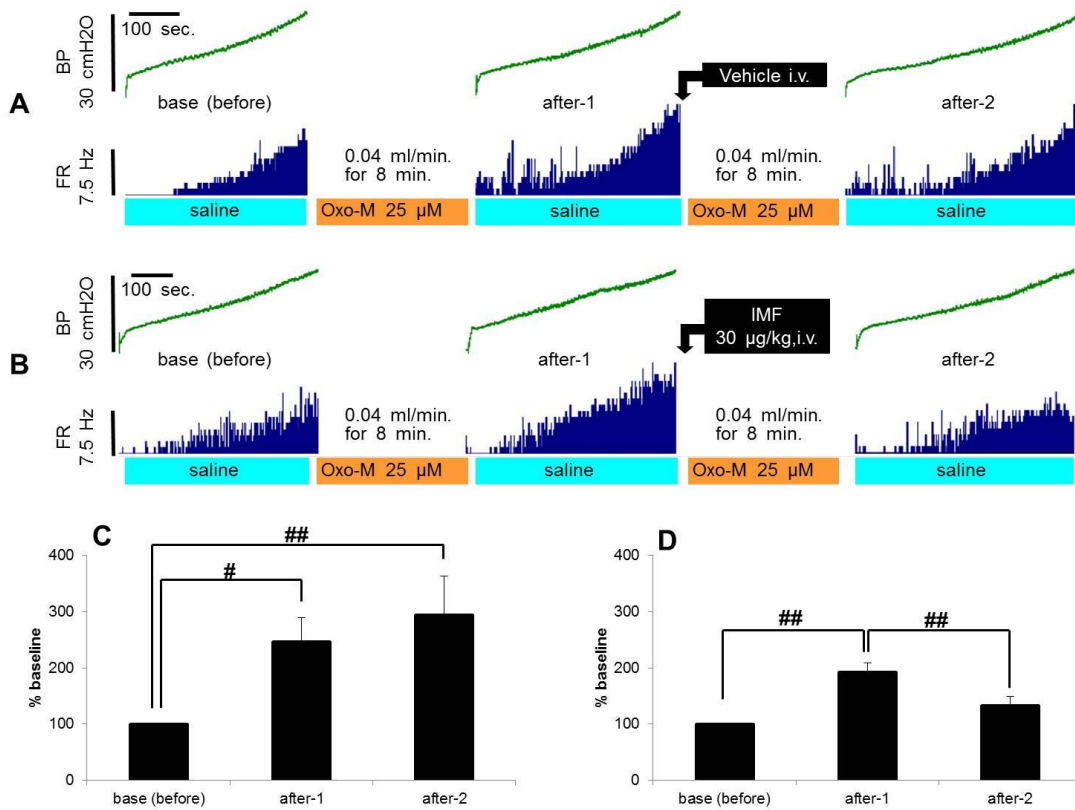


Figure 2. Representative traces of bladder pressure (BP) and firing rates (FR) of mechanosensitive afferent nerve activities of Oxo-M-sensitive C-fibers with vehicle- (A) or IMF-administration (B)

The effects of intravesical instillation of Oxo-M alone and in the presence of vehicle(C) or IMF (D) on the SAAs of Oxo-M-sensitive C-fibers.

After-1: after Oxo-M alone, After-2: Oxo-M in the presence of vehicle (C) or IMF (D)

The values are expressed as a percentage of base-line activity (mean \pm S.E.M.).

$P < 0.05$, ## $P < 0.01$: significant differences between groups (two-way ANOVA followed by Tukey's test)

References

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Disclosures

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