

IMIDANFENACIN, A NOVEL ANTICHOLINERGIC AGENT, SELECTIVELY INHIBITS CAPSAICIN-SENSITIVE C-FIBERS AMONG THE PRIMARY BLADDER MECHANOSENSITIVE AFFERENT NERVES OF THE RAT

Hypothesis / aims of study

Imidafenacin (IMF) is an antimuscarinic drug with high affinity for muscarinic M1 and M3 receptors, and has been launched in Japan as a new overactive bladder (OAB) therapeutic agent (1). It has been demonstrated that systemic administration of oxybutynin (a non-selective anticholinergic agent) suppress mechanosensitive bladder afferent in a time-dependent manner (2). We investigated effects of IMF on single-unit afferent activities (SAAs) of the mechanosensitive primary bladder afferent nerve fibers in rats. As a previous study indicates that C-fibers can be classified as capsaicin-sensitive and insensitive subgroups (3), the relationship of the IMF's effect with capsaicin-sensitivity was also determined.

Study design, materials and methods

Female Sprague-Dawley rats were anesthetized with urethane. The SAAs generated from left L6 dorsal roots were identified by electrical stimulation of the left pelvic nerve and bladder distension. Nerves with conduction velocities (CV) more than 2.5 m/s were designated as A δ -fibers and those with CV less than 2.5 m/s as C-fibers. After measuring the baselines of SAA during constant filling cystometry, three experimental protocols were performed in separate animals. First: IMF was administered intravenously (i.v.) at doses of 0.3, 3, and 30 μ g/kg cumulatively. SAA measurement was repeated three-minutes after each dose of administration to evaluate the dose-dependency of the immediate drug-effect (Fig. 1A). Second: IMF was administered only at the highest dose (30 μ g/kg, i.v.), and twenty-minutes after administration, SAA measurement was repeated to evaluate the time-dependency (Fig. 1B). Third: IMF was administered at doses of 3 and 30 μ g/kg, i.v. cumulatively, and then SAA measurement was repeated three-minutes after of each-administration. Finally, capsaicin was instilled (10^{-5} M) into the bladder to investigate the relationship with capsaicin-sensitivity (Fig. 1C).

Results

Totally 58 single-unit afferent fibers were isolated from 46 rats (A δ -fibers: n=14, C-fibers: n=44). C-fiber SAAs significantly decreased when evaluated three minutes after IMF-administration only at the highest dose (30 μ g/kg) used. On the other hand, IMF even at the highest dose affected A δ -fiber SAAs (Fig. 2A) although bladder compliance significantly increased at higher doses (3 and 30 μ g/kg). When evaluated 20-minutes after the highest dose of IMF-administration, neither A δ - nor C-fibers SAAs significantly changed (Fig. 2B). Regarding capsaicin-sensitivity, C-fibers could be divided into two groups: capsaicin-sensitive (n=9) and capsaicin-insensitive (n=15). IMF inhibited SAAs of the capsaicin-sensitive, but not of the capsaicin-insensitive fibers (Fig.3).

Interpretation of results

In the first protocol, IMF showed an immediate suppressive effect only on C-fiber SAAs but not on A δ -fiber SAAs but it was significant only at the highest dose used. As bladder compliance increased with higher doses of IMF-administration, it is not denied that the effect on C-fiber SAAs resulted from the decreased compliance. Moreover, the immediate effect was not reproduced when evaluated 20-minutes after administration. We wondered if IMF could affect only a subpopulation of C-fibers, but not whole C-fibers, and thus made the third protocol by dividing into two subgroups based on the capsaicin-sensitivity and evaluated the IMF-effect in each group. In fact, IMF significantly decreased the SAAs of Cap-sensitive C-fiber, whereas Cap-insensitive C-fibers were not affected by IMF-administrations. Thus it is conceivable that the inhibitory action of IMF was masked as unaffected when evaluated overall SAAs of C-fibers.

Concluding message

The present study demonstrates that imidafenacin can selectively inhibit the mechanosensitive bladder afferent activity of capsaicin-sensitive C-fibers, but not A δ - and capsaicin-insensitive C-fibers, in the urethane-anesthetized rat.

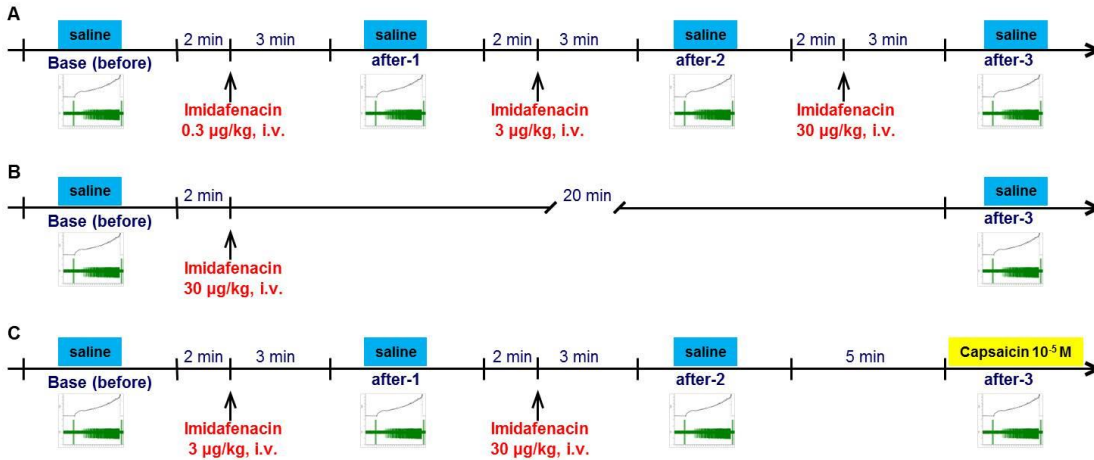


Fig. 1. Experimental set-up and procedures.

A: Experimental protocol of before and after IMF administrations in dose-dependently.

B: Experimental protocol of before and 20-minutes after IMF administration (only one dose).

C: Experimental protocol of before and after IMF administrations and Cap-instillation.

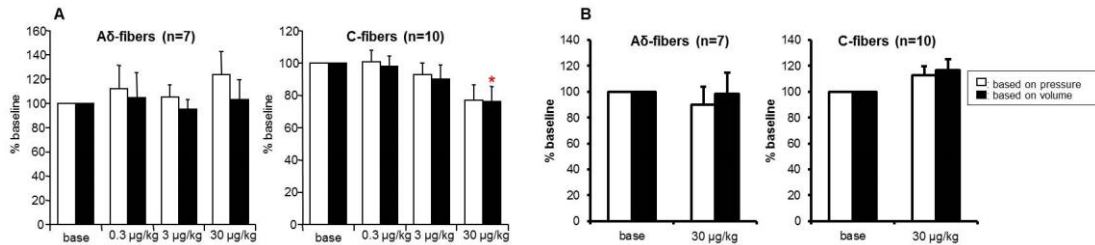


Fig. 2. Responses to intravenous administrations of IMF.

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

A: before and 3-minutes after IMF administrations in dose-dependently (0.3, 3, and 30 μ g/kg).

* $P < 0.05$: significant differences from base (one-way ANOVA followed by Dunnett's test, repeated measure).

B: before and 20-minutes after IMF administration (30 μ g/kg).

No significant differences were found between base and after 30 μ g/kg of IMF-administration (paired Student's t-test).

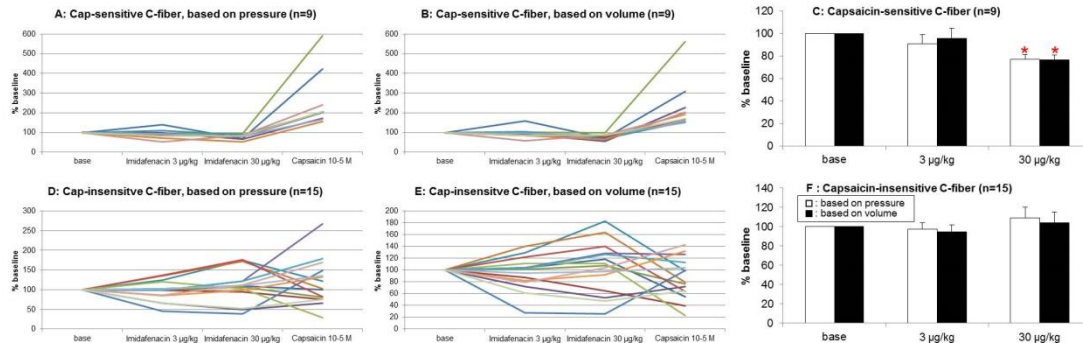


Fig. 3. Influence of IMF-administration (3 and 30 μ g/kg) on pressure- or volume-related individual mechanosensitive afferent nerve activity in C-fibers of Cap-sensitive (A, B) and Cap-insensitive (D, E). Each value represents as percentage of base-line activity.

C and F: Responses to intravenous administrations of IMF in C-fibers of Cap-sensitive and Cap-insensitive. The values are expressed as a percentage of base-line activity (mean \pm S.E.M.).

* $P < 0.05$: significant differences from base (one-way ANOVA followed by Dunnett's test, repeated measure).

References

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Disclosures

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