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DIRECT INFLUENCE OF SYSTEMIC DESENSITIZATION BY RESINIFERATOXIN ON THE ACTIVITIES OF A-DELTA- AND C-FIBERS IN THE RAT PRIMARY MECHANOSENSITIVE AFFERENTS

Hypothesis / aims of study

It has been proposed that resiniferatoxin (RTX), which has a structure similar to that of capsaicin (CAP) and acts as a highly potent CAP analogue, produces long-lasting desensitization of C-fiber activity in the bladder afferents (1, 2). A recent animal study revealed that bladder mechanosensitive C-fibers could be classified as CAP-sensitive or –insensitive subgroup by using acute intravesical RTX-instillation, and that approximately two thirds of the mechanosensitive C-fibers were CAP-insensitive subgroup (3). In the present study, we examined whether systemic treatment with RTX can desensitize the single-unit afferent activities (SAAs) of Aδ- and C-fibers in the rat primary bladder mechanosensitive afferent nerves.

Study design, materials and methods

Female Sprague-Dawley rats were divided into two groups (RTX-treated: N=8, vehicle-treated: N=9). RTX (0.3 mg/kg) or its vehicle (10% EtOH) injected subcutaneously after the first eye-wipe behaviour test with CAP (20 μl/eye, for 90 seconds). Forty-eight hours after the injection, second eye-wipe behaviour test was performed, then urethane (1.2 g/kg) was injected intraperitoneally. After a laminectomy, bilateral L6 dorsal roots were cut, and fine filaments were dissected from the left L6 dorsal roots and placed across a bipolar electrode for monitoring SAAs. Nerve fibers primarily originating from the bladder were identified by electrical stimulation of the left pelvic nerve and by bladder distension. Nerves of which conduction velocity (CV) is more than 2.5 m/second were determined as Aδ-fibers and those with less than 2.5 m/second as C-fibers. The SAAs measurements with constant bladder filling (saline instillation at 0.1 ml/minute until the intravesical pressure reached 30cmH_2O) were performed. Bladder compliance was calculated between the start and end of this bladder filling.

Results

After RTX-treatment, but not vehicle-treatment, eye-wipe behaviour with CAP was abolished completely (Figure 1A). Bladder compliance tended to increase in the RTX-treated group than in vehicle-treated group, but this was not statistically significant (Figure 1B). Totally 101 single afferent fibers were isolated (Aδ-fibers: n = 39, CV: 7.60 ± 0.89 m/sec, C-fibers: n = 62 CV: 1.58 ± 0.05 m/second). When compared with the vehicle-treated group, the RTX-treated group showed less activities of both Aδ- and C-fibers in response to the bladder filling, and these less activities appeared during the whole filling phase in in Aδ-fibers and during the initial half filling phase in C-fibers (Figure 2).

Interpretation of results

The results of eye-wipe behaviour test indicated that systemic RTX-treatment produced the desensitization of CAP-sensitive responses in the present study. Under this desensitized-condition, both Aδ- and C-fibers innervating the rat bladder were responsive to bladder distension, suggesting the presence of RTX-desensitization-resistant components, which are most probably CAP-insensitive fibres, in both Aδ- and C-fibers of mechanosensitive afferent nerves of the rat bladder. Moreover, these responses of both Aδ- and C-fibers were weaker compared to those in the vehicle-treated rats. As it has been reported that mechanosensitive Aδ-fibers of the rat bladder did not respond to acute intravesical instillation of either CAP or RTX (3), indicating CAP-insensitive, the present result suggests that mechanosensitive Aδ-fibers may be partially denervated non-selectively by systemic RTX-treatment. As similar as Aδ-fibers, the mechanosensitive C-fbers may be non-selectively denervated by the RTX-treatment, or the CAP-insensitive subgroup may be less responsive to bladder distension than that of CAP-sensitive.

Concluding message

The present results indicate the existence of mechanosensitive CAP-insensitive Aδ- and C-fibers in rat primary bladder afferent nerves, and suggest that systemic RTX-treatment may induce non-selectively partial denervation even on mechanosensitive CAP-insensitive Aδ- and C-fibers of the rat bladder.

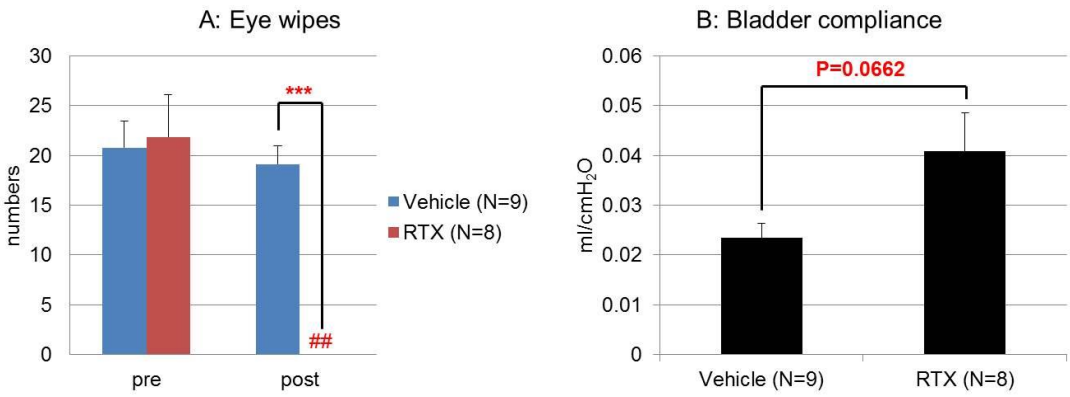

Figure 1. A: Results of eye wipe behaviour test with CAP between pre- (first) and post-treatment (second) of vehicle or RTX injection. B: Responses of bladder compliance in vehicle- or RTX-treated group. ***P<0.001: significant difference between vehicle- vs. RTX-treated group (unpaired t-test). $^{\#}P$<0.05, $^{\#\#}P$<0.01: significant differences from pre-treatment (paired t-test).

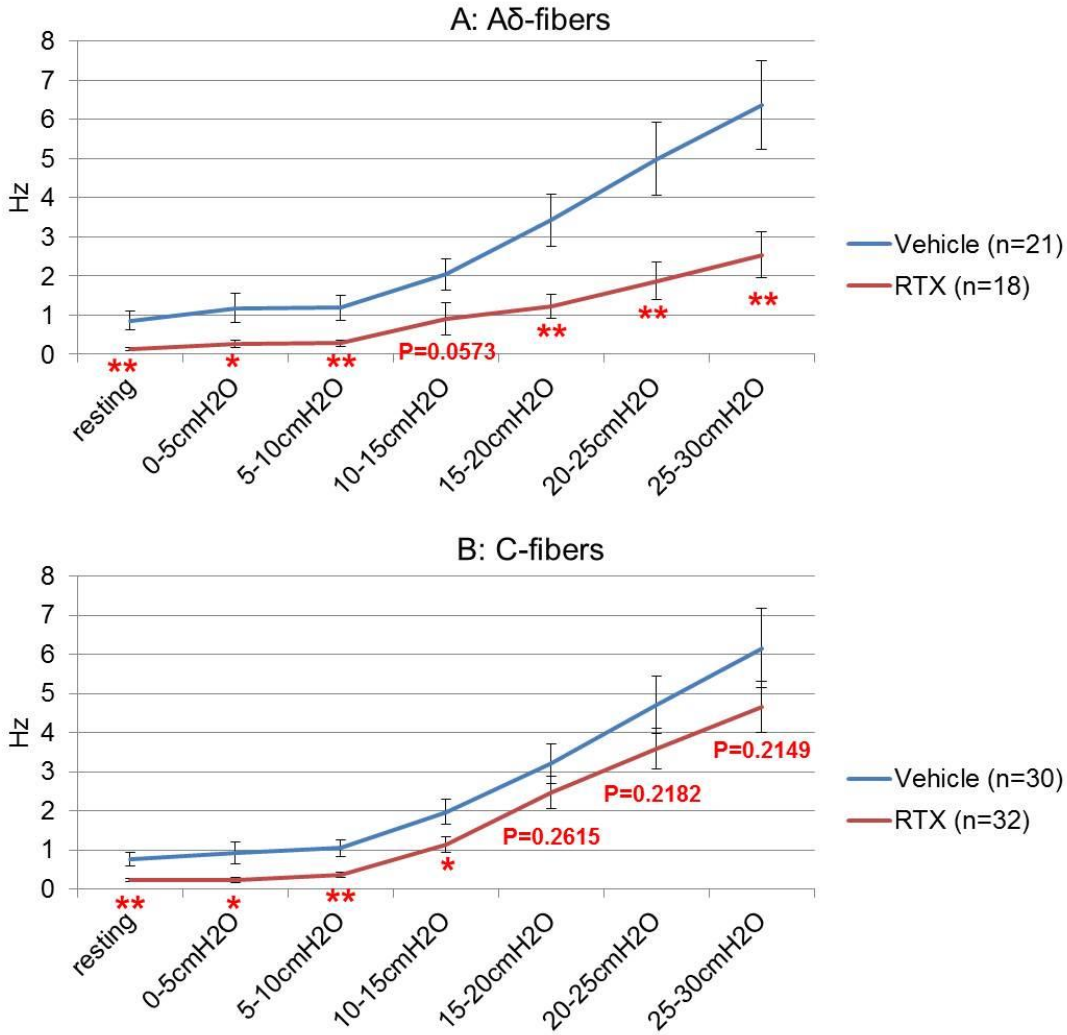

Figure 2. Influence of RTX-desensitization on mechanosensitive SAAs of the Aδ-fibers (A) and C-fibers (B).*P<0.05, **P<0.01: significant differences from vehicle-treated group (unpaired Student's t-test)

References

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Disclosures

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