INHIBITION OF TRPV4 REDUCES THE ACTIVITY OF MECHANO-SENSORY AFFERENT FIBERS OF URINARY BLADDER IN RATS WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS

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INTRODUCTION

The transient receptor potential vanilloid 4 (TRPV4) has been described as a mechanical and osmotic pressure sensor[1]. Expression of TRPV4 has been observed in the bladder urothelium[2] and activation of TRPV4 in normal bladders has been shown to increase the activity of a sub-population of C-fibres[3]. Furthermore, studies using cystometry in mice lacking TRPV4 showed that this receptor is involved in the voiding reflex[3,4]. The goal of the present study was to assess the effects of a TRPV4 antagonist on the action potential discharges of afferent fibres in inflamed bladders.

METHODS

Sprague Dawley rats (175-225 g) were used in this study. Inflammation of the bladder was induced by i.p. injection of cyclophosphamide (CYP) 150 mg/kg 48 h before experiment. Under deep anesthesia, the bladder and associated nerves were removed and placed in an *in vitro* chamber for electrophysiological recordings.

Mechanical stimulation of the bladder was performed by a slow infusion of saline solution (660 µl/min) while multi-unit afferent activity was recorded from the pelvic nerve. After 3 baseline stimulations, the TRPV4 antagonist (HC067047) was applied extra-vesicularly in the bath to reach a final concentration of 0 (vehicle control), 1, 5 and 10 µM in Tyrode solution + 1% DMSO. Results were compared to baseline responses.

Afferent activity was measured by counting the number of spikes per second for various intravesical pressure values (0, 1, 2, 3, 5, 7 ,10, 20, 30 and 40 mmHg) during an ascending pressure ramp. Area under the curve could then be calculated and normalized versus baseline stimulation.

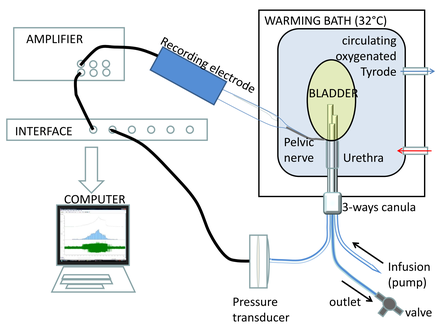


Figure 1: Electrophysiological set-up of the bladder nerve preparation.

RESULTS

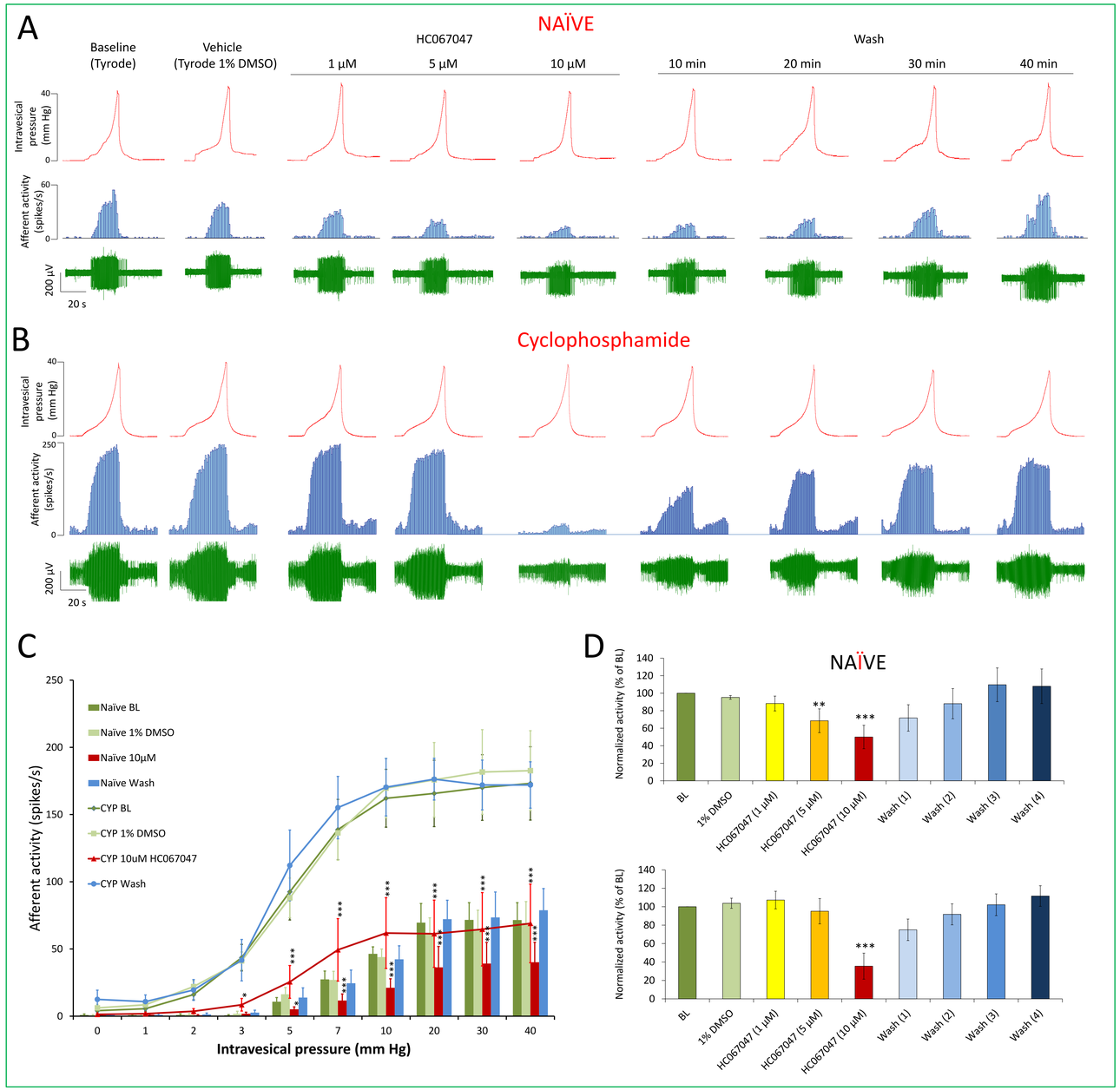


Figure 2: Representative recordings of multi-unit, afferent activity of the bladder during mechanical distension showing the effect of HC067047 for (**A**) naïve and (**B**) inflamed animals.
C: Activity of bladder afferents in response to mechanical distension under various conditions. Bars = Naive, Lines = CYP animals.
D: Activity of bladder afferent normalized to the area under the curve of baseline stimulus for each condition (naïve and CYP)
*P<0.05, ** P<0.01 *** P<0.001 vs BL, (n=6 per group). One-way repeated measures ANOVA with Dunnett's post-hoc analysis for multiple comparison versus one control group.
BL = baseline, HC067047 = TRPV4 antagonist.

CONCLUSIONS

❑ TRPV4 is involved in mechanical sensory system of the urinary bladder under normal and inflamed conditions.

❑ Inhibition of TRPV4 reduced the afferent activity of inflamed bladders to a level similar to naïve animals.

❑ Inhibition of TRPV4 during inflammation might help to treat bladder dysfunction at the level of sensory initiation.

REFERENCES

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