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INHIBITORY EFFECT OF RETIGABINE, A KV7 CHANNEL ACTIVATOR, ON RHYTHMIC BLADDER CONTRACTIONS AND MECHANOSENSITIVE PRIMARY BLADDER AFFERENT ACTIVITIES IN RATS

Hypothesis / aims of study

Voltage-gated K^+ 7 (Kv7) channels are proposed to reduce neural excitability and can inhibit nociceptive stimulation and transmission (1). Retigabine, a Kv7 selective activator, is a new class of antiepileptic drug used clinically and is an effective analgesic in animal models of chronic inflammatory and neuropathic pain (1). Kv7 channels are also expressed in the rat urinary bladder (2). Retigabine increases bladder capacity in acetic-acid- and capsaicin-induced cystitis rat models (2), but also reduces both the contractility and the overall tonus of rat bladder tissue (3). These results suggest that Kv7 channels may be a possible target to modulate bladder storage function. We investigated effects of retigabine on rhythmic bladder contractions (RBCs) and single unit afferent nerve fiber activities (SAAs) of the primary bladder mechanosensitive afferent nerves in urethane-anesthetized rats.

Study design, materials and methods

Totally 29 female Sprague-Dawley rats (200-251 g) were used. Under anesthesia with urethane (1.2 g/kg intraperitoneally), through a laparotomy, a catheter was inserted into the bladder through the dome and the bladder neck was ligated to prevent leakage. After the bladder had been emptied, saline was instilled into the bladder at a rate of 0.033 ml/min until RBCs were induced, and then the instillation rate was changed to 0.0033 ml/min to maintain reproducible RBCs. After RBCs were induced reproducibly for a period of 10 minutes, vehicle (saline) or retigabine was administrated at doses of 0.1-3 mg/kg intravenously (i.v.) cumulatively, and the amplitude and frequency of RBCs were analysed for 15 minutes before and after the drug-administration. In separate animals, SAAs were measured. SAAs were recorded at the left L6 dorsal roots and identified by electrical stimulation of the left pelvic nerve and by bladder distension. Nerves were classified as an Aδ- or C-fiber by conduction velocity (2.5 m/second). The SAA measurements with constant bladder filling (at 0.08 ml/min until the intravesical pressure reached 30 cmH_2O) were repeated three times and the third measurement served as the base-line. Then, vehicle or retigabine was administrated intravenously at three doses, 0.01-1 mg/kg cumulatively, and the SAAs measurements during cystometry were repeated after each-administration.

Results

After retigabine-administrations, both frequency and amplitude of RBCs were decreased in a dose-dependent manner, but the effect was more potent at decreasing the frequency rather than the amplitude. The decrease in the frequency with retigabine-administration at the doses of 0.3 and 3 mg/kg, and that in the amplitude at 3 mg/kg were significantly greater than those with vehicle-administration (Figure 1). In the afferent measurements, thirty-two single afferent fibers (Aδ-fibers: n=16, C-fibers: n=16) were isolated from 17 rats. The SAAs of both Aδ- and C-fibers significantly decreased with retigabine-administrations in a dose-dependent manner, and these decreases were significantly greater than those with vehicle-administration (Figures 2 and 3).

Interpretation of results

The results of the RBCs study suggest that retigabine can act on the afferent pathways rather than efferent pathways. In addition, the direct measurements of SAAs revealed that retigabine can inhibit both Aδ- and C-fibers of mechanosensitive afferents of the rat bladder. The possible sites of the retigabine's inhibitory action may be peripheral including the dorsal root ganglion as no reflex arc through the L6 dorsal roots was preserved in the present set-up.

Concluding message

The present results demonstrate that the selective Kv7 channel activator, retigabine, can inhibit the frequency of RBCs and mechanosensitive primary bladder afferent activities of both Aδ- and C-fibers in the rat. The activation of Kv7 channel may a promising tool for modulating bladder hypersensitive disorders, such as overactive bladder and bladder pain syndrome.

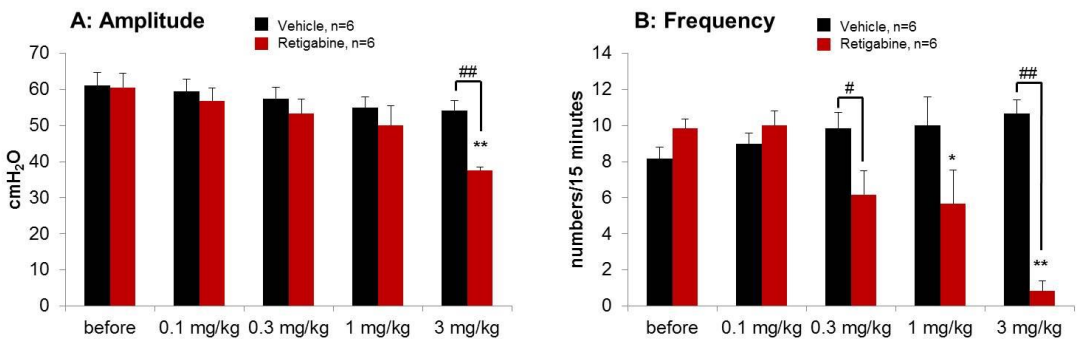

Figure 1. The amplitude (A) and frequency (B) of RBCs before and after vehicle- and drug-administrations. *P<0.05, **P<0.01: significant differences from before drug-administration (one-way ANOVA followed by Dunnett's test). $^{\#}P$<0.05, $^{\#\#}P$<0.01: significant differences between groups (unpaired Student's t-test).

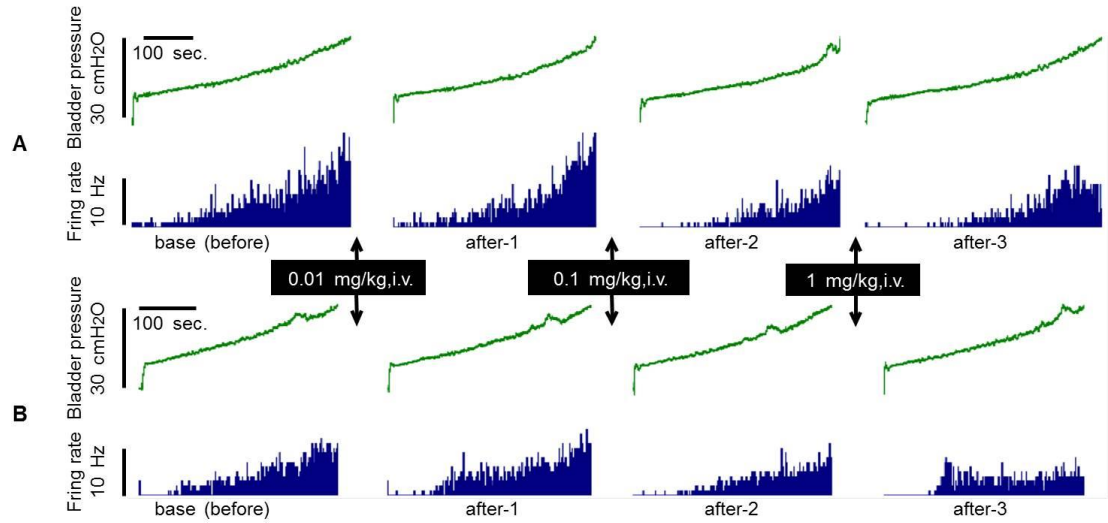

Figure 2. Representative recordings of bladder pressure and firing rate of Aδ-fiber (A) and C-fiber (B) during bladder filling with saline before (Base) and after retigabine-administrations.

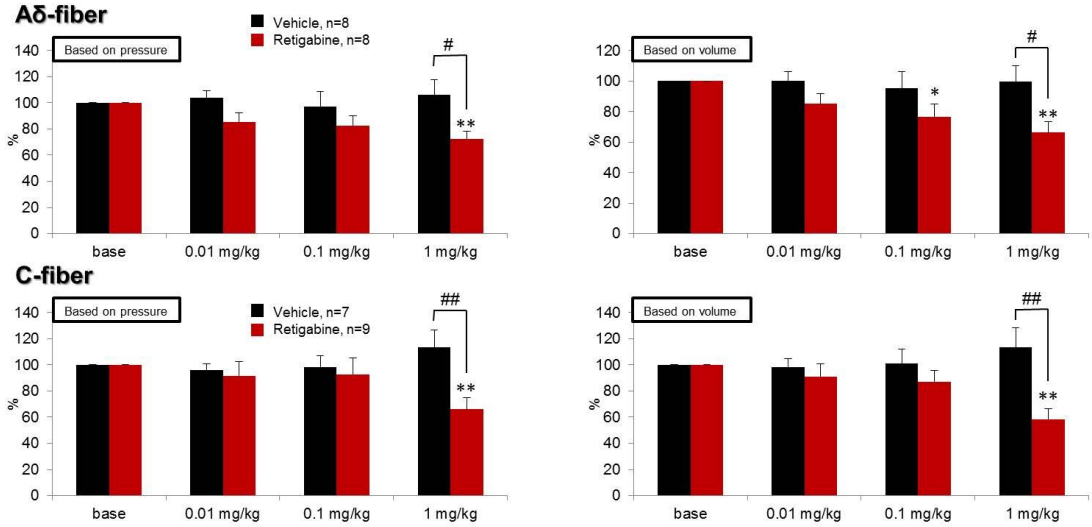

Figure 3. Responses to administrations of vehicle or retigabine of the Aδ-fibers (upper graphs) and C-fibers (lower graphs) integrated during the whole filling phase. The values are expressed as a percentage of base-line activity (mean ± S.E.M.). *P<0.05, **P<0.01: significant differences from base (one-way ANOVA followed by Dunnett's test (repeated measures)). $^{\#}P$<0.05, $^{\#\#}P$<0.01: significant differences between groups (unpaired Student's t-test)

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Disclosures

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