

HYPEREXCITABILITY OF AFFERENT NEURONS INNERVATING THE BLADDER IS ASSOCIATED WITH REDUCTION IN KV1.4 CHANNEL EXPRESSION IN RATS WITH CHRONIC CYSTITIS

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INTRODUCTION AND OBJECTIVE: Hyperexcitability of bladder afferent pathways has been proposed to contribute to urinary frequency and bladder pain in chronic bladder inflammation including interstitial cystitis. However, the detailed mechanisms inducing afferent hyperexcitability after bladder inflammation are not fully understood. Thus, we investigated changes in the properties of bladder afferent neurons (B-AN) in L6-S1 dorsal root ganglia from rats with chronic bladder inflammation

METHODS: Chronic cystitis was induced by intravesical application of 0.4 N HCl. Eight days after the treatment, cystometry and recordings of afferent nerve activity in the pelvic nerve were performed under urethane anesthesia. Whole-cell patch-clamp recordings and immunohistochemical staining were also performed in dissociated B-AN identified by retrograde transport of Fast blue injected into the bladder wall.

RESULTS: Chronic cystitis rats exhibited urinary frequency that was inhibited by pretreatment with capsaicin, and increased afferent firings of the pelvic nerve. In whole-cell patch-clamp recordings, the majority of B-AN in sham rats exhibited high-threshold, long-duration action potentials and capsaicin-sensitivity [cap(+)]. These neurons also showed phasic firing during sustained membrane depolarization (1.3 ± 0.2 spikes/800 msec). However, cap(+) B-AN from chronic cystitis rats exhibited lower thresholds for spike activation than those from sham rats. Approximately 70% of cap(+) B-AN from cystitis rats exhibited tonic firing (10.9 ± 1.5 spikes/800 msec). The peak density of A-type K^+ currents during depolarizations to 0 mV from a holding potential of -120 mV in cap(+) B-AN from chronic cystitis rats (42.9 ± 3.5 pA/pF) was significantly smaller compared with sham rats (109.4 ± 4.5 pA/pF), although the plateau current density of sustained K^+ currents elicited in cap(+) B-AN by depolarizations to 0 mV from a holding potential of -40 mV was not different in sham and chronic cystitis rats. Immunohistochemical studies revealed that the expression of Kv1.4, which can form transient A-type K^+ channels, was reduced in B-AN from chronic cystitis rats while the expression of Kv1.2 was unchanged.

CONCLUSIONS: These data suggest that a reduction in Kv1.4 channel expression could contribute to B-AN hyperexcitability induced by chronic bladder inflammation. Similar changes in bladder afferent pathways may contribute to chronic cystitis-induced bladder overactivity and pain conditions.

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