

INVOLVEMENT OF PROSTATE-TO-BLADDER AFFERENT CROSS-SENSITIZATION IN BLADDER OVERACTIVITY IN A RAT MODEL OF PROSTATIC INFLAMMATION

Hypothesis / aims of study

Patients with benign prostatic hyperplasia (BPH) often exhibit lower urinary tract symptoms (LUTS), including overactive bladder (OAB) symptoms such as urinary frequency and urgency. Intra-prostatic inflammation has been proposed to be involved as a mechanism inducing male LUTS, and it is possible that intra-prostatic inflammation leads to neurogenic inflammation in the bladder by means of shared neural pathways connecting two organs. We previously reported that intra-prostatic formalin injection causes tissue inflammation restricted inside the prostate, leading to bladder overactivity (2012 ICS). In this study, we investigated the molecular and functional changes of dorsal root ganglion (DRG) neurons that innervate the prostate and bladder in a rat model of chemically induced prostatitis to elucidate the role of prostatic inflammation in storage LUTS seen in patients with BPH.

Study design, materials and methods

Male SD rats were injected with 100 μ L of 5% formalin into the ventral lobes of the prostate. Toluidine blue staining was performed for the bladder and the number of mast cells was counted in prostate sections. NGF expression in the bladder was evaluated by Western blotting. Organ-specific afferent neurons were labelled by retrograde axonal transport of fluorescent dyes, Fast Blue (FB) or Dil, injected into the bladder wall or the prostate, respectively. Dye-labelled afferent neurons in S1 DRG were dissected using laser-capture microdissection methods, and mRNA levels of TRP and ATP receptors were measured by real-time RT-PCR. Patch-clamp recordings were also performed in capsaicin-sensitive FB- and double-labelled afferent neurons dissociated from L6-S1 DRG.

Results

Compared to vehicle-treated rats, the number of activated mast cells was significantly increased in the bladder of formalin-injected rats (6.4 ± 1.7 vs. 16.9 ± 3.0 , $p < 0.05$). NGF expression in the bladder was increased by 2.2-fold in formalin-injected rats compared to vehicle-treated control rats ($p < 0.05$) (Fig. 1). TRPV1, TRPA1 and P2X2 mRNA were increased in Dil, FB and double-labelled neurons compared to non-labelled neurons from formalin-injected rats compared to vehicle-treated control rats (Fig. 2). In patch-clamp recordings, membrane potential thresholds for action potential activation were decreased significantly in FB-labelled bladder afferent neurons (-28.7 ± 1.4 mV vs. -21.3 ± 2.2 mV) as well as double-labelled, prostate/bladder-innervating neurons (-28.3 ± 1.4 mV vs. -19.5 ± 1.1 mV) from formalin-treated rats, compared to control rats.

Interpretation of results

Based on the results of this study, we hypothesize the mechanisms inducing bladder afferent sensitization after prostatic inflammation as follows. When prostate/bladder-innervating dichotomized afferents are irritated by intra-prostatic inflammation, neurotransmitters such as substance P, calcitonin gene-related peptide, or neurokinin A are released from afferent terminals not only in the prostate but also in the bladder through activation of dichotomized afferents. Then, mast cells are activated in the bladder wall and they release chemical mediators such as histamine, leucotrien, or tryptase, which lead to neurogenic inflammation of the bladder. Additionally, neurotransmitters released from nerve terminals distributed in the urothelium could also induce NGF expression, which then stimulates and sensitizes bladder afferent pathways. These sequential events may be involved in the mechanism by which prostatic inflammation contributes to storage LUTS in men with symptomatic BPH regardless of the size of prostate enlargement.

Concluding message

Formalin-induced inflammation localized in the prostate activated mast cells and enhanced NGF expression in the bladder, and increased excitability and expression of TRP and P2X2 ATP receptors in not only dichotomized afferents, but also bladder afferent neurons. Cross-sensitization through prostate-to-bladder dichotomized afferents after intra-prostatic inflammation is a potential mechanism inducing bladder overactivity in BPH patients.

Fig. 1 Western blotting for NGF in bladder

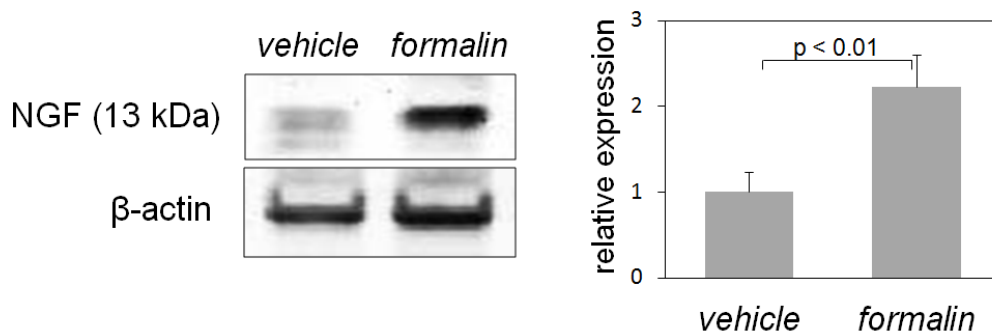
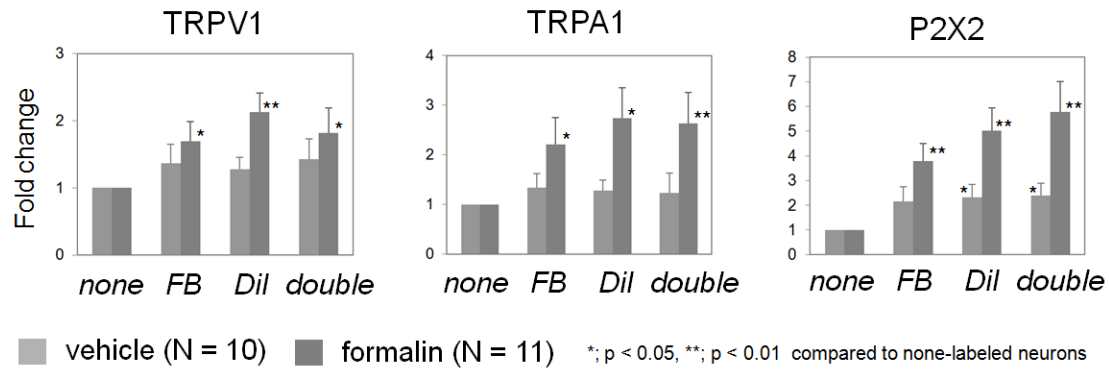


Fig. 2 RT-PCR in LCM-dissected neurons



Disclosures

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