Effects of intravesical instillation of liposome-conjugated antisense oligonucleotide targeting nerve growth factor on bladder hypersensitivity in a rat model of non-bacterial prostatic inflammation

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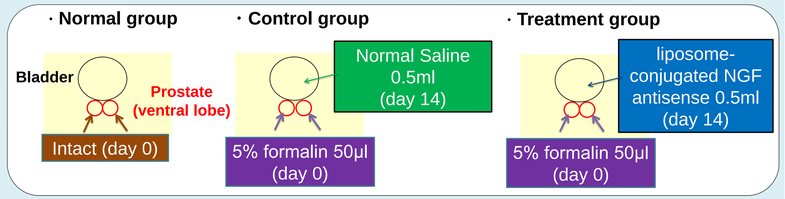
Introduction

- In animal models, prostatic inflammation (PI) reportedly induces bladder overactivity via prostate-to-bladder cross-organ afferent sensitization through activation of the pelvic nerve.
- Local upregulation of nerve growth factor (NGF) in the bladder has been implicated in lower urinary tract dysfunction such as bladder overactivity due to afferent sensitization.
- Previous reports further demonstrated that NGF is an important mediator to induce bladder afferent hyperexcitability, which contributes to lower urinary tract dysfunction (LUTD) and that local suppression of NGF in the bladder improves bladder overactivity in rat models of cystitis or colitis
- The present study aimed to examine the effect of instillation of liposomes-conjugated NGF antisense oligonucleotide (OND) into the bladder on local overexpression of NGF and bladder hypersensitivity in a rat model of PI.

Methods

- Male SD rats at 8 weeks old were used
- Grouping n=6 per group

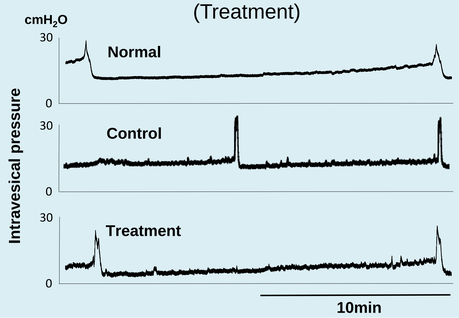


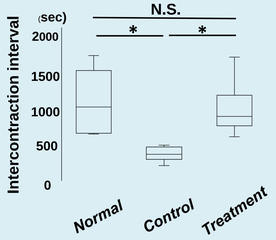
- On day 0, PI was induced by intraprostatic 5% formalin injection (50 μl per each ventral lobe).
- On day 14, phosphorothioated NGF antisense OND (0.5ml, 12μM) complexed with liposomesbladder with a 30G needle after draining urine under anaesthetized with isoflurane, and then kept for 60 minutes.
- On day 28, we evaluated awake cystometry (CMG) and harvested tissues to analyze protein and mRNA levels of NGF in the bladder mucosa, and mRNA levels of C-fiber afferent markers and a potassium channel subunit in L6-S1 dorsal root ganglia (DRG).

Result

Cystometry

Bladder overactivity (=frequent urination) induced by prostatic inflammation (Control) was reduced by NGF-OND treatment (Treatment)



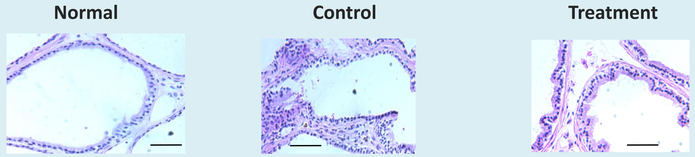


* : p < 0.05, Dunn's multiple comparisons test

Histological Evaluation

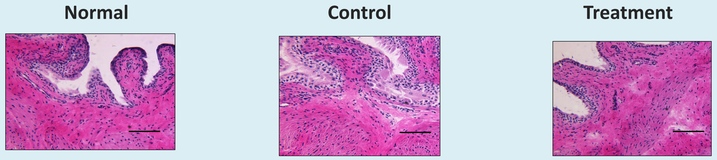
Hematoxylin-eosin staining

- **Prostate**



Epithelial atrophic changes and inflammatory cell infiltration in stroma were observed in the prostatic tissue from Control group compared to Normal group. These changes were lesser in Treatment group compared to Control. Scale bars : 100μm

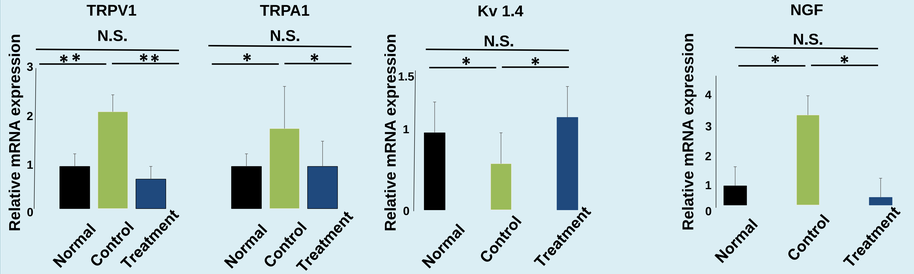
- **Bladder**



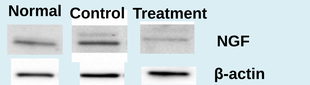
There were no inflammatory findings in the bladder of any groups. Scale bars : 100μm

Relative mRNA and protein expression levels in the bladder mucosa and L6-S1 DRG

- **In L6-S1 DRG**
- **In the bladder mucosa**



- **Western blot (In the bladder mucosa)**



* * : p < 0.01, * : p < 0.05, Dunn's multiple comparisons test

mRNA levels of TRPV1 and TRPA1 in DRG of Treatment group were significantly lower and Kv 1.4 subunit levels were higher than Control group while there were no significant differences between Treatment and Normal groups. Both mRNA and protein levels of NGF in the bladder mucosa in Treatment group were significantly lower compared to Control group while there were no significant differences between Treatment and Normal groups.

Conclusion

- NGF locally expressed in the bladder mucosa is likely to be an important mediator to induce bladder overactivity with upregulation of C-fiber afferent markers and downregulation of an A-type K^+ channel subunit in L6-S1 DRG following prostatic inflammation (PI).
- Liposome-based, local NGF-targeting therapy would be effective for not only bladder overactivity and afferent sensitization, but also PI.
- Local blockade of NGF in the bladder could be a therapeutic modality for male LUTS due to BPH with prostatic inflammation.

Reference

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2. . Kawamorita, N., Yoshikawa, S., Kashyap, M., Tyagi, P., Arai, Y., Chancellor, M.B., Yoshimura, N.: Liposome-based Intravesical therapy targeting nerve growth factor (NGF) ameliorates bladder hypersensitivity in rats with experimental colitis. Journal of Urology, 195: 1920-1926, 2016.

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