Effects of oral administration of a histamine 1-receptor antagonist on bladder hypersensitivity and local mast cell tryptase overexpression in a rat model of prostatic inflammation

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Introduction

- Animal models of prostatic inflammation (PI) reportedly exhibit bladder overactivity via prostate-to-bladder cross-organ afferent sensitization through activation of the pelvic nerve. However, the underlying mechanisms for PI-induced afferent sensitization are not fully elucidated
- Histamine released from mast cells activated by tissue inflammation has been implicated as an important mediator causing pain and itch sensation, and inhibition of histamine H1 receptors is reportedly effective for the treatment of pain and other bladder symptoms in patients with chronic prostatitis/chronic pelvic pain syndrome. In addition, mast cell tryptase (MCT) has been shown to be a sensitive and specific marker for the presence of mast cells in tissues
- The purpose of this study was to examine the effect of oral administration of a histamine 1-receptor (HT1R) antagonist on bladder hypersensitivity and local MCT expression in a rat model of PI

Methods

- Male SD rats were divided into three groups as in Figure 1
- Grouping n=6 per group
- PI was induced by 5% formalin injection into prostate ventral lobes

Figure 1. Methods

Group	Control	Placebo	Treatment
Oral gavage	Desloratadine (HT1R antagonist) 4mg/kg/day	Placebo	Desloratadine
Prostatic injection	intact	5% formalin	5% formalin

Study design

- Oral treatment was performed for 14 days after PI induction
- Awake cystometry (CMG) was performed, and tissues were harvested from non-CMG rats for histological and molecular analyses

Result

Table 1. Measurements of cystometric parameters

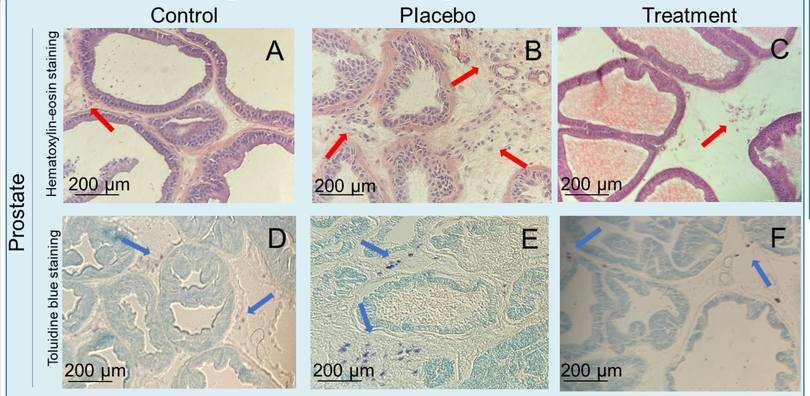
	ICI (s)	BP (cmH$_2$O)	TP (cmH$_2$O)	MVP (cmH$_2$O)	NVC	VV (ml)	PVR (ml)	BVE (%)
Control	907 ± 81*	6.3 ± 1.1	14.2 ± 1.3	35.7 ± 2.5	0.3 ± 0.2	0.59 ± 0.05*	0.05 ± 0.01**	92.5 ± 1.7**
Placebo	720 ± 112	7.8 ± 0.6	13.9 ± 1.5	36.3 ± 3.5	0.6 ± 0.4	0.38 ± 0.03	0.28 ± 0.06	58.9 ± 7.7
Treatment	956 ± 133**	6.5 ± 0.3	11.6 ± 1.1	32.9 ± 2.3	0.1 ± 0.1	0.71 ± 0.15	0.05 ± 0.03**	94.3 ± 2.2**

****; P < 0.0001, ***; P < 0.001, **; P < 0.01, *; P < 0.05, vs Placebo, (n = 6 in each group), Tukey's multiple comparisons test

- ICI: Intercontraction intervals
- BP: Baseline pressure
- TP: Threshold pressure
- MVP: Maximal voiding pressure
- NVC: Non voiding contractions (number/micturition)
- VV: Voided volume
- PVR: Post voided residual volume
- BVE: Bladder voiding efficiency

Improvements of bladder overactivity & voiding dysfunction by HT1R blocker

Figure 2. Histological Evaluation



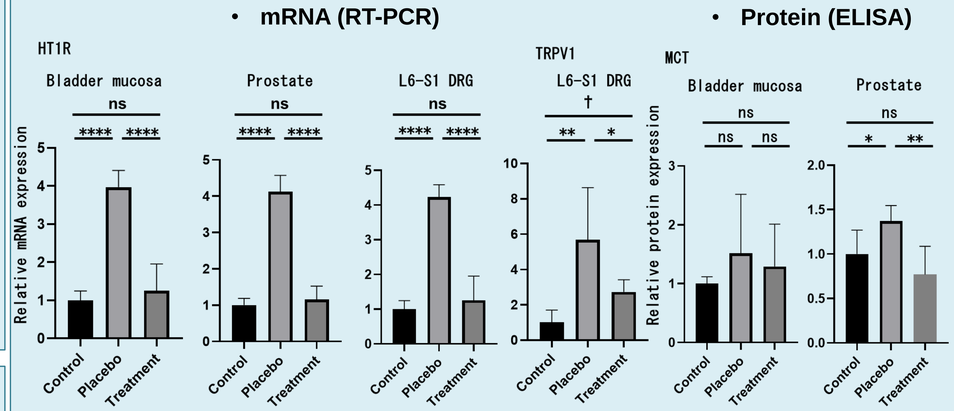
Hematoxylin-eosin staining of transverse sections of prostate ventral lobes (A - C) and toluidine blue staining of them (D - F) from Control, Placebo and Treatment rats on day 28 (n = 6 in each group) without performing CMG

The prostatic ventral lobe of Placebo rat shows a lot of inflammatory cells infiltration in the stroma (B, red arrow) including mast cells (E, blue arrow) . Scale bars; 200 μm

Improvement of prostatic inflammation by HT1R blocker

There were no inflammatory findings in the bladder of any groups

Figure 3. mRNA and protein expression levels



ns; not significant,
†; P<0.01,Control vsTreatment,
; P<0.05, **; P<0.01,*; P<0.0001, vs Placebo**
Tukey's multiple comparisons test

Improvements of HT1R overexpression (bladder/prostate/DRG), TRPV1 overexpression (DRG) and MCT upregulation (prostate) after HT1R blocker treatment

After measuring the amount of MCT in each specimen, the concentration was calculated as the amount divided by the total protein concentration, then normalized to the concentration of Control group respectively.

Conclusion

- The histamine-1 receptor expressed in the bladder, prostate and sensory pathways could be an effective target for the treatment of irritative lower urinary tract dysfunction (LUTD) induced by prostatic inflammation

Reference

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