

SUPPRESSION OF BLADDER OVERACTIVITY BY ESTROGEN RECEPTOR (ACTIVATION IN RATS WITH CHRONIC NON-BACTERIAL PROSTATITIS

Hypothesis / aims of study

Although chronic non-bacterial prostatitis (CNBP) is one of the common urological diseases among men, effective treatments for this disease are still not available. CNBP often causes irritative lower urinary tract symptoms such as frequent urination or urgency. Estrogen receptor β (ER β) has recently been recognized as a therapeutic target for inflammatory diseases such as inflammatory bowel disease, or cystitis, because activation of ER β could suppress inflammatory conditions with upregulation of ER β [1]. In addition, upregulation of nerve growth factor (NGF) or gap junctional protein connexin43 (Cx43) in the bladder is considered to be a cause of overactive bladder conditions. Furthermore, NGF is known to induce activation of MAP kinase (MAPK), leading to an increase in Cx43 expression [2]. However, it is not known whether changes in the expression of MAPK, Cx43 and NGF in the bladder are involved in the development of bladder symptoms in CNBP. Therefore, we investigated alternations in the expression of ER β , MAPK, Cx43 and NGF in the bladder mucosa using a rat model of NBP.

Study design, materials and methods

Male Sprague–Dawley rats (8 weeks old) were used. Prostatic inflammation was induced by 5% formalin injection into ventral lobes of the prostate and saline was injected in the control group (CG, n=4). Rats with formalin-induced prostatitis were divided into the ER β agonist treatment group (TG, n=4) and the placebo group (PG, n=4). TG rats was treated with 3 α diol, which is reported to be a selective ligand for ER β , dissolved in olive oil at a dose of 3mg/kg daily from 2 days before induction of prostatitis for 30days whereas PG rats received olive oil only. In each group, continual filling cystometry was performed in a conscious condition on day 28 after induction of prostatitis. Urodynamic parameters including non-voiding contraction (NVC) during the storage phase, voiding interval (VI) and postvoid residual volume (RV) were investigated. After cystometry, the bladder was excised and separated into mucosa and detrusor muscle layers under a microscope. Expression levels of ER β , MAPK, Cx43, and NGF mRNA in the bladder mucosa were investigated by real-time PCR in each group. Statistical analysis was performed using Mann-Whitney U test. P values less than 0.05 were considered statistically significant.

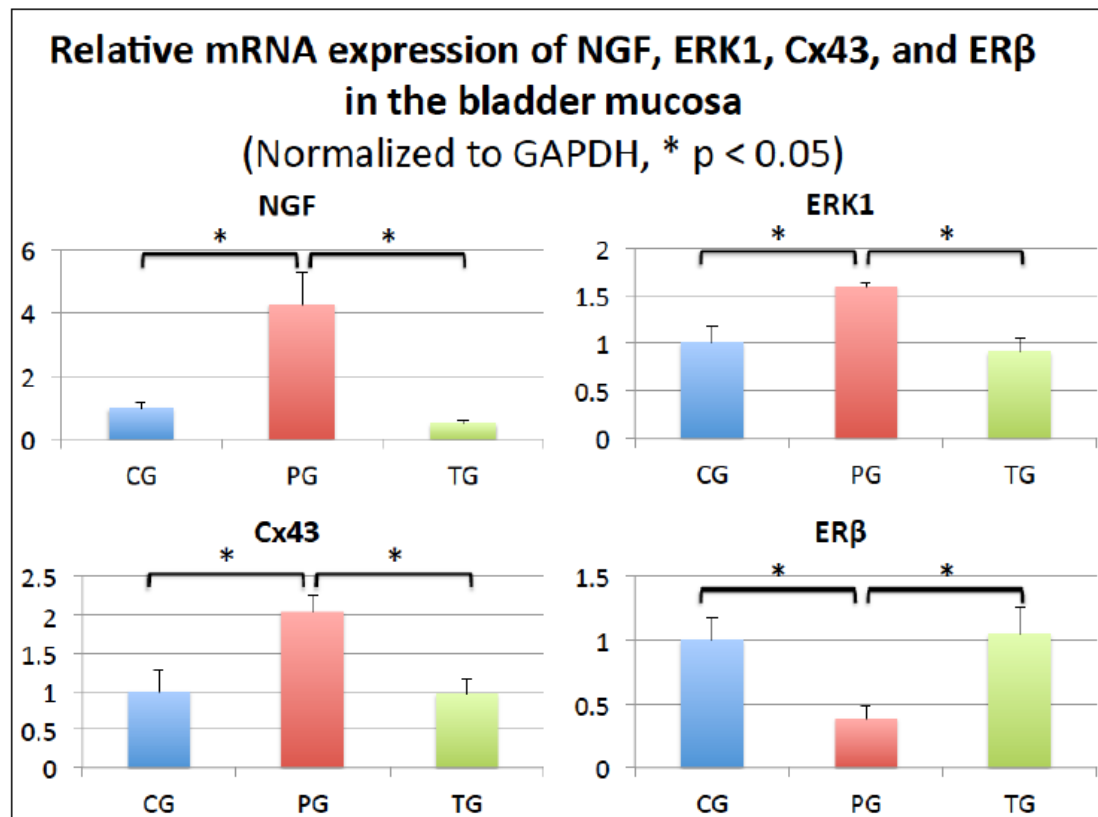


Figure1 Relative mRNA expression of bladder over active condition related genes in the bladder mucosa

Results

In cystometric evaluation, the mean number of NVCs was significantly greater in PG rats than that in CG rats ($P < 0.05$), and VI were significantly decreased in PG rats compared to CG rats ($P < 0.05$) but not in TG rats. There was no significant difference in RV between each group. In RT-qPCR analyses, mRNA expression of NGF, MAPK, and CX43 was significantly increased not only in the prostate, but also in the bladder mucosa in PG rats compared to CG rats ($P < 0.05$). On the other hand, ER β expression

was significantly decreased in PG rats compared to CG rats in both prostate and bladder mucosa ($P < 0.05$). In contrast, TG rats showed decreased mRNA expression of NGF, MAPK, and CX43 in the prostate and bladder mucosa compared to PG rats. Furthermore, ER β mRNA expression in the prostate and bladder mucosa was significantly increased in TG rats ($P < 0.05$) compared to PG rats (Figure1).

Interpretation of results

Patients with CNBP often exhibit irritative bladder symptoms such as urinary frequency or urgency. In this study, prostatitis rats showed bladder overactive conditions evidenced by increased NVCs and decreased VI in association with increased expression of NGF, MAPK, and Cx43 in the bladder mucosa after prostatic inflammation, suggesting that upregulation of Cx43 via activation of MAPK by NGF might be involved in the induction of bladder overactivity possibly due to prostate-to-bladder cross-organ sensitization.

This study also showed that ER β expression in the prostate and the bladder was reduced after prostatitis and that ER β stimulation by 3 α diol in prostatitis rats (TG) improved bladder overactivity as shown by decreased NVCs and increased VI in association with normalization of ER β , NGF, MAPK, and CX43 mRNA expression in the prostate and bladder mucosa when compared to placebo-treated prostatitis group (PG). These results indicate that ER β activation has anti-inflammatory effects to reduce bladder overactivity as well as expression of NGF and its downstream molecules in the bladder mucosa.

Concluding message

We demonstrated that NBP in rats induces bladder overactivity in association with molecular changes in the bladder mucosa, possibly attributed to prostate-to-bladder cross-organ sensitization, and that ER β activation is effective to reduce prostatic inflammation and bladder overactive conditions in rats with NBP. Therefore, ER β could be a therapeutic target for the treatment of irritative bladder symptoms in patients with CNBP.

References

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2. Mori K, Noguchi M, Tobu S, Sato F, Mimata H, Tyagi P, et al. Age-related changes in bladder function with altered angiotensin II receptor mechanisms in rats. *Neurourology and Urodynamics*. 2015.

Disclosures

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