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INVOLVEMENT OF INCREASED EXPRESSION OF ESTROGEN RECEPTOR B IN THE ANTI-INFLAMMATORY EFFECTS OF DUTASTERIDE IN A RAT MODEL OF NON-BACTERIAL PROSTATIC INFLAMMATION

Hypothesis / aims of study
There is increasing evidence showing that prostatic inflammation is associated with the development of histological benign prostatic hyperplasia (BPH) and male lower urinary tract symptoms (LUTS) [1]. It has also been reported that dutasteride, which inhibits 5α-reductase, might have anti-inflammatory effects in the prostate of patients with lower urinary tract symptoms. In addition, it is shown that estrogen receptor β (ERβ) can be upregulated in prostatic tissues from patients treated with dutasteride [2]. Furthermore, ERβ agonists reportedly upregulate the expression of ERβ with anti-inflammatory effects. Therefore, there might be a possibility that the anti-inflammatory effect of dutasteride is associated with modulation of ERβ pathways during the treatment of BPH/LUTS. Therefore, in order to clarify mechanisms underlying the anti-inflammatory effect of dutasteride, we evaluated the expression of proinflammatory cytokines such as IL18 and IL1β, and ERs such as ERα and ERβ in the prostate using a rat model with formalin-induced prostatic inflammation.

Study design, materials and methods
Male SD rats of 10 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=5). Rats with prostatic inflammation were divided into dutasteride treatment (TG, n=5) and placebo groups (PG, n=5). TG rats were treated with dutasteride at a dose of 0.5mg/kg daily from 2 days before induction of prostatic inflammation whereas PG rats received vehicle only. Twenty-eight days later, conscious cystometry was performed to measure non-voiding contractions (NVCs), voiding interval (VI) and postvoid residual volume (RV). After cystometry, the prostate was excised for analyses of mRNA expression levels of ERα, ERβ, IL1β and IL18 by real-time PCR.

Results
The mean number of NVCs was significantly greater in PG rats than that of CG rats ($P<0.05$), and VI were significantly decreased in PG rats compared to CG rats ($P<0.05$); however, it was not significantly different between CG and TG rats. There was no significant difference in RV among three groups. mRNA expression of ERα, IL1B and IL18 were significantly increased in PG rats compared to CG rats ($P<0.05$), but not significantly different between CG and TG rats. On the other hand, the mRNA expression level of ERβ was significantly decreased in PG rats compared to CG rats ($P<0.05$), but not different compared to TG rats (Figure1). The relative mRNA expression ratio of ERβ against ERα (ERβ/ERα) in PG rats was significantly decreased compared to CG rats ($P<0.05$), whereas ERβ/ERα ratio in TG rats was significantly increased compared to PG rats ($P<0.05$).

Interpretation of results
LUTS such as urinary frequency or urgency are often seen in BPH patients. In the present study, rats with prostatic inflammation showed bladder overactive conditions evidenced by increased NVCs and decreased VI. We speculated that the prostate-to-bladder sensitization might be involved in the induction of bladder overactivity following prostatic inflammation in this model. We also showed that ERβ expression in the prostate was reduced after prostatic inflammation and that dutasteride administration improved prostatic inflammation in formali-injected rats treated with dutasteride (TG), as evidenced by decreased expressions of IL18 and IL1B, which are associated with increased ERβ/ERα ratio in the prostate and improved bladder overactivity as shown by decreased NVCs and increased VI compared with the placebo-treated prostatic inflammation group (PG). These results indicate that the treatment with dutasteride could upregulate the expression of ERβ, which lead to proper balance between ER expressions in the prostate. This normalization of ER expression in the prostate might be implicated for the anti-inflammatory effects of dutasteride to improve bladder overactivity, prostatic inflammation and expression of the related molecules in the prostate.

Concluding message
Dutasteride improved not only prostatic inflammation evidenced by the decrease of IL1β and IL18 mRNA levels, which are reported as possible mediators of prostatic inflammation and hyperplasia [3], but also the bladder overactive condition. Furthermore, anti-inflammatory effects of dutasteride were associated with normalization of the ERβ/ERα ratio, which was decreased after prostatic inflammation. Therefore, upregulation of ERβ might be an important process for inducing anti-inflammatory effects to help improve symptoms following the dutasteride treatment of BPH/LUTS.

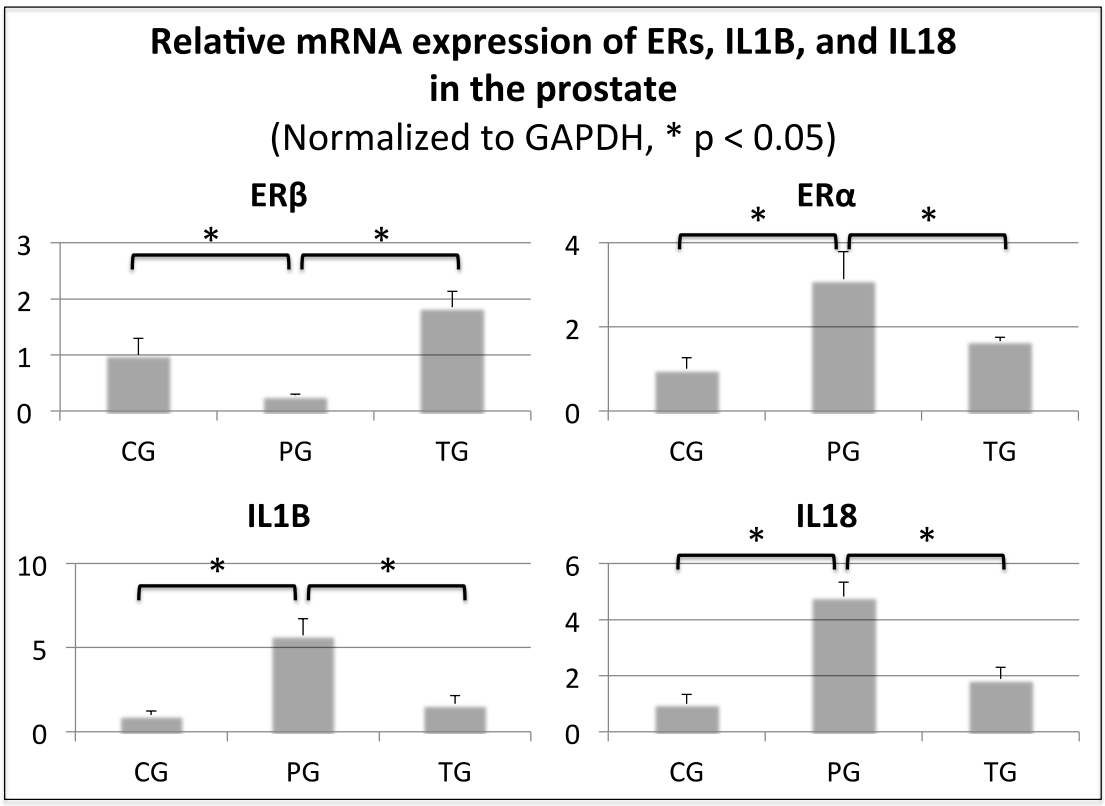

Figure1 Relative mRNA expression of inflammatory cytokines and ERs in the prostate

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Disclosures

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