Introduction and Objective
Bladder inflammation causes various functional changes in the production of inflammatory cytokines and bladder afferent pathways, which might contribute to the hyperexcitability of afferents and subsequently induces frequent urination [1,2]. α1-AR antagonists have been reported to improve the detrusor overactivity in several animal models with urinary dysfunction [2]. However, the effects of α1-AR antagonists on bladder overactivity with inflammation are not well understood. Therefore, we examined the protective effects of an α1-AR antagonist, silodosin, on bladder function in cyclic phosphamide (CYP)-induced cystitis rats with and without desensitization of capsaicin (CAP) sensitive afferent pathway.

Materials and Methods
Male Wistar rats (340-440 g) had been administered silodosin (0, 100 or 300 µg/kg/day) once daily for one week till sacrifice. Two days before sacrifice, a single injection of CYP (150 mg/kg, i.p.) or saline was carried out. Continuous cystometry (saline 12 ml/h) was performed under urethane (1.5 g/kg i.p.) anesthesia. Data without histological scoring were compared among untreated t-test or one-way ANOVA, followed by Fisher’s PLSD test. Histological scoring was analyzed using nonparametric Kruskal-Wallis analysis of variance first. When differences among groups were detected, the group mean values were compared using the Mann-Whitney U test with Bonferroni’s correction for multiple comparison. P values less than 0.05 were considered statistically significant. All values were expressed as mean ± SEM.

Results
Study (1): The animals were divided into four groups (n=6-8 in each group): 1. vehicle treated saline group, 2. vehicle treated CYP group, 3. silodosin (100 µg/kg) treated CYP group, 4. silodosin (300 µg/kg) treated CYP group. After urodynamic experiments, bladders were harvested and tissue levels of inflammatory cytokine (IL-6) and myeloperoxidase (MPO) were measured. The histological evaluation was performed by H&E staining and based on the score of edema area or leukocyte infiltration as described in a previous study [3]. *: Significantly different from the Vehicle + Saline group (P<0.05). #: Significantly different from the Vehicle + CYP group (P<0.05).

Study (2): CAP (125 mg/kg) or vehicle was subcutaneously injected (given in divided doses over 2 consecutive days) 4 days before urodynamic experiments. An eye wipe test (100 µg/mL CAP solution) was performed on each rat just before the anaesthesia to evaluate the efficacy of desensitization. §: Significantly different from CAP (-) treated Vehicle + CYP group (P<0.05). ⊠: Significantly different from CAP (-) treated Silod300 + CYP group (P<0.05).

Interpretation of results
CYP has been reported to cause urinary bladder overactivity characterized by increased frequent urination, bladder inflammation and activation of nociceptive sensory neurons [4]. The present data show that pretreatment with silodosin partially inhibits the frequent urination in the CYP-induced cystitis model, but silodosin has no effect on the CYP-induced shortening of ICI in the model treated with CAP. Furthermore, we demonstrated that silodosin had no anti-inflammatory effect in the bladder of rats treated with CYP. Some α2-ARs are known to be expressed and function on nociceptive sensory neurons in the urinary tract of the rat [4]. Moreover, in a previous study, silodosin inhibited the intravesical prostaglandin-induced detrusor overactivity via suppressing the afferent activity [1]. These findings suggest that the treatment with silodosin could suppress CYP-induced detrusor overactivity through inhibition of CAP sensitive afferent without any anti-inflammatory effect in the bladder.

Concluding message
Silodosin might have a potential to inhibit the frequent urination through the blockade of α1-ARs on the nociceptive sensory neurons.

Reference

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Conflict of interest
Motoaki Saito reports a grant from the Daichi-Sankyo Pharmaceutical Co. Ltd (Tokyo, Japan).