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EFFECT OF ALPHA1 ADRENOCEPTOR ANTAGONIST SILODOSIN ON CYCLOPHOSPHAMIDE-INDUCED CYSTITIS RATS

Hypothesis / aims of study

Bladder inflammation causes various functional changes in the productions of inflammatory cytokine and bladder afferent pathways, which might contribute to the hyperexcitablity of C-fiber afferents and then induces frequent urination [1]. Some α_1 adrenoceptor antagonists have been reported to improve the detrusor overactivity in several animal models with urinary dysfunction [2]. However, effects of α_1 adrenoceptor antagonists on bladder overactivity with inflammation are not well understood. We examined effects of an α_1 adrenoceptor antagonist, silodosin on urinary bladder function in cyclophosphamide (CYP)-induced interstitial cystitis rats with and without desensitization of capsaicin sensitive C-fiber afferent pathway.

Study design, materials and methods

Male Wistar rats (340-400 g) had been administered silodosin (0, 100 or 300 μg/kg/day, p.o.) once daily for one week till sacrifice. Two days before sacrifice, a single injection of CYP (150 mg/kg, i.p.) or saline was administered. Continuous cystometry (saline 12 mL/h) was performed under urethane (1.0 g/kg i.p.) anaesthesia. A statistical comparison of differences among the groups was performed using analysis of variance and Fisher's multiple comparison tests in general information and urodynamic parameter.

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) were measured. The histological evaluation was performed by H&E staining and based on score of edema area and number of leukocytes.

Study (2): Capsaicin (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 was performed on each rat just before the anaesthesia to evaluate the efficacy of C-fiber desensitization.

Results

Study (1): Intercontraction intervals (ICI) and single voided volume (SVV) in vehicle treated CYP group were significantly lower than those in the vehicle treated saline group. The post void residual urine and maximum voiding pressure in the vehicle treated CYP group were not significantly altered compared to the vehicle treated saline group. Treatment with a high dose of silodosin significantly increased the ICI and SVV in the rat treated with CYP. On the other hand, the treatment with silodosin had no effect on the CYP-induced bladder inflammation responses such as elevations of mean bladder weight, bladder body weight ratio and tissue levels of IL-6, and edema and leukocyte infiltration in histology (Table 1).

Study (2): The capsaicin-induced C-fiber desensitization was confirmed in an eye wipe test (data not shown). Treatment with silodosin had no effect on the ICI and SVV in CYP group treated with capsaicin (Figure 1).

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 [3].

The presented data showed that treatment with silodosin partially inhibited the frequent urination in the CYP-induced interstitial cystitis model, but silodosin had no effect on the CYP-induced shortening of ICI in the model treated with capsaicin. Moreover, silodosin had no anti-inflammatory effect in the bladder of rat with CYP-induced cystitis. Some α_1 adrenoceptors are known to be expressed and function on nociceptive sensory neurons in the urinary tract of the rat [3]. Moreover, in a previous study, silodosin inhibited the intraurethral PGE_2-induced detrusor overactivity through a suppression of C-fiber afferent activity [2]. These findings suggest that the treatment with silodosin could suppress CYP-induced detrusor overactivity through inhibition of capsaicin sensitive afferent C-fiber but not anti-inflammatory effect in the bladder.

Concluding message

Silodosin might have a potential to inhibit the frequent urination through the blockade of α_1 adrenoceptor on the nociceptive sensory neurons.

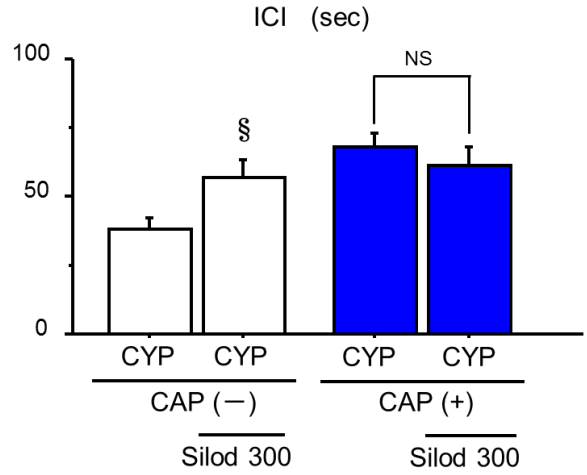
Table 1. Urodynamic and inflammatory parameters in the rat.

Group	Vehicle + Saline	Vehicle + CYP	Silod100 + CYP	Silod300 + CYP
Urodynamic parameter				
ICI (sec)	173.1 ± 11.1	36.2 ± 3.8*	47.4 ± 5.1*	64.5 ± 6.0*#
SVV (mL)	0.59 ± 0.05	0.09 ± 0.01*	0.12 ± 0.02*	0.18 ± 0.02*#
Inflammatory parameter				
IL-6 (pg/mg protein)	50.6 ± 7.1	76.8 ± 5.5*	90.1 ± 11.9*	71.5 ± 4.8*
Edema (score)	9.7 ± 4.0	63.9 ± 3.4*	65.6 ± 5.8*	53.38 ± 4.8*
Leukocyte (score)	20.1 ± 3.6	80.1 ± 4.7*	69.6 ± 3.5*	74.4 ± 4.1*

Data are shown as mean ± SEM. ICI: intercontractile interval; SVV: single voided volume; Vehicle + Saline: Wistar rats treated with vehicle (p.o.) and saline (i.p.); Vehicle + CYP: Wistar rats treated with vehicle (p.o.) and CYP (i.p.); Silod100 + CYP: Wistar rats treated with silodosin (100 μg/kg, p.o.) and CYP (i.p.); Silod300 + CYP: Wistar rats treated with silodosin (300 μg/kg, p.o.) and CYP (i.p.). Histological evaluation was performed to analyse edema area, each tissue slice was divided into four sections and edema area in each section scored as 0-3. The scores for all sections were added, divided by 12 and multiplied by 100. To analyse the number of leukocyte infiltration each tissue slice was divided into eight subsections, and leukocyte infiltration scored in each subsection as 0-3. The scores for all eight sections were added, divided by 24, and multiplied by 100.

*: Significantly different from the Vehicle + Saline group ($P < 0.05$). #: Significantly different from the Vehicle + CYP group ($P < 0.05$).

Figure 1. The effect of silodosin on CYP-induced intercontractile intervals with or without capsaicin in the rat.



Data are shown as mean ± SEM.
CAP: capsaicin; NS: no significance; § : Significantly different from the capsaicin untreated CYP group ($P < 0.05$).

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Disclosures

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