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Journal

Geriatric Nephrology and Urology, 51(1)

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Publication Date

2019

DOI

10.1007/s11255-018-2021-8

Peer reviewed

HHS Public Access

Author manuscript

Int Urol Nephrol. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Int Urol Nephrol. 2019 January ; 51(1): 53–59. doi:10.1007/s11255-018-2021-8.

Investigations of urethral sphincter activity in mice with bladder hyperalgesia before and after drug administration of gabapentin

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Abstract

Purpose: This study investigated the effect of gabapentin on lower urinary tract dysfunction focusing on urethral activities and cystitis-induced visceral hyperalgesia in a mouse model of painful bladder syndrome/ interstitial cystitis (PBS/IC). The electromyography of urethral sphincter was difficult to obtain, but contained useful information to examine the drug effect in mice.

Methods: Female C57BL/6J mice were intraperitoneally (ip) dosed with either saline or 200 mg/kg of cyclophosphamide (CYP) 48 hours before experimental evaluation. Cystitis mice were treated with administration of Gabapentin (25 or 50 mg/kg, ip). Bladder and external urethral sphincter (EUS) functions were obtained and analyzed during continuous bladder infusion. The visceral pain-related visceromotor reflex (VMR) was recorded in response to isotonic bladder distension.

Results: Cystitis mice showed shorter inter-contraction intervals and increased occurrence of non-voiding contractions during bladder infusion, with increased VMR during IBD, indicating cystitis-induced bladder hyperalgesia. Gabapentin (50 mg/kg) suppressed effects of CYP on cystometry, but not on EUS activity, during bladder infusion. The effect on urodynamic recordings lasted 4 hours. VMR was significantly reduced by gabapentin.

Conclusions: The present study showed that CYP-induced cystitis in mice is a model of visceral hyperalgesia affecting detrusor contractions, not urethral activations. The technique of using EUS electromyography to evaluate the drug effects on urethral activities is novel and useful for future investigations. Gabapentin can be as a potential treatment for detrusor overactivity and PBS/IC.

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Conflict of Interest: All the authors declare that he/she has no conflict of interest.

Ethical approval: The "Principles of laboratory animal care" (NIH publication No. 86-23, revised 1985) were followed. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Keywords

external urethral sphincter; electromyography; cyclophosphamide; visceral pain

INTRODUCTION

Painful bladder syndrome/ interstitial cystitis (PBS/IC) is a prevalent disease affecting over a million people in the United States. The disease is associated with increased urinary frequency, urgency, and pain originating from the urinary bladder [1]. Although medical treatments and procedures, such as bladder instillation, hydrodistension, and oral pharmaceutical drugs are available for PBS/IC, many of these treatments are effective only in a percentage of patients [1,2].

Gabapentin is clinically used to treat PBS/IC. It is an anti-epileptic medication that can bind to the α−2-delta subunit of voltage-dependent calcium channels leading to a reduction of the influx of calcium into neurons throughout central nervous system [3]. As a result, it shows the beneficial effect on chronic pain by inhibiting the C afferent activity [4-7]. A combined treatment in PBS/IC patients for four weeks by giving a low dose of gabapentin (300 mg) with amitriptyline for overactive bladder symptoms significantly reduces urinary urgency, frequency, and bladder pain [8]. More studies indicate that the neurogenic detrusor overactivity can be suppressed by gabapentin in the children with the repair of spinal bifida and refractory overactive bladder [4,6]. However, the drug effect of gabapentin on voiding function, especially the urethral activities, in the type of cystitis-induced bladder hyperalgesia is not thoroughly understood.

Animal studies have been suggested that cyclophosphamide (CYP) induce the detrusor overactivity and bladder hyperalgesia, similar to the PBS/IC [9-12], There is no evidence showing the urethral function associated with the detrusor contractions in the mouse model of CYP-induced cystitis. The electromyography of urethral sphincter was difficult to obtain, but contained useful information to examine the drug effect in mice. This study is the first few of studies to investigate the drug effect of gabapentin on the urethral activations during voiding. Besides, the visceromotor reflex (VMR) is used as an indicator of the level of visceral pain triggered by bladder distension because it is known for quantifying the level of nociception in CYP-induced cystitis rodent models [9,13,14]. Therefore, we investigated the effects of gabapentin on cystometry, urethral activation and visceral-pain related VMR in a mouse model of cystitis-induced hyperalgesia.

MATERIALS AND METHODS

Animal model

All experiments were approved and carried out in accordance with National Institutes of Health guidelines, and approved by the Institutional Animal Care and Use Committees at University of Southern California and University of California Irvine, CA, USA. Twenty female C57BL/6J mice (aged 4-6 weeks, 20-25g) were used in the study. The mice received

either intraperitoneally (ip) administered 0.2 mL saline (controls, n=10) or CYP (200 mg/kg, n=10), 48 hours prior to urodynamic recordings.

Surgical preparations for urodynamic recordings and VMR

Urethane (1.5 g/kg) were subcutaneously given to the animals 1 hour before surgical preparation. The pubic symphysis was removed to expose the urethra and external urethral sphincter (EUS). Two fine, insulated silver wire electrodes (0.05 mm in diameter, A-M system, WA) with 2-mm exposed tip were bilaterally inserted into the EUS, approximately 2-3 mm from the bladder neck, to record the electromyographic (EMG) activity of EUS [15-17]. Additional two wire electrodes with 2-mm exposed tips were embedded into the external oblique muscle to obtain VMR. Finally, a polyethylene-50 catheter (Instech Laboratories, MA) was inserted into the bladder dome and secured with a cotton thread. This catheter was then connected to an infusion pump (Kent Scientific, CT) and a pressure sensor (Biopac Systems Inc., CA) via a 3-way connector to infuse the bladder and to obtain cystometry. The bladder was infused with 0.9% normal saline (0.03 mL/min). The cystometry, EUS EMG activity, and VMR were recorded and analyzed by using a data acquisition system (MP150, Biopac Systems Inc., CA) [17].

VMR during isotonic bladder distension (IBD)

After obtaining baseline of urodynamic recordings, the urethra outlet was occluded by the 5-0 silk suture. VMR was then measured during IBD (10 to 50 cmH_2O) by distending the bladder to a constant pressure through rapidly changing the height of a saline-filled reservoir. The bladder achieved to each constant pressure within 1 sec and sustained for 120 seconds. Following each level of the desired intravesical pressure (IVP), the bladder was emptied and allowed to rest for 120 seconds.

Gabapentin administration

Gabapentin (Sigma-Aldrich, MO) was dissolved in 0.9% normal saline, and intraperitoneally administered to the control and cystitis mice. After the acquisition of baseline urodynamic recordings and VMR during IBD, control and cystitis mice were randomly assigned into following groups: control mice with (1) 25 mg/kg (n=5) and (2) 50 mg/kg (n=5), cystitis mice with (3) 25 mg/kg (n=5) and (4) 50 mg/kg (n=5). After drug administrations, both urodynamic evaluation and VMR during IBD were obtained again within 30 minutes. Further drug effects on urodynamic recordings were also examined at 1 and 4 hours after the initial administration at each dose.

Statistical Analysis

Three consecutive voiding cycles were measured at the second hour after the beginning of the urodynamic recordings. The outcome measurements were analyzed including the actual maximum IVP, resting pressure after voiding (RP), inter-contraction intervals (ICI), bladder capacity, and non-voiding contractions (NVCs). The bladder capacity was calculated by the latency of the first void (minute) × infusion rate (ml/min). The EUS EMG activity was also analyzed including the maximum amplitude, duration, and area under the curve (AUC) [17]. VMR AUC measured at the 120-seconds period during IBD.

The non-parametric Mann-Whitney test were applied to determine differences in the measurements of urodynamic recordings between the control and cystitis groups without the drug. The non-parametric Wilcoxon matched-paired test were used among the control and cystitis groups before and after drug administration. Data was presented as both mean and standard error (mean ± SE). A value of $p<0.05$ indicates significant differences. GraphPad Prism 6 (GraphPad Software, CA) was applied for statistical analysis and graph demonstrations.

RESULTS

Urodynamic recordings, including cystometry and EUS EMG activity, and VMR during IBD, were investigated in control (n=10) and CYP-induced cystitis (n=10) mice, as well as following administration of gabapentin at either 25 or 50 mg/kg in these two groups.

Urodynamic recordings before and after drug administration in control mice

The control mice (n=10) underwent the urodynamic recordings (Fig. 1A) and VMR during IBD to obtain the baseline before drug administration. Then, the control mice received the administration of gabapentin (25 or 50 mg/kg, n=5 at each dose). The urodynamic recordings were obtained at 1 hour and 4 hours after drug administration (Table 1). The urodynamic recordings from the control mice were not significantly affected by gabapentin (Table 1).

Urodynamic recordings without drug in cystitis mice

The cystitis mice (n=10) significantly showed increased maximum IVP and shorter ICI when compared to the controls (unpaired t-test, n=10, p=0.04 and 0.02, respectively, Table 1). The cystitis mice also showed the smaller bladder capacity compared to controls (p=0.03, Table 1). RP was not significantly increased when compared to controls (p=0.21, Table 1). The numbers of NVCs were also significantly increased in the cystitis mice (p=0.001, Table 1; Fig. 1B). The maximum amplitude, AUC, and duration of EUS-EMG activity did not show any significant differences in the cystitis mice (p=0.87, 0.25, and 0.96, respectively, Table 1).

Urodynamic recordings after administration of gabapentin in cystitis mice

Gabapentin was given to the cystitis mice (n=10) after baseline urodynamic recordings were recorded. One hour after administration of gabapentin (25 and 50 mg/kg, n=5 at each dose), the maximum IVP was significantly decreased (Table 1). NVCs were significantly suppressed by gabapentin (Table 1, Fig. 1). At 4 hours following administration of gabapentin (25 and 50 mg/kg, Figs. 1C-D), the ICI was significantly prolonged as well as the NVCs was significantly reduced (Table 1) in the cystitis mice. However, the EUS EMG did not significantly change after administration of gabapentin in both doses (Table 1).

VMR during IBD

The control mice (n=10) showed the mild responses of VMR induced by the bladder distension at each IVP level. Administration of gabapentin (25 or 50 mg/kg, n=5 in each

dose) did not change the VMR at 10, 20, and 30 cmH2O in these control mice (Figure 4). The higher dose (50 mg/kg) significantly reduced VMR AUC at 40 and 50 cmH_2O.

CYP-induced cystitis resulted in visceral nociception as evidenced by a significant increase of VMR AUC during IBD when the bladder pressure was increased from 10 to 50 cmH_2O (Fig. 2). The effects of gabapentin (25 or 50 mg/kg, n=5 in each dose) on VMR were evaluated one hour following drug administration. The lower dose (25 mg/kg) did not change VMR AUC. However, the higher dose (50 mg/kg) significantly reduced VMR AUC at 20 cmH_2O and higher IVP levels during IBD.

DISCUSSION

This study investigated the voiding function and visceral-nociception in the mouse model of acute CYP-induced cystitis. The present study demonstrated that cystitis resulted in detrusor overactivity as evidenced by increased voiding frequency and non-voiding contractions. The EUS EMG activity associated with voiding contractions in mice was also reported. Gabapentin (50 mg/kg, ip) significantly reduces detrusor overactivity and ameliorates the visceral nociception in the cystitis mice.

Effects of gabapentin on urodynamic and VMR in control mice

We first evaluated the effect of gabapentin on the urodynamic recordings and VMR during IBD in control mice. Surprisingly, gabapentin did not significantly change the urodynamic outcomes compared to the baseline before treatment. It is also believed that gabapentin reduces the pain sensation and bladder hyperalgesia by suppressing the C fibers hypersensitivity [4,5]. After nerve lesions or repeated stimulation, C fibers become abnormally sensitive and cause pathological neuronal responses to a noxious stimulus. Since the control mice were neurologically intact, the C fibers remain the normal function and sensitivity. Therefore, gabapentin did not affect the functional assessments. However, when the bladder was distended over the maximum IVP (28 cmH2O, Table 1) in control mice at 40 and 50 cmH2O, the higher dose of gabapentin (50 mg/kg) significantly reduced VMR AUC. It may be resulted from the C-fiber hyper-sensitivity due to the over-distension of the bladder. Thus, gabapentin showed the suppression on VMR at higher IVP levels in control mice.

Effects of CYP on cystometry and urethral activities

In the present study, the cystitis mice showed significantly decreased ICI as well as increased NVCs that indicating detrusor overactivity. These results point to C-fibers being activated and sensitized by CYP-induced inflammation [13]. Maximum IVP significantly increased in cystitis mice compared to controls while the RP remained the same. The increase of IVP indicated that the voiding-associated abdominal wall contraction produced an increment of intra-abdominal pressure which promoted the total bladder pressure against resistance to drive urine flow [18]. Thus, the increase of abdominal wall contractions resulted in the increment of the abdominal wall EMG activity, and led to the increase of VMR.

The EUS EMG activity associated with bladder contraction was first examined in the mice with CYP-induced cystitis. Surprisingly, the EUS EMG activity during the expulsed duration was not altered by cystitis. Although the epithelium of the bladder and urethra may be damaged as reported [14], the somatic efferent pathway may not be directly affected by CYP-induced inflammation. A study demonstrated that chronic low-dose administration of CYP in male mice caused detrusor overactivity, increased urinary frequency, and referred bladder hyperalgesia without impairment of physiological state and overt damage of bladder tissue [13]. This may explain why the EUS EMG activity remained the same in the cystitis mice. Furthermore, only a minority of the mice exhibit bursting-like EUS activity during voiding [15]. Unlikely, the rats commonly exhibit EUS bursting, which is essential for efficient voiding [19,20], The CYP-induced cystitis rats show stronger active periods but shorter silent periods of EUS bursting indicating the decreased urethral relaxation during voiding. The cystitis mice in the present study may not exhibit EUS bursting, and not able to show the significant changes of EUS activity before and after drug administrations.

Effects of gabapentin on detrusor overactivity and visceral pain-related VMR in cystitis mice

The drug effect of gabapentin on bladder function and CYP-induced bladder hyperalgesia was examined. The dose of 50 mg/kg significantly prolonged the ICI and reduced NVCs during bladder infusion indicating the improvements of urgency and voiding efficiency. The effect was maintained for at least 4 hours. In the present study, VMR during IBD is a well-established method to evaluate the visceral hyperalgesia, and is directly related to the voiding function. 50 mg/kg of gabapentin in cystitis mice, but not in control mice, reduced VMR AUC at the lower IVP levels showing that the cystitis mice had hyper-sensitivity in response to bladder distension below voiding threshold. In our experimental settings, the dose of 50 mg/kg achieved the optimal condition of a significant reduction of detrusor overactivity and amelioration of visceral hyperalgesia.

CONCLUSIONS

Urinary urgency, frequency, discomfort and/or bladder pain are primary symptoms in PBS/IC patients. The present study is limited to the mouse model whereas the effects of gabapentin on neuropathic pain and PBS/IC in the humans are examined [1,2,8]. The strengths of this study using the mouse model of cystitis-induced hyperalgesia provide the important information inclusive of urethral investigation and the effect of gabapentin on treating PBS/IC and detrusor overactivity that are not thoroughly studied in animal models and humans. The techniques of using EUS EMG to examine the urethral activities were overcome to provide the useful information before and after drug administration. The present study has demonstrated that gabapentin (50 mg/kg) ameliorated detrusor overactivity and visceral pain-related VMR, but not urethral activation, caused by cystitis-induced hyperalgesia. The dosages of gabapentin need to be considered extensively in order to maintain the efficient voiding during treatments. Future studies will have to investigate effects of long term treatment with gabapentin on detrusor overactivity and bladder hyperalgesia in the chronic cystitis models. These long-term studies will have beneficial

information, including the improvement of detrusor overactivity and voiding function along with the pain relief, to the study designs of clinical/translational studies in humans.

ACKNOWLEDGEMENTS

The authors thank Jackie Mao for technical assistance at Urology, University of Southern California, CA, USA. We also thank Dr. Mitsuharu Yoshiyama at Urology, University of Yamanashi Graduate School of Medical Sciences, Japan for detailed instructions to obtain EUS EMG in mice.

Compliance with Ethical Standards: The study was supported by IUGA basic science grant to Ghoniem, and by NIH (DK106181) to Chang.

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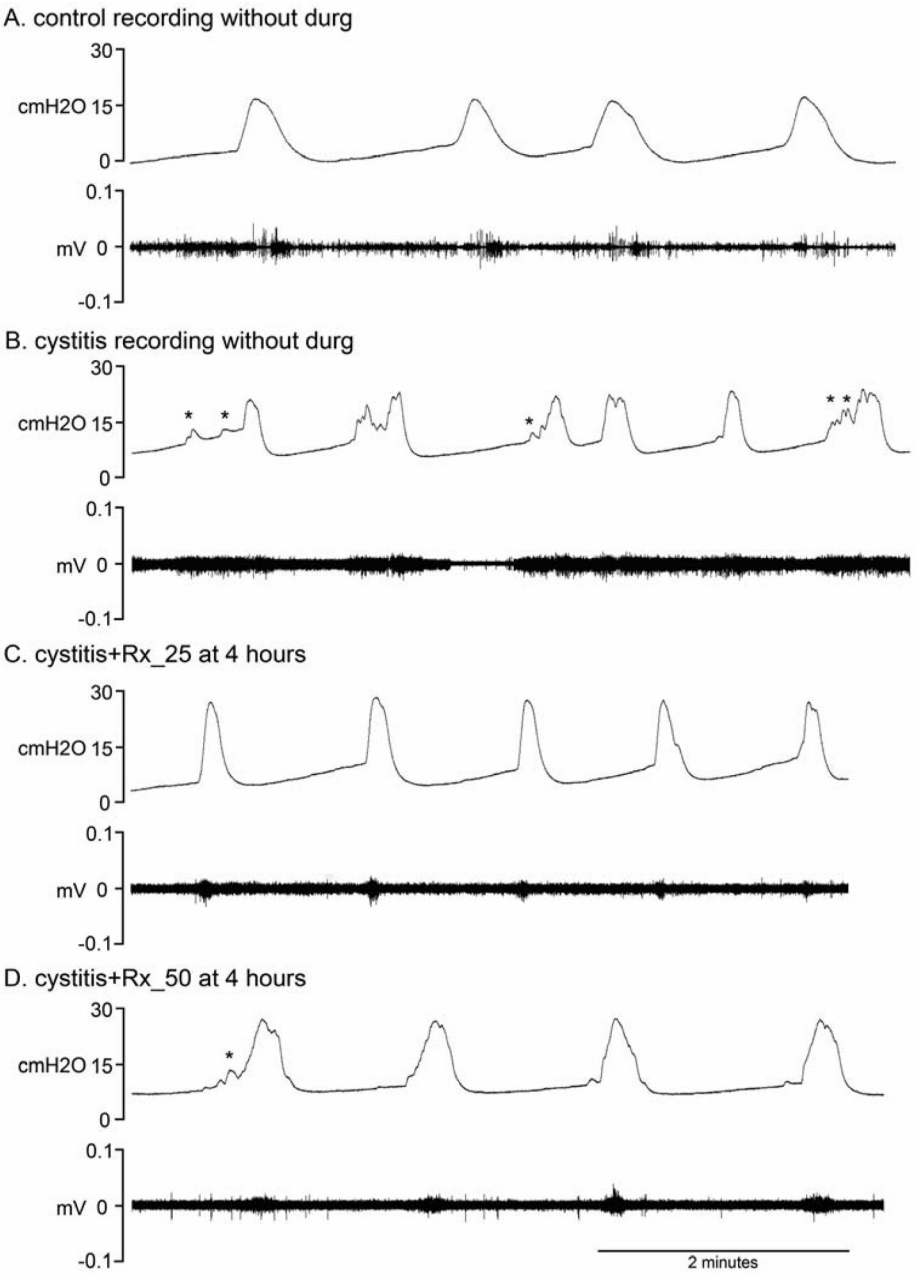

Fig. 1:

Representative examples of urodynamic recordings in the control mouse (A) and cystitis mice before (B) and after drug administrations (C-D). In this cystitis mouse, the voiding and non-voiding contractions were more frequent during saline infusion. Urodynamic recordings obtained 4 hours after administrations of gabapentin (ip) of 25 mg/kg (C, cystitis+RX_25) and 50 mg/kg (D, cystitis+RX_50). Asterisks indicate the non-voiding contractions.

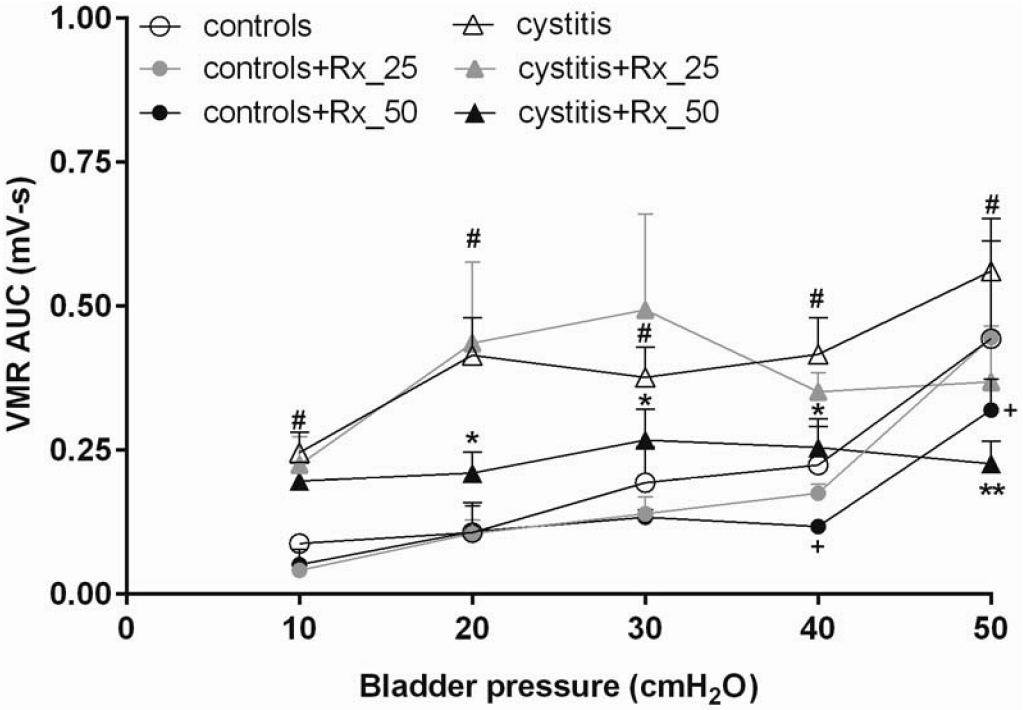

Fig. 2:

The effect of gabapentin on VMR during IBD. The bladder was distended by saline from 10 to 50 cmH_2O. In control mice, 25 mg/kg of gabapentin (control+Rx_25) did not suppress VMR AUC at any IVP levels. 50 mg/kg of gabapentin (control+Rx_50) significantly suppressed VMR AUC when the IVP at 40 and 50 cmH_2O in control mice. The cystitis mice showed a significant increase of VMR AUC at each IVP level compared to controls. 25 mg/kg of gabapentin (cystitis+Rx_25) did not suppress VMR AUC. However, 50 mg/kg of gabapentin (cystitis+Rx_50) significantly suppressed VMR AUC when the IVP was higher than 20 cmH_2O. + $p<0.05$ indicated statistical significance in the group of control+Rx_50 compared to the control mice without drug. # $p<0.05$ indicated statistical significance between the controls and cystitis mice. * $p<0.05$ and ** $p<0.01$ indicated statistical significance in the group of cystitis+Rx_50 compared to the cystitis mice without drug.

Table 1:

Averaged urodynamic outcomes in the control and cystitis mice before and after administrations of gabapentin (ip) at 25 mg/kg (control+Rx_25 and cystitis+Rx_25) and 50 mg/kg (control+Rx_50 and cystitis+Rx_50).

		Control (N=10)	control+Rx_25 (N=5)		control+Rx_50 (N=5)		Cystitis (N=10)	control+Rx_25 (N=5)		control+Rx_50 (N=5)	
			1 hour	4 hour	1 hour	4 hour		1 hour	4 hour	1 hour	4 hour
CMG	IVP (cm H2O)	28 ± 5	23 ± 6 (p=0.52)	28 ± 2 (p=0.15)	27 ± 2 (p=0.71)	21 ± 3 (p=0.46)	36 ± 1 † (p=0.04)	25 ± 3 * (p=0.02)	28 ± 1 * (p=0.01)	27 ± 3 * (p=0.04)	31 ± 4 (p = 0.17)
	RP (cm H2O)	11 ± 1	9 ± 1 (p=0.76)	8 ± 2 (p=0.40)	10 ± 1 (p=0.23)	10 ± 1 (p=0.33)	12 ± 2 (p=0.35)	11 ± 1 (p=0.64)	11 ± 1 (p=0.72)	12 ± 1 (p=0.42)	11 ± 1 (p=0.20)
	ICI (sec)	96 ± 6	99 ± 14 (p=0.46)	89 ± 11 (p=0.81)	104 ± 15 (p=0.98)	90 ± 3 (p=0.08)	67 ± 7 † (p=0.03)	58 ± 10 (p=0.48)	61 ± 11 (p=0.85)	73 ± 1 (p=0.16)	96 ± 24 * (p=0.04)
	NVCs (times/hr)	0	0	0	0	0	44 ± 5 †† (p=0.001)	13 ± 4 * (p=0.03)	12 ± 5 * (p=0.03)	13 ± 9 * (p=0.04)	5 ± 2 * (p=0.02)
	Bladder capacity (μL)	29 ± 2	27 ± 3 (p=0.66)	22 ± 6 (p=0.45)	38 ± 8 (p=0.25)	25 ± 6 (p=0.81)	14 ± 4 † (p=0.03)	16 ± 1 (p=0.82)	14 ± 2 (p=0.96)	13 ± 3 (p=0.96)	12 ± 3 (p=0.90)
EUS EMG	Amplitude (mV)	0.05 ± 0.01	0.04 ± 0.02 (p=0.32)	0.03 ± 0.01 (p=0.28)	0.03 ± 0.01 (p=0.27)	0.03 ± 0.01 (p=0.16)	0.05 ± 0.01 (p=0.78)	0.03 ± 0.05 (p=0.41)	0.02 ± 0.01 (p=0.38)	0.04 ± 0.01 (p=0.21)	0.03 ± 0.01 (p=0.09)
	AUC (mv sec)	0.07 ± 0.02	0.03 ± 0.01 (p=0.18)	0.03 ± 0.01 (p=0.22)	0.04 ± 0.01 (p=0.52)	0.08 ± 0.01 (p=0.42)	0.05 ± 0.02 (p=0.13)	0.02 ± 0.01 (p=0.08)	0.05 ± 0.02 (p=0.28)	0.02 ± 0.01 (p=0.45)	0.03 ± 0.01 (p=0.34)
	Duration (sec)	4 ± 1	4 ± 1 (p=0.18)	3 ± 1 (p=0.42)	5 ± 2 (p=0.40)	3 ± 1 (p=0.60)	6 ± 1 (p=0.13)	4 ± 1 (p=0.85)	3 ± 1 (p=0.74)	4 ± 1 (p=0.15)	4 ± 1 (p=0.14)

CMG: cystometry. EUS: external urethral sphincter. EMG: electromyogram. IVP: maximum intravesical pressure. RP: resting pressure after voiding. ICI: inter-contraction intervals. NVCs: Non-voiding contractions. AUC: area under the curve.

† p<0.05

†† p<0.01 indicate statistical significances between control and cystitis mice without drug.

* p<0.05

** p<0.01 indicate statistical significances compared to the cystitis mice without drug.