Sex-related differences in activity of lower urinary tract in response to intravesical acid irritation in decerebrate unanesthetized mice

Mitsuharu Yoshiyama,1,2 Hideki Kobayashi,1 Isao Araki,1 Shuqi Du,1 Hidenori Zakoji,1 and Masayuki Takeda1

1Department of Urology, University of Yamanashi Interdisciplinary Graduate School of Medicine and Engineering, Chuo, Yamanashi, and 2Yamanashi Rehabilitation Hospital, Fuefuki, Yamanashi, Japan

Submitted 6 May 2008; accepted in final form 21 July 2008

Yoshiyama M, Kobayashi H, Araki I, Du S, Zakoji H, Takeda M. Sex-related differences in activity of lower urinary tract in response to intravesical acid irritation in decerebrate unanesthetized mice. Am J Physiol Regul Integr Comp Physiol 295: R954–R960, 2008.—Sex-related differences in lower urinary tract (LUT) activity responding to intravesical infusion of diluted acetic acid (A/A, pH 3.0) were investigated during cystometrograms in decerebrate unanesthetized mice. A/A produced a decrease of intercontraction intervals in both female and male animals, and the extent of the decrease in male mice was much less than in female mice (19 ± 5% (P = 0.03) vs. 65 ± 5% (P = 0.03); n = 6 for each), exhibiting a marked difference between the two groups in response to acid irritation of the LUT (P = 0.002). A/A reduced maximal voiding pressure (MVP) (19 ± 4%, P = 0.03) but had no effect on pressure threshold for inducing voiding contraction (PT) (P = 0.56) in females, whereas A/A did not change MVP (P = 1.00) but increased PT (16 ± 4%, P = 0.03) in males. A/A decreased bladder compliances of female and male mice in a similar fashion (44 ± 10% vs. 24 ± 7%, P = 0.03 for each). In male mice, A/A produced persistent dribbling of fluid after voiding contraction phase, which was virtually not seen in females. The present study demonstrates the differences between female and male mice in response to noxious stimulation in the LUT: the female bladder is more sensitive to the acid irritation, while the male urethra is more irritable to the noxious stimulus. Identification of mechanisms underlying sex-specific characteristics might be helpful for elucidating pathogenesis of painful bladder syndrome.

NUMEROUS IN VIVO PHYSIOLOGICAL and pharmacological studies examining bladder and urethral activity have been conducted exclusively in one sex of animals in each experimental design, and thus it is uncertain whether functional responses of female and male lower urinary tracts are similar. There are only a few articles detailing differences between females and males in the lower urinary tract functions. Of the available reports, for example, one previous study comparing female and male rats in cystometry revealed that volume thresholds for inducing micturition were changed in accordance with altered intravesical infusion rates in the female rat, whereas these were constant regardless of the bladder filling rates in the male (24). The study suggested the possibility that mechanosensory afferent responses to intensity of the mechanical stimulus were different between the female and male animals.

Epidemiologic studies have demonstrated sex-specific differences in prevalence and incidence of certain diseases. In the urological field, it has been well documented that prevalence and incidence of interstitial cystitis, which is a syndrome consisting of severe refractory bladder symptoms such as suprapubic pain, urinary frequency, and urgency without a specific identifiable cause, for women are significantly higher than those for men (10). What pathophysiological factors are involved in these sex-related differences?

Here, we proposed the possibilities that sex differences in mechanisms responsible for transmitting inflammatory pain signals are associated with degree and frequency of presenting symptoms in interstitial cystitis or painful bladder syndrome and thus that nociceptive afferent processing of the two sexes has different characteristics in the transmissions. Thus the present study was conducted to compare between female and male mice responses in the lower urinary tract to acid irritation and to explore clinical relevance in the differences.

A preliminary report of this study has been presented in abstract form (41).

MATERIALS AND METHODS

Animal preparation. Six female and six male mice (C57BL/6, 12–13 wk old, Charles River Laboratories, Yokohama, Japan) weighing 19.3 ± 0.3 and 23.9 ± 0.4 g, respectively, were used in this study. The animals were housed under a 12:12-h light-dark cycle with controlled humidity and temperature. Standard pellet diet and water were available ad libitum. All animal procedures were reviewed and approved by the University of Yamanashi Institutional Animal Care and Use Committee. All efforts were made to minimize animal suffering and to reduce the number of animals used. The animals were anesthetized with sevoflurane (2–3%) in oxygen (flow rate 0.2 l/min) during surgery before decerebration. The trachea was cannulated with a polyethylene tube (PE-90, Clay-Adams, Parsippany, NJ) to facilitate respiration. The bladder was exposed by way of a midline abdominal incision. The bladder end of a polyethylene catheter (PE-50, Clay-Adams) was heated to create a collar and passed through a small incision at the apex of the bladder dome, and a suture was tightened around the collar of the catheter. The catheter was exited near the xiphoid process.

Precollicular decerebration was performed according to a published method (32) that included ligating both carotid arteries, followed by midline incision of head skin with a scalpel and removal of the skull and forebrain with a fine rongeur and a blunt spatula, respectively. Sevoflurane was then discontinued. After no further intracranial hemorrhage was visually detected, both lateral flaps of the incised head skin were sutured together. Experiments were started 2 h after the decerebration and conducted under unanesthetized conditions (40, 41, 45–47, 52–56).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
analysis of variance (ANOVA) were used for statistical analyses, if applicable. The correlation analysis between various CMG parameters, except for ICI versus ACT, BCD versus 1st PD, BCD versus 2nd PD, and ACT versus 2nd PD, which partly included each other, was performed with Spearman rank-order correlation calculations. For all analyses, \( P < 0.05 \) was considered significant.

**Drugs.** Sevoflurane (Maruishi Pharmaceutical, Osaka, Japan) and A/A (99.7%; Nacalai Tesque, Kyoto, Japan) were used in the present study. To make diluted A/A solution for intravesical infusion, several drops of 99.7% acetic acid were added to 20 ml of physiological saline and the pH was adjusted to 3.0 under monitoring (with compact pH meter B-212, Horiba, Kyoto, Japan) (final concentration = 0.23%).

**RESULTS**

Figures 2 and 3 show cystometric activity during intravesical infusion of saline (Figs. 2 and 3, top) and diluted A/A (Figs. 2 and 3, bottom) in female and male mice, respectively.

Before A/A infusion, baseline values of cystometric parameters in female and male mice were measured as presented in Table 1. In male mice, MVP was correlated with ICI (\( r = 1.00 \)) and ACT (\( r = 1.00 \)) (Fig. 4A), while CPP was correlated with 2nd PD (\( r = 1.00 \)) (Fig. 4B) (\( P = 0.003 \) in each analysis). No statistically significant correlations, however, were found between these parameters in female mice.

Bladder activity was gradually changed during A/A infusion, and the peak effects, which were evaluated for analysis, were achieved within 40 min of acid intravesical infusion in both sexes.

In female mice (\( n = 6 \)) A/A infusion significantly decreased MVP (mean = 19 ± 4%), BCP (mean = 44 ± 10%), ICI (mean = 65 ± 5%), and ACT (mean = 62 ± 5%), whereas it increased RP (mean = 65 ± 14%) (Fig. 5). The acid irritation did not change PT (\( P = 0.56 \)), CPP (\( P = 0.09 \)), 1st PD (\( P = 0.56 \)), 2nd PD (\( P = 0.16 \)), or BCD (\( P = 0.84 \)) (Fig. 5). No statistically significant correlations were found during A/A as well as saline infusion CMGs between any parameters in female mice.

In male mice (\( n = 6 \)) the A/A irritation increased RP (mean = 44 ± 13%), PT (mean = 16 ± 4%), 2nd PD (mean = 115 ± 25%), and BCD (mean = 86 ± 15%), whereas it

---

**Fig. 1.** A: representative voiding cycle during cystometry in a mouse. B: a bladder contraction extended from that on right in A. Voiding occurred during the period indicated in B. ICI, intercontraction interval; BCD, bladder contraction duration; 1st PD, 1st phase contraction duration; 2nd PD, 2nd phase contraction duration; PT, pressure threshold for inducing micturition contraction; MVP, maximal voiding pressure; CPP, closing peak pressure; RP, resting pressure. Actual collecting time (ACT) and bladder compliance (BCP) were calculated as 2nd PD + ICI and infusion rate \( \times (ICI/60)/(PT - RP) \) respectively.

---

Saline was infused into the bladders for 2 h before baseline values were measured. Bladder activity was monitored by way of the cystometry catheter connected to a pressure transducer. Cystometric recordings were performed by continuously-infusing physiological saline (30 \( \mu l/min \)) at room temperature into the bladder to elicit repetitive voids, which allowed data collection for a large number of voiding cycles (26). As shown in Fig. 1, the cystometric parameters measured during continuous cystograms (CMGs) were maximal voiding pressure (MVP, mmHg), which is the peak intraluminal pressure during voiding; closing peak pressure (CPP, mmHg), which is the lowest pressure immediately after a voiding contraction; intercontraction interval (ICI, s), which is the time lag between two voiding cycles; and bladder compliance (BCP, \( \mu l/mmHg \)), which was calculated as fluid volume infused between two time points of RP and the following PT (i.e., infusion rate \( \times ICI/60 \)) \( (\mu l)/(PT - RP) \) (mmHg) (14, 18, 43, 47). Bladder contraction duration (BCD, s) is the sum of the first phase duration (1st PD, s) and the second phase duration (2nd PD, s). Actual collecting time (ACT, s) consists of ICI and 2nd PD, which indicates the actual storage phase until induction of the following voiding contraction during continuous CMGs.

Acetic acid (A/A) infusion into the bladder has been used widely as a model for lower urinary tract irritation (57). Effects of diluted A/A (pH 3.0) intravesically infused for 1 h on bladder activity were evaluated after the baseline infusion of saline. After the A/A infusion, saline was again infused into the bladder to examine recovery of the irritated lower urinary tract.

**Data analysis and statistics.** Three consecutive storage phases and voiding contractions immediately before and during A/A infusion were evaluated as baseline control (i.e., saline infusion) and effect of acidic irritation, respectively. All values are expressed as means ± SE. Mann-Whitney test, Wilcoxon matched pairs test, and two-way
different responses between female and male mice in ICI, present study revealed that intravesical acid irritation produced tract responding to intravesical noxious stimulation. The sex-specific differences in reflex activity of the lower urinary tract were evaluated as identical to the ICIs during A/A infusion in the male mice. The increase of BCD in males was attributed to prolongation of 2nd PD, one of the components composing BCD (Figs. 3 and 5). During A/A infusion CMGs, MVP was correlated with ICI (r = 0.94) and ACT (r = 0.94) (Fig. 6A) and 2nd PD (r = 0.87) (data not shown), while CPP was correlated with 2nd PD (r = 0.87) (Fig. 6B) (P < 0.05 in each analysis).

Figure 7 shows the changes of parameter values in the lower urinary tract activity after as well as during the A/A infusion expressed in percentage of baseline (i.e., during initial saline infusion). The subsequent intravesical saline infusion during the recovery period reversed the female lower urinary tract activity altered by acid irritation within 2 h, whereas it rather suppressed the male bladder activity and tonus (Fig. 7, B–E, G, H).

**DISCUSSION**

To our knowledge, this is the first report demonstrating sex-specific differences in reflex activity of the lower urinary tract responding to intravesical noxious stimulation. The present study revealed that intravesical acid irritation produced different responses between female and male mice in ICI, decreased ICI (mean = 19 ± 5%), ACT (mean = 28 ± 4%), and BCP (mean = 24 ± 7%) (Fig. 5). The A/A infusion had no effect on MVP (P = 1.00), CPP (P = 0.31), and 1st PD (P = 0.76) (Fig. 5). The A/A infusion produced persistent “fluid dribbling” at the 2nd PD in all male mice (Fig. 3), which was not seen in female mice (Fig. 2). Because of the repeated fluid leakage in the 2nd PD, for analysis the ACT values were evaluated as identical to the ICIs during A/A infusion in the male mice. The increased RP and decreased BCP in both female and male bladders were more sensitive to the noxious stimulation than male bladders. ICI has been generally evaluated as a parameter indicative of afferent excitability (26). Some attention, however, should be paid to the fact that ICI can be affected by diverse factors including volume threshold for inducing micturition, voided volume, residual volume (i.e., voiding efficiency), detrusor tonus (i.e., related to bladder compliance), or combinations of these. In the present study, intravesical A/A increased RP and decreased BCP in both female and male mice. The altered RP can be indicative of residual volume change. However, it seems likely that the increase of RP is

**Table 1. Comparisons between female and male mice in cystometric parameters**

<table>
<thead>
<tr>
<th>Group</th>
<th>PT, mmHg</th>
<th>MVP, mmHg</th>
<th>CPP, mmHg</th>
<th>RP, mmHg</th>
<th>BCP, μl/mmHg</th>
<th>1st PD, s</th>
<th>2nd PD, s</th>
<th>BCD, s</th>
<th>ICI, s</th>
<th>ACT, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>6.1 ± 0.8</td>
<td>22.8 ± 1.2</td>
<td>17.0 ± 2.5</td>
<td>1.8 ± 0.3</td>
<td>32.9 ± 7.4</td>
<td>8.0 ± 0.5</td>
<td>17.8 ± 2.5</td>
<td>25.8 ± 2.6</td>
<td>257 ± 47</td>
<td>275 ± 48</td>
</tr>
<tr>
<td>Male</td>
<td>4.9 ± 0.3</td>
<td>24.6 ± 1.5</td>
<td>18.2 ± 3.6</td>
<td>2.2 ± 0.2</td>
<td>44.9 ± 8.2</td>
<td>9.7 ± 1.1</td>
<td>25.6 ± 4.6</td>
<td>35.3 ± 4.6</td>
<td>195 ± 28</td>
<td>221 ± 31</td>
</tr>
</tbody>
</table>

Values are means ± SE for 6 mice/group. PT, pressure threshold for inducing micturition contraction; MVP, maximal voiding pressure; CPP, closing peak pressure; RP, resting pressure; BCP, bladder compliance; 1st PD, 1st phase duration of bladder contraction; 2nd PD, 2nd phase duration of bladder contraction; BCD, bladder contraction duration; ICI, intercontraction interval; ACT, actual collecting time. No differences were found between female and male mice in all parameters indicated (by Mann-Whitney test).

**Fig. 4.** Data collected during saline infusion CMGs were calculated by the Spearman rank-order correlation analysis. Coefficients (r) between MVP and ICI or ACT (A) and between CPP and 2nd PD (B) are shown.

**Fig. 3.** Top: typical bladder activity during continuous saline infusion CMG (30 μl/min) in a male mouse. Bottom: effects of intravesical infusion of diluted acetic acid (pH 3.0) on bladder activity. Note that diluted acetic acid produces little change in MVPs and ICIs. *Fluid dribbling.

ACT, BCD, 2nd PD, MVP, CPP, and PT, whereas it caused common changes in both sexes in RP and BCP. Of the evaluated parameters, only 1st PD was not affected by acid irritation to the lower urinary tract. The detailed cystometric analyses were conducted to facilitate better understanding of the complex autonomic functions.

The most intriguing discovery in the present study was that intravesical acid irritation more markedly decreased ICI and ACT in female mice than in male mice, suggesting that female bladders were more sensitive to the noxious stimulation than male bladders. ICI has been generally evaluated as a parameter indicative of afferent excitability (26). Some attention, however, should be paid to the fact that ICI can be affected by diverse factors including volume threshold for inducing micturition, voided volume, residual volume (i.e., voiding efficiency), detrusor tonus (i.e., related to bladder compliance), or combinations of these. In the present study, intravesical A/A increased RP and decreased BCP in both female and male mice. The altered RP can be indicative of residual volume change. However, it seems likely that the increase of RP is
attributed to the decreased BCP and that the influence of residual volume change seems to be minimal because values obtained by a calculation of BCP/HP during A/A infusion were similar to those during baseline saline infusion in both groups. Thus we concluded that the decreased ICI or decreased ACT was due to decreased volume threshold for inducing micturition (i.e., increase of afferent excitability) produced by A/A infusion and that the afferent sensitivity to acid irritation in female mice was certainly greater than that in males. Alternatively, the result may be dependent on differences between females and males in acid permeability of the epithelium.

A/A infusion increased BCD in males, whereas it did not change the parameter in females. This difference was due to different responses of second phase contraction to the A/A irritation between the two groups. In male mice A/A induced persistent dribbling of fluid out of the urethral orifice accompanying intravesical pressure fluctuation (Fig. 3), which was not seen in female mice (Fig. 2), during the second phase contraction. The leakage of fluid occurring in the second phase contraction seems to be induced as a response to acid irritation to urethra because it appeared immediately after voiding (i.e., after the 1st phase contraction) but not at storage phase, suggesting a possible involvement of the “urethra-to-bladder” reflex (13, 19) in the mechanism. In conclusion, the functional response of the urethra to acid irritation is different between the two sexes, and the male urethra is more irritable to acid stimulus.

In the present study MVP was decreased by A/A infusion in females, whereas it was not changed in males. Decrease of MVP can be attributed to decreased detrusor contractility, reduced urethral resistance during micturition, or both. In this respect, there has been no report of in vitro or in vivo physiological studies detailing the sex differences in detrusor and urethral responses to acid. The present study also did not determine the mechanism responsible for the MVP change by A/A in female mice. It is of value to compare detrusor and urethral contractile responses to low pH between females and males in an in vitro experimental setting. Previous studies showed that a lower concentration of A/A (0.1%) did not

Fig. 5. Effects of intravesical infusion of diluted acetic acid (pH 3.0) on cystometric parameters in female (○) and male (●) mice. sl, Saline infusion; aa, diluted acetic acid (pH 3.0) infusion. Comparisons between saline and acetic acid were made by Wilcoxon matched pairs test (*P < 0.05). Two-way repeated-measures ANOVA was used to examine whether cystometric responses to diluted acetic acid intravesical infusion were different between female and male mice (#P < 0.05, ##P < 0.01, ###P < 0.001). n.s., Not significant.

Fig. 6. Data collected during acetic acid infusion CMGs were calculated by the Spearman rank-order correlation analysis. Coefficients (r) between MVP and ICI or ACT (A) and between CPP and 2nd PD (B) are shown.
change MVP in urethane-anesthetized female rats (20, 57) but increased MVP in conscious female rats (30). The increased MVP in the conscious animal might be caused by an excessive behavioral response such as increase of abdominal pressure due to the acid irritation passing through the urethra.

CPP is indicative of intravesical pressure increase during bladder neck/proximal urethra closing. CPP of females responded differently to A/A from that of males (according to 2-way ANOVA), albeit that the A/A irritation did not statistically change the CPP in either female or male mice. The second phase contraction in which the CPP is involved does not exhibit micturition during the normal voiding cycle (40), and its functional role or significance has not been determined (4). A recent study, on the other hand, showed that a /-adrenergic agonist, isoproterenol, decreased CPP without changing MVP and the decrease of CPP in muscarinic M2 receptor-deficient mice was more marked than that in wild-type mice (16). Birder et al. (4) reported that activation of transient receptor potential vanilloid (TRPV)4 channels by the selective agonist /-phorbol 12,13-didecanoate increased CPP. These studies suggest that CPP is at least related to the mechanisms via the /-adrenergic system and TRPV4 channels in the bladder. Further investigations are warranted to elucidate the relevance of CPP change.

PT of males was altered by A/A differently than PT of females (Fig. 5A). Fluid volume infused into the bladder to induce a voiding contraction (i.e., ACT × infusion rate, /) and bladder tone (i.e., related to BCP, /mmHg) approximately have positive and negative relationships, respectively, with PT (mmHg) in each voiding cycle. Thus changes of the ACT versus BCP relationship by A/A irritation significantly affected the PT changes in the two groups. Because BCPs of female and male mice were decreased by A/A in a similar fashion (Fig. 5E), the difference in PTs was largely dependent on degrees of ACT reduction by A/A (Fig. 5J).

Increased RP and decreased BCP were common changes by A/A intravesical infusion in both female and male mice. Changes of these parameters are significantly related. Increases of RP in the present study were largely due to decreased BCP (i.e., increased bladder tone), although change in RP can be also affected by change in residual volume. These can be confirmed by comparing values obtained by a calculation of RP × BCP before and during A/A infusions.

A/A decreased BCP equivalently in female and male mice. The change in BCP suggested the possibility that pH 3.0 A/A could pass through the mucosa and reach the detrusor, affecting its tonus during urine storage. Of interest is that normal saline infusion after A/A (i.e., during recovery time) reversed the values of CMG parameters changed by A/A within 2 h in females, whereas it rather suppressed bladder contractions and further decreased BCP in males. These discrepancies in male mice should be evaluated in future studies.

There were significant correlations in MVP versus ICI or ACT and CPP versus 2nd PD in males, while no significant correlations in evaluated parameters were found in females. ICI and ACT are parameters affected by afferent excitability, sympathetic implication, or a combination of both (26, 46), although they can be also altered by intravesical residual fluid after voiding. MVP is determined by detrusor contractility (i.e., at least parasympathetic component) and urethral resistance (i.e., sympathetic and somatic components) (12, 43, 46, 47). Taken together, it seems likely that sympathetic control, at least, has a key role in significant correlations between MVP and ICI/ACT in male mice. On the other hand, lower CPP can be indicative of larger sympathetic participation via /-adrenoceptors in the detrusor (16), and thus less time (i.e., shorter 2nd PD) is required until the detrusor starts playing a role in the storage phase, in which the sympathetic mechanisms are dominant. Such correlations, however, were not found in female mice, and the reasons are unknown.
The present study was performed in decerebrate unanesthetized mice. Decerebration, which removes the forebrain receiving signals from the peripheral organs and supplying both excitatory and inhibitory inputs to the brain stem, has been established for in vivo urological research (27, 40, 41, 45–47, 52–56) and allows the study of involuntary “reflex” activity of the lower urinary tract as the brain stem (i.e., including periaqueductal gray and pons), spinal cord (i.e., including thoracic sympathetic neurons and lumbosacral parasympathetic neurons), and peripheral nerves in which neural circuits responsible for voiding and storage (12) are intact. On the other hand, conscious (9, 18, 43, 49, 50) and anesthetized (14, 24, 26, 42, 48, 51, 57, 58) rodents are mainstays for in vivo studies. Voluntary micturition “behavior” in conscious animals, however, can be affected by stress from circumstances (31, 36) or drugs that change the mood of the animal (37, 44), and thus greater attention should be paid to the use of the model. Anesthesia such as urethane may cause pharmacological interactions (52) and disturb efficient voiding (56), while it remains a choice because of its convenience and suitability in in vivo neurophysiological and pharmacological experiments to study “reflex” micturition (25, 29).

These studies demonstrated that there were significant sex-related differences in the reflex bladder response to noxious stimulation by diluted A/A (pH 3.0), revealing that the female bladder is more sensitive and vulnerable to the irritation. The result is compatible with previously reported epidemiologic studies in human populations (6, 8, 38) and laboratory experiments in animals (1, 3, 7, 17, 34, 35) showing that the female is highly sensitive to noxious stimuli and pain. On the other hand, our present results suggest the possibility that the male urethra is affected more evidently. What mechanisms are involved in these differences in the lower urinary tract responses? A previous study using immunohistochemical technique revealed large quantitative differences between female and male mice in gene expression of progesterone receptors and estrogen receptors in the bladder and urethra (33). It has been suggested that estrogens modulate pain (2, 11) and inflammatory response (23) and that progesterone receptors and estrogen receptors are involved in signal transmission of pain (15, 22). Furthermore, our recent study (21) validated sex-specific differences in quantities of gene expressions of TRPV1 (5) and acid-sensing ion channels (ASICs) (39), both of which were channels sensitive to extracellular protons (i.e., pH), in both mucosal and muscle layers of the mouse bladder. The differential quantities of these channels distributed in bladders of females and males can be associated with sex-related sensitivity to noxious acidic stimulus (e.g., inflammation), and thus it seems reasonable to target these channels for the treatment of pain in the lower urinary tract.

Perspectives and Significance

The present results suggest that there are sex-related differences in lower urinary tract activity in response to intravesical acid stimulus, which may be associated with the differences in prevalence and incidence of interstitial cystitis or painful bladder syndrome that is more frequently found in women. The sites responsible for the differences can be at the local organs, the peripheral nervous system, and/or the central nervous system (i.e., urothelium, detrusor, dorsal root ganglia, spinal cord, brain stem, or combinations of these), and the underlying mechanisms can be various (e.g., via TRPV1, ASICs, estrogen receptors, progesterone receptors, nerve growth factor, interleukin-1, 5-hydroxytryptamine, bradykinin) (5, 21, 28, 33). Further investigations are necessary to elucidate the mechanisms involved in the sex differences and to develop treatments for the bladder pain.

ACKNOWLEDGMENTS

Present address of S. Du: Dept. of Urology, First Affiliated Hospital, China Medical University, 155 Nanjingbei St., Heping District, Shenyang, Liaoning 110001 China.

GRANTS

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant No. 19591839) (M. Yoshimaya).

REFERENCES

SEX-SPECIFIC DIFFERENCES IN CYSTOMETRY OF MICE


