Improvement in bladder storage function by tamsulosin depends on suppression of C-fiber urethral afferent activity in rats.

IMPROVEMENT IN BLADDER STORAGE FUNCTION BY TAMSULOSIN DEPENDS ON SUPPRESSION OF C-FIBER URETHRAL AFFERENT ACTIVITY IN RATS

OSAMU YOKOYAMA, ANWAR YUSUP, NOBUYUKI OYAMA, YOSHITAKA AOKI, YOSHIJI MIWA, HIRONOBU AKINO

From the Department of Urology, Faculty of Medical Science, University of Fukui, Fukui, Japan

Running head: α_1-blocker and C-fiber urethral afferents

Key words: C-fiber, α_1-blockers, detrusor overactivity, prostaglandin

Corresponding author:

Osamu Yokoyama

Department of Urology, Faculty of Medical Science, University of Fukui

23-3 Shimoaizuki, Matsuoka, Fukui 910-1193, Japan

TEL +81-776-61-8396

FAX +81-776-61-8126

E-mail: oyoko@fmsrsa.fukui-med.ac.jp

ABSTRACT

Purpose: α_1-blockers improve voiding symptoms by reducing prostatic and urethral smooth muscle tone. However, the mechanism underlying improvements in storage symptoms is not known. Topical application of prostaglandin (PG) E_2 to the rat lower urinary tract stimulates the micturition reflex (MR). Using an animal model, we investigated whether the α_1-blocker tamsulosin acts on C-fiber afferent activity, and if so the location of this effect.

Materials and Methods: To induce desensitization of C-fiber afferent activity resiniferatoxin (0.3 mg/kg, RTX) was subcutaneously injected in female Sprague-Dawley rats 2 days prior to experiments. Simultaneous recordings of urethral pressure and rhythmic bladder pressure were made under urethane anesthesia. PGE_2 (0.4 mg/ml) was continuously administered intravesically or intraurethrally to rats pretreated with RTX (RTX rats) or rats without pretreatment (non-RTX rats). We investigated the effects on MR of intravenous ($2.2x10^{-1}$ – $2.2x10^{3}$ nM/kg) or intrathecal (0.001 – 0.1 nmol) administration of tamsulosin.

Results: Bladder contraction interval (BCI) was markedly reduced after intravesical or intraurethral administration of PGE_2 in non-RTX rats, but was unchanged in RTX rats. This effect was antagonized by an EP1 receptor antagonist (ONO-8711). Intravenous administration of tamsulosin significantly increased BCI in non-RTX rats receiving intraurethral PGE_2, but had no effect on non-RTX rats receiving intravesical PGE_2. Intrathecal administration of tamsulosin produced a slight and insignificant increase in BCI in non-RTX rats receiving intraurethral PGE_2.

Conclusion: These results suggest that PGE_2 enhances MR through C-fiber afference and that tamsulosin had an inhibitory effect on the C-fiber urethral afferent nerves, thereby improving bladder storage function.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is an age-related increase in the volume of the prostate, which leads to voiding and storage dysfunction caused by bladder outlet obstruction (BOO). The functional importance of α_1-adrenoceptors (α_1-ARs) in the sympathetic nerve terminals of the prostate has been indicated, and it has been shown that dynamic obstruction is mediated by α_1-AR stimulation. Medical treatment of voiding, storage or both symptoms suggestive of BOO is now the initial choice of therapy, and α_1-AR blockers remain the most widely used pharmacological agents aimed at the dynamic component of prostatic obstruction.[1]

Recent attention has focused on the classification of neural supply to the bladder and prostate. Presently, α_1-ARs are generally subdivided into α_{1A}-, α_{1B}-, and α_{1D}-AR subtypes.[2] The α_{1a}-AR subtype predominates in the prostatic stroma at the mRNA and protein level, and is responsible for the dynamic component of obstruction and related voiding symptoms.[3] The α_{1d}-AR subtype is expressed in the detrusor, prostate, peripheral ganglia, and spinal cord in humans and rats.[4-7] Recently, a number of experimental findings have indicated the involvement of the α_{1D}-AR subtype in the storage symptoms.[5,8] Because α_1- AR blockers act during the storage phase to allow an increase in bladder capacity and a decrease in urgency, it is thought that they exert an

inhibitory effect on afferent nerves. However, the mechanism by which these blockers improve storage symptoms remains unknown.

Prostanoids, in particular prostaglandin (PG) E_2, have been implicated as endogenous modulators of bladder function under both physiological and pathophysiological conditions.[9] PG synthesis occurs locally in the bladder muscle and mucosa, and is initiated by various physiological stimuli such as detrusor muscle stretch and nerve stimulation, as well as by injury and mediators of inflammation. Several investigators have shown that PGE_2 can contract isolated human as well as animal detrusor muscle.[9] This effect is unlikely to contribute to voiding contraction even if PGE_2 does facilitate the action of the endogenous efferent neurotransmitter acetylcholine.[10] *In vivo*, endogenous prostanoids may enhance voiding efficiency through a direct or indirect effect on sensory nerves.[11] Topical application of PGE_2 to the bladder stimulates the micturition reflex (MR) in humans and rats.[12,13] Increases in COX-2 expression and PGs in the bladder wall have been shown to play an important role in the development of detrusor overactivity caused by BOO.[14,15] To our knowledge, however, the influence of intraurethral PGE_2 on MR has not been investigated.

In the present study, we investigated whether tamsulosin,[16] an α_{1A}-and α_{1D}-AR blocker, acts on C-fiber afferents by comparing its effect on induced detrusor overactivity in C-fiber-desensitized and C-fiber normal rats. We also studied the effect of intravenous (iv) and intrathecal (it) administration of tamsulosin on the detrusor overactivity induced by intravesicular or intraurethral PGE_2.

MATERIALS AND METHODS

A total of fifty-two female Sprague-Dawley rats weighing 225-268 g (mean = 252 g) were used. They were housed at a constant temperature (23 ± 2ºC) and humidity (50-60%) under a regular 12-h light/dark cycle (lights on 7:00 AM - 7:00 PM). Tap water and standard rat chow were freely available. All experiments were performed in strict accordance with the guidelines of the Institutional Animal Care and Use Committee of the University of Fukui.

Simultaneous recordings of urethral and rhythmic bladder pressure

To induce desensitization of C-fiber afferent activity, we subcutaneously injected resiniferatoxin (0.3 mg/kg, RTX) 2 days prior to experiments. All surgical and urodynamic procedures were performed under urethane anesthesia (1.0 g/kg). The bladder and proximal urethra were exposed through a midline abdominal incision. Urethral activity, measured as urethral perfusion pressure, was monitored using a polyethylene catheter (size 3; i.d. 0.5 mm, o.d. 1.0 mm; Kunii Co. Ltd., Tokyo, Japan) with the tip embedded in a cone-shaped plug that was introduced transvesically through an incision in the bladder dome and then seated securely in the bladder neck.[17] The cone-shaped plug was fashioned from Eppendorf pipette tip. The catheter end was then exteriorized at the external urethral meatus. To monitor intravesicular pressure, the bladder end of a catheter (size 4; i.d. 0.8 mm, o.d. 1.3 mm; Kunii Co. Ltd., Tokyo, Japan) was heated to create a collar and passed through the same incision of the bladder dome. This arrangement permitted the functional separation of bladder and urethral activity without the risk of surgical damage to the vesicourethral innervation associated

with a urethral ligation or total urethrotomy. The bladder catheter was connected to a pump (TE-311; Terumo Co. Ltd., Tokyo, Japan) for infusion of physiological saline and to a pressure transducer (TP-200T; Nihon-Kohden Co., Ltd., Tokyo, Japan) by means of a polyethylene T-tube. The urethral catheter was connected to a pump for continuous saline infusion (0.075 ml/min) and to a pressure transducer by means of a polyethylene T-tube.

Experimental protocol

After a 30-min postsurgical stabilization period, pressure recordings from the bladder and urethra were started. The bladder was filled with saline at a rate of 0.1 ml/min to induce the micturition reflex, which was evident by rhythmic, large-amplitude bladder contractions. Bladder filling was then discontinued and isovolumetric pressure was recorded. The urethra was continuously infused with saline (0.075 ml/min). Thus, isovolumetric bladder and urethral perfusion pressure were recorded independently and simultaneously. The values of the three parameters (bladder contraction interval, BCI; bladder contraction pressure, BCP; and bladder contraction duration, BCD) were obtained from the micturition reflex measurements (Fig. 1).

Drug administration

PGE_2 (0.4 mg/ml) dissolved in 0.1 M phosphate buffer (pH 7.4) was continuously administered intravesically or intraurethrally to rats pretreated with RTX (RTX rats) or rats without pretreatment (non-RTX rats). To confirm whether the effect of PGE_2 on MR was mediated by the EP1 receptor, ONO-8711 {6-[(2S,3S)-3-(4-chloro-2-methylphenylsulfonylaminomethyl)-bicyclo[2.2.2]octan-2-yl

]-5Z-hexenoic acid}, a selective EP1 antagonist chemically synthesized at Ono Pharmaceutical Co., Ltd. (Osaka, Japan), was given by intravenous administration. The effect of tamsulosin (Astellas Pharma Inc., Tokyo, Japan) on intravesical or intraurethral PGE_2-stimulated MR was investigated at iv doses of $2.2 \times 10^{-1} – 2.2 \times 10^{3}$ nM/kg and it doses of 0.001 – 0.1 nmol.

Data analysis

Data are expressed as the mean ± standard error of the mean (SEM). Statistical comparisons were performed using one- or two-way repeated measures analysis of variance (ANOVA), with subsequent individual comparisons conducted using Fisher's PLSD test. The two groups were compared using Mann Whitney's U-test or Wilcoxon signed-ranks test. A level of $p < 0.05$ was considered statistically significant.

RESULTS

Effects of PGE_2 on micturition reflex

BCI was markedly reduced after intravesical or intraurethral administration of PGE_2 in non-RTX rats (Figs. 1, 2, 3), but was unchanged in RTX rats. Intravesical and intraurethral administration of PGE_2 decreased BCI by 40.9% and 23.1%, respectively, with these ratios expressed as 0% in Fig. 3 as baseline ratios for the next experiment. These effects were antagonized by the EP1 receptor antagonist ONO-8711 (1 mg/kg, iv). PGE_2 by intravesical administration gradually increased voiding threshold pressure (Fig. 1), whereas that by intraurethral administration had no effect (Fig. 2).

Effects of tamsulosin on PGE_2-stimulated micturition reflex

Intravenous administration of tamsulosin significantly increased BCI in rats receiving intraurethral PGE_2 ($p < 0.05$), but had no particular effect on those receiving intravesical PGE_2 (Figs. 3, 4, 5). The percentage increases in BCI in rats receiving intraurethral and intravesical PGE_2 at 2.2×10^3 nM/kg tamsulosin were 89.4% and 18.9%, respectively. The high dose of tamsulosin did not increase BCI in rats receiving intravesical PGE_2, whereas ONO-8711 (1 mg/kg iv) completely reversed the influence of PGE_2 on BCI (Fig. 5). Further, in rats not receiving PGE_2, tamsulosin showed no significant effect on BCI (Fig. 3), and had no effect on BCI in RTX rats. The high dose of tamsulosin (2.2×10^3 nM/kg) decreased BCP in rats receiving intraurethral or intravesical PGE_2 and in rats not receiving PGE_2 by 26.1%, 8.2%, and 47.5%, respectively (Fig. 6). Further, tamsulosin by intravenous administration had no effect on BCD in any treatment group (Fig. 7), although intrathecal administration produced a slight and insignificant increase in BCI in rats receiving intraurethral PGE_2.

DISCUSSION

Our findings indicate that PGE_2 produces an excitatory effect on MR by stimulation of C-fiber afferent nerves via the EP1 receptor. This effect of PGE_2 was seen on application to either the bladder or the urethra. Tamsulosin by intravenous administration had an inhibitory effect on this agonistic effect on MR of intraurethral but not intravesical PGE_2 and did not produce a decrease in BCP at low doses. Tamsulosin by intrathecal administration, in contrast, had only a slight and insignificant inhibitory effect on intraurethral PGE_2-stimulated MR. These results support the

hypothesis that this α_1-AR blocker improves detrusor overactivity by inhibiting C-fiber afferent activity in the urethra rather than in the spine, and this effect does not depend on the inhibition of C-fiber afferent activity in the spine.

Studies in rats and humans have demonstrated that intravesical administration of PGE_2 results in detrusor overactivity.[12,13] PGE_2 produces its endogenous activity via the EP receptor family of G protein-coupled receptors, of which four subtypes have been identified to date. Using EP1 receptor knockout mice, Schröder demonstrated that the EP1 receptor was not essential for normal micturition but did play a role in the development of detrusor overactivity caused by PGE_2 and BOO.[15] In the present study, continuous intravesical administration of PGE_2 caused a significant decrease in BCI in non-RTX rats, whereas ONO-8711 antagonised this effect. These findings indicate that these effects of PGE_2 are attributable to the stimulation of EP1 receptors. Further, RTX rats did not respond to intravesical PGE_2, leading us to hypothesize that PGE_2 produces its excitatory influence on MR by stimulating C-fiber afferent nerves via the EP1 receptor.

In the present study, the excitatory effects on MR produced by intravesical administration of PGE_2 were also seen in non-RTX rats receiving intraurethral administration, but not in RTX-rats. The mechanism of this overactivity is unknown, but may be inititiated by a PGE_2–mediated increase in urethral afferent activity. It has been suggested that detrusor overactivity caused by BOO may be initiated from the bladder outlet region rather than from the bladder itself.[18] In cats, urethral perfusion triggered spontaneous bladder contraction of such intensity and frequency that bladder filling was

not possible.[19] Pharmacological activation of urethral afferent nerves by intraurethral capsaicin elicited a biphasic change in MR,[17] initially decreasing BCI within minutes, followed 15 to 30 min later by complete MR blockage. Immunohistochemical data have indicated the presence of capsaicin-sensitive primary afferent fibers in the rat proximal urethra.[20] Considering these findings and the antagonistic effect of ONO-8711 on PGE_2-stimulated MR, urethral C-fiber afferent activity may be a trigger to the induction of detrusor overactivity via the EP1 receptor in rats.

A recent study reported that α_{1d}-AR mRNA is present in the human detrusor, that the ratio of α_{1d}-AR mRNA is higher than that of α_{1a}-AR mRNA, and that the α_{1D}-AR subtype is closely related to the storage symptoms encountered in patients with BPH.[4] The ratio of α_{1d}-AR subtype to all α_1-AR subtype mRNAs has been reported to be higher in the obstructed rat bladder.[5] α_1- AR blockers with significant affinity for the α_{1D}-AR subtype are therefore thought able to improve storage symptoms related to BOO. Nomiya et al. found that mRNAs of the α_{1a}-, α_{1b}-, and α_{1d}-AR subtypes are expressed at low levels in the obstructed human bladder, whereas β_3–AR mRNA is highly expressed.[7] They suggested that bladder α_1-ARs are not likely to be responsible for the detrusor overactivity and storage symptoms in patients with BPH.

In the present study, tamsulosin had an inhibitory effect on intraurethral PGE_2-stimulated MR, but not on intravesical PGE_2-stimulated MR. This result lead us to hypothesize that tamsulosin exerts an inhibitory effect on C-fiber afferent nerves in the urethra. Tamsulosin is a combined α_{1A} and α_{1D}-AR antagonist which exerts a relaxant effect on urethral rather than bladder smooth muscle. The α_1-AR subtype

predominates in prostatic stroma at the mRNA and protein level, and is responsible for the dynamic component of obstruction.[3] Taken together, these findings suggest that tamsulosin exerts an inhibitory effect on C-fiber urethral afferent nerves by decreasing urethral tonus, and thereby improving of storage symptoms. However, using urethane treated animal increases the risk that effects of α_1-AR blockers in the spinal cord will be masked by the urethane. In order to really confirm C-fiber urethral afferent nerves, it is ideally necessary to record the activity from identified C-fibers. Further research on the underlying mechanisms of the interaction between α_1-AR and C-fiber afferent activity in the urethra may lead to new therapeutic modalities targeted at detrusor overactivity.

CONCLUSION

In vivo animal study reveals that exogenous PGE_2 enhances MR through effects on C-fiber efferent nerves in both the bladder and urethra. Tamsulosin has an inhibitory effect on C-fiber urethral afferent nerves, thereby improving bladder storage function. These findings are likely to be applicable to the human subject and to explain the mechanism that α_1-AR blockers improve storage symptoms.

REFERENCES

1. Stoevelaar, H.J., Van De Beek, C., Casparie, A.F., McDonnel, J. and Nijs, H.G.T.: Treatment choice for benign prostatic hyperplasia: a matter of urologic preference? J Urol, **161**: 133, 1999

2. Bylund, D.B., Eikenberg, D.C., Hieble, J.P., Langer S.Z., Lefkowitz, R.J., Minneman,

K.P. et al.: International Union of Pharmacology nomenclature of adrenoceptors. Pharmacol Rev, **46:** 121, 1994

3. Michelotti, G.A., Price, D.T., and Schwinn, D.A.: Alpha1-adrenergic receptor regulation: basic science and clinical implications. Pharmacol Ther, **88**: 281, 2000

4. Malloy, B. J., Price, D. T., Price, R. R., Bienstock, A. M., Dole, M. K., Funk, B. L., et al.: Alpha$_1$-adrenergic receptor subtypes in human detrusor. J Urol, **160:** 937, 1998

5. Hampel, C., Dolber, P.C., Smith, M.P., Savic, S.L., Th roff, J.W., Thor, K.B. et al.: Modulation of bladder alpha1-adrenergic receptor subtype expression by bladder outlet obstruction. J Urol, **167:** 1513, 2002

6. Smith, M.S., Schambra, U.B., Wilson K.H., Page, S.O. and Schwinn, D.A.: Alpha1-adrenergic receptors in human spinal cord: specific localized expression on mRNA encoding α_1-adrenergic receptor subtypes at four distinct levels. Brain Res Mol Brain Res, **63**: 254, 1999

7. Nomiya, M. and Yamaguchi, O.: A quantitative analysis of mRNA expression of α1 and α-adrenoceptor subtypes and their functional roles in human normal and obstructed bladders. J Urol, **170 (2 Pt 1):** 649, 2003

8. Chen, Q., Takahashi, S., Zhong, S., Hosoda, C., Zheng, H.-I., Ogushi, T., et al: Function of the lower urinary tract in mice lacking α_{1d}-adrenoceptor. J Urol, **174**: 370, 2005

9. Andersson K.E.: Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. Pharmacol Rev, **45**: 253, 1993

10. Borda, E., Contreras-Ortiz, N., Gutnisky, R. and Gimeno, M.F.: In vitro effect of

acetylcholine and bethanechol on the contractions of the human detrusor muscle. Influence of prostaglandins. Arch Int Pharmacodyn Ther, **259**: 31, 1982

11. Maggi, C.A., Giuliani, S., Conte, B., Furio, M., Santicioli, P., Meli, P. et al: Prostanoids modulate reflex micturition by acting through capsaicin-sensitive afferents. Eur J Pharmacol, **145**: 105, 1988
12. Schussler, B.: Comparison of the mode of action of prostaglandin E_2 (PGE_2) and sulprostone, a PGE_2-derivative, on the lower urinary tract in healthy women. A urodynamic study. Urol Res, **18**: 349, 1990
13. Ishizuka, O., Mattiasson, A., Andersson, K.E.: Prostaglandin E_2-induced bladder hyperactivity in normal, conscious rats: involvement of tachykinins? J Urol, **153**: 2034, 1995
14. Park, J.M.,Yang, T., Arend, L.J., Schnermann, J.B., Peters, C.A., Freeman, M.R. et al: Obstruction stimulates COX-2 expression in bladder smooth muscle cells via increased mechanical stretch. Am J Physiol, **276**: F129, 1999
15. Schröder, A., Newgreen, D., Andersson, K.E.: Detrusor responses to prostaglandin E_2 and bladder outlet obstruction in wild-type and EP1 receptor knockout mice. J Urol, **172**: 1166, 2004
16. Richardson, C.D., Donatucci, C.F., Page, S.O., Wilson, K.H. and Schwinn, D.A.: Pharmacology of tamsulosin: saturation-binding isotherms and competition analysis using cloned alpha 1-adrenergic receptor subtypes. Prostate, **33**: 55, 1997
17. Jung, S.Y., Fraser, M.O., Ozawa, H., Yokoyama, O., Yoshiyama, M., de Groat, W.C., Chancellor, M.B.: Urethral afferent nerve activity affects the micturition reflex;

implication for the relationship between stress incontinence and detrusor instability. J Urol, **162**:204, 1999

18. Yokoyama, O., Nagano, K., Kawaguchi, K., Ueki, O., Ohkawa, M.: The influence of prostatic urethral anesthesia in overactive detrusor in patients with benign prostatic hyperplasia. J Urol **151**, 1554, 1994
19. Kiruluta, H.G., Downie, J.W. and Awad, S.A.: The continence mechanisms: the effect of bladder filling on the urethra. Invest Urol, **18**: 460, 1981
20. Su, H.C., Wharton, J., Polak, J.M., Mulderry, P.K., Ghatei, M.A., Gibson, S.J., et al: CGRP immunoreactivity in afferent neurons supplying the urinary tract: combined retrograde tracing and immunohistochemistry. Neuroscience, **18**: 727, 1986

FIGURE LEGENDS

Figure 1. Simultaneous recordings of isovolumetric bladder and urethral perfusion pressure before (A) and 10 min after (B) intravesical administration of prostaglandin (PG)E_2. Intravesical PGE_2 facilitated rhythmic bladder contraction and gradually increased voiding threshold pressure. BCI: Bladder Contraction Interval, BCP: Bladder Contraction Pressure, BCD Bladder Contraction Duration.

Figure 2. Simultaneous recordings of isovolumetric bladder and urethral perfusion pressure before (A) and 10 min after (B) continuous intraurethral administration of PGE_2. Intraurethral PGE_2 facilitated rhythmic bladder contraction but did not increase voiding threshold pressure.

Figure 3. Effects of intravenous tamsulosin ($2.2 \times 10^{-1} - 2.2 \times 10^{3}$ nM/kg) on bladder

contraction interval (BCI) in urethane-anesthetized rats. Intraurethral and intravesical administration of PGE_2 significantly reduced BCI (circles and triangles, respectively). BCI values after intravesical or intraurethral administration of PGE_2 are expressed as 0%. Increases in BCI were recognized at increasing doses of tamsulosin in rats receiving intraurethral PGE_2, whereas no change was seen in rats receiving intravesical PGE_2. Single asterisk indicates $p < 0.05$ vs rats receiving intravesical PGE_2. No change in BCI was seen with increasing doses of tamsulosin in rats not receiving PGE_2 (squares).

Figure 4. Effect of intravenous tamsulosin (2.2 nM/kg) on simultaneous recordings of isovolumetric bladder and urethral perfusion pressure bladder contraction interval in urethane-anesthetized rats receiving intraurethral administration of PGE_2. Note that tamsulosin increased bladder contraction interval.

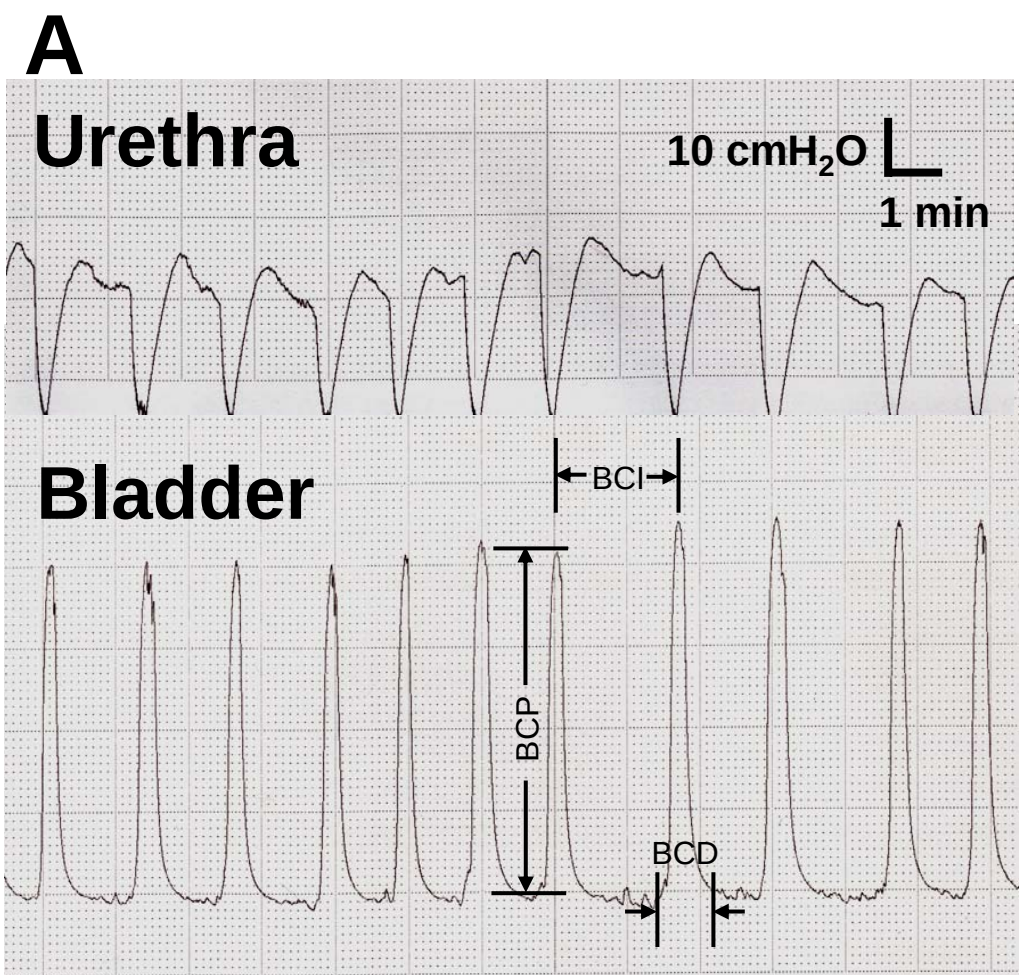
Figure 5. Effect of a high dose (2.2×10^3 nM/kg) of intravenous tamsulosin on simultaneous recordings of isovolumetric bladder and urethral perfusion pressure in urethane-anesthetized rats receiving intravesical administration of PGE_2 (A). Note that tamsulosin slightly increased bladder contraction interval (BCI). Intravenous administration of ONO-8711 increased BCI at a dose of 1 mg/kg (B).

Figure 6. Effect of intravenous tamsulosin (2.2×10^{-1} – 2.2×10^3 nM/kg) on bladder contraction pressure (BCP) in urethane-anesthetized rats. Intraurethral and intravesical administration of PGE_2 significantly reduced BCP (circles and triangles, respectively). BCP values after intravesical or intraurethral administration of PGE_2 was expressed as 0%. In rats not receiving PGE_2 (squares) BCP values before administration of

tamsulosin are expressed as 0%. Decreases in BCP were seen with a high dose (2.2 x 10^3 nM/kg) of tamsulosin in rats receiving intraurethral PGE_2 and in rats not receiving PGE_2. Single asterisk indicates $p < 0.05$ vs before administration of tamsulosin.

Figure 7. Effect of intravenous tamsulosin (2.2 x 10^{-1} – 2.2 x 10^3 nM/kg) on bladder contraction duration (BCD) in urethane-anesthetized rats. Intraurethral and intravesical administration of PGE_2 significantly reduced BCD (circles and triangles, respectively). BCD values after intravesical or intraurethral administration of PGE_2 are expressed as 0%. BCD values before administration of tamsulosin are expressed as 0% in rats not receiving PGE_2 (squares). No changes were found in the three treatment groups.

Fig. 1



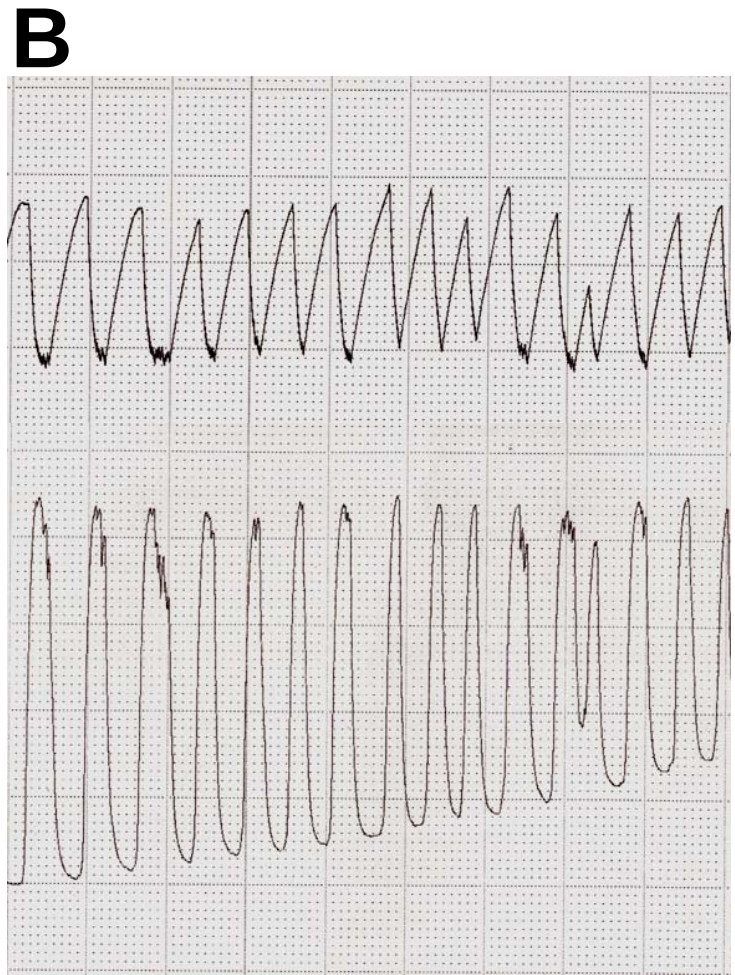


Fig. 2

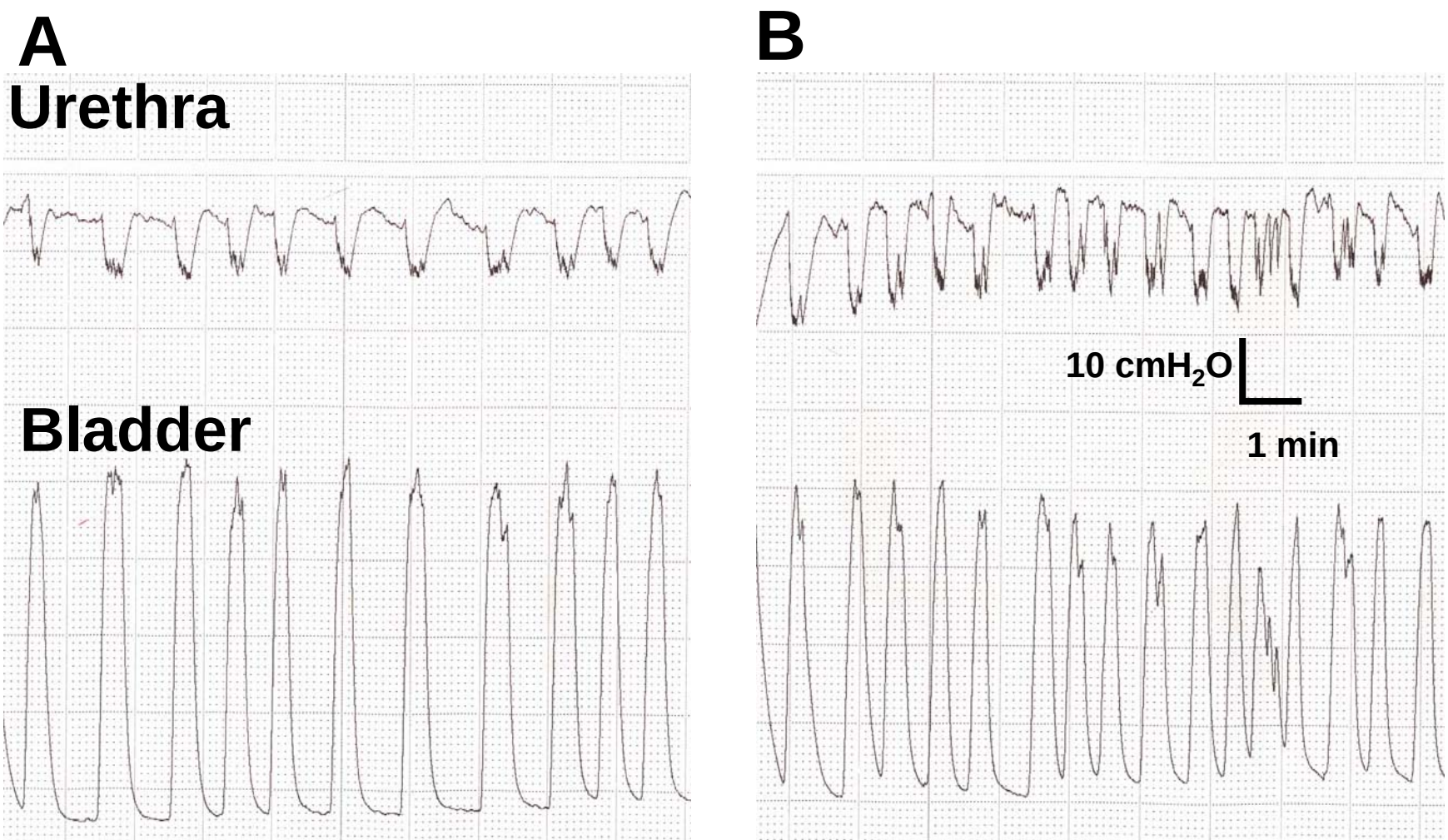


Fig. 3

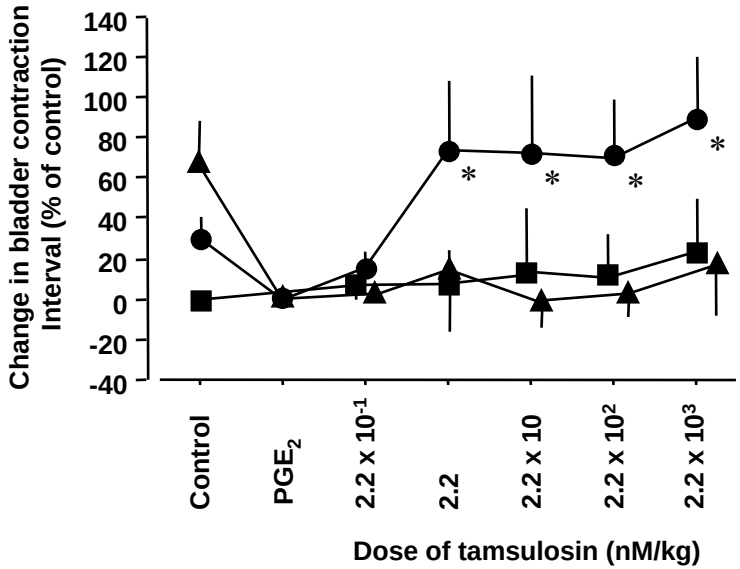

Change in bladder contraction
Interval (% of control)
140
120
100
80
60
40
20
0
-20
-40
*
*
*
*
Control
PGE2
2.2 x 10-1
2.2
2.2 x 10
2.2 x 102
2.2 x 103
Dose of tamsulosin (nM/kg)

Fig. 4

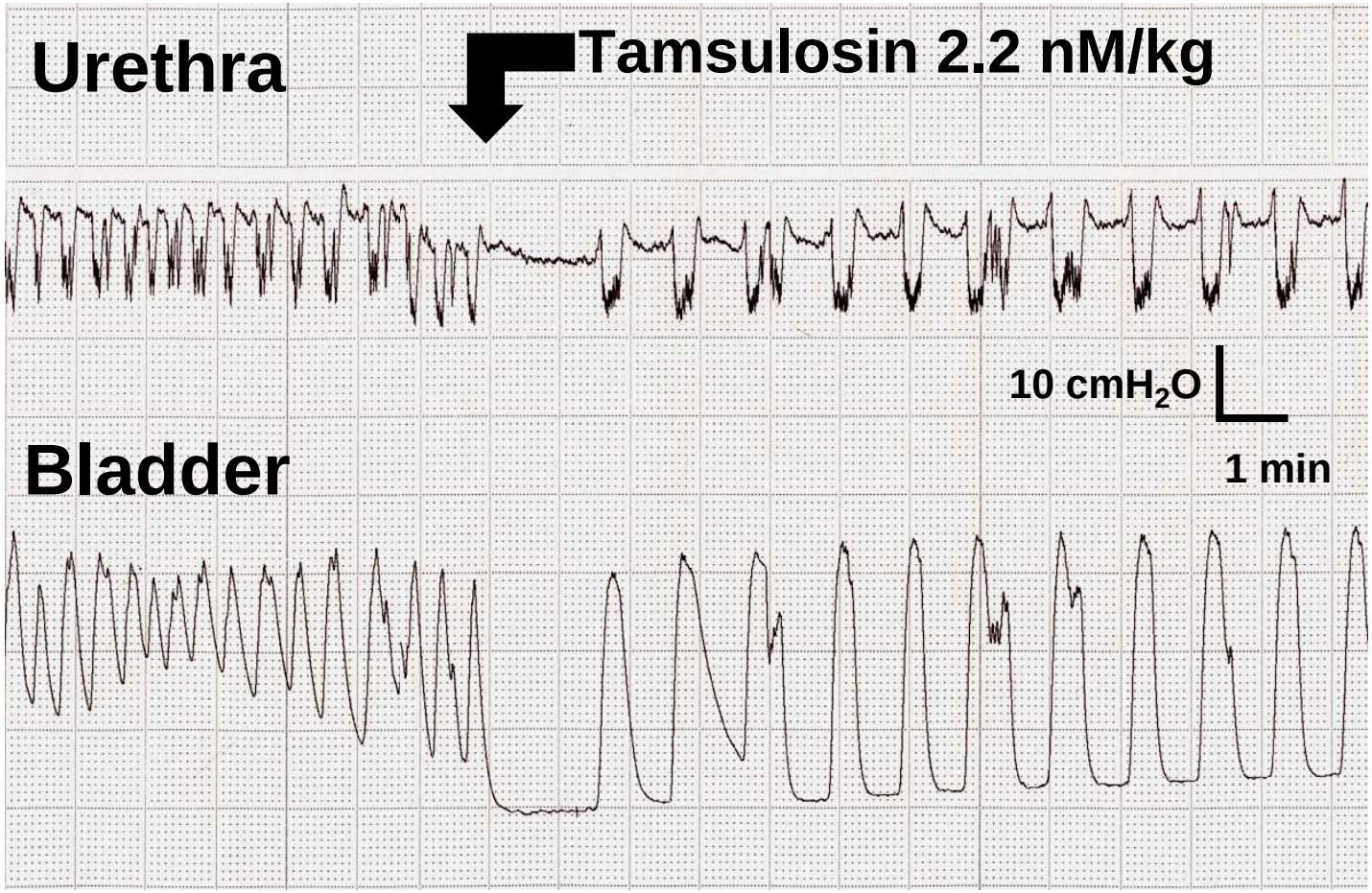


Fig. 5

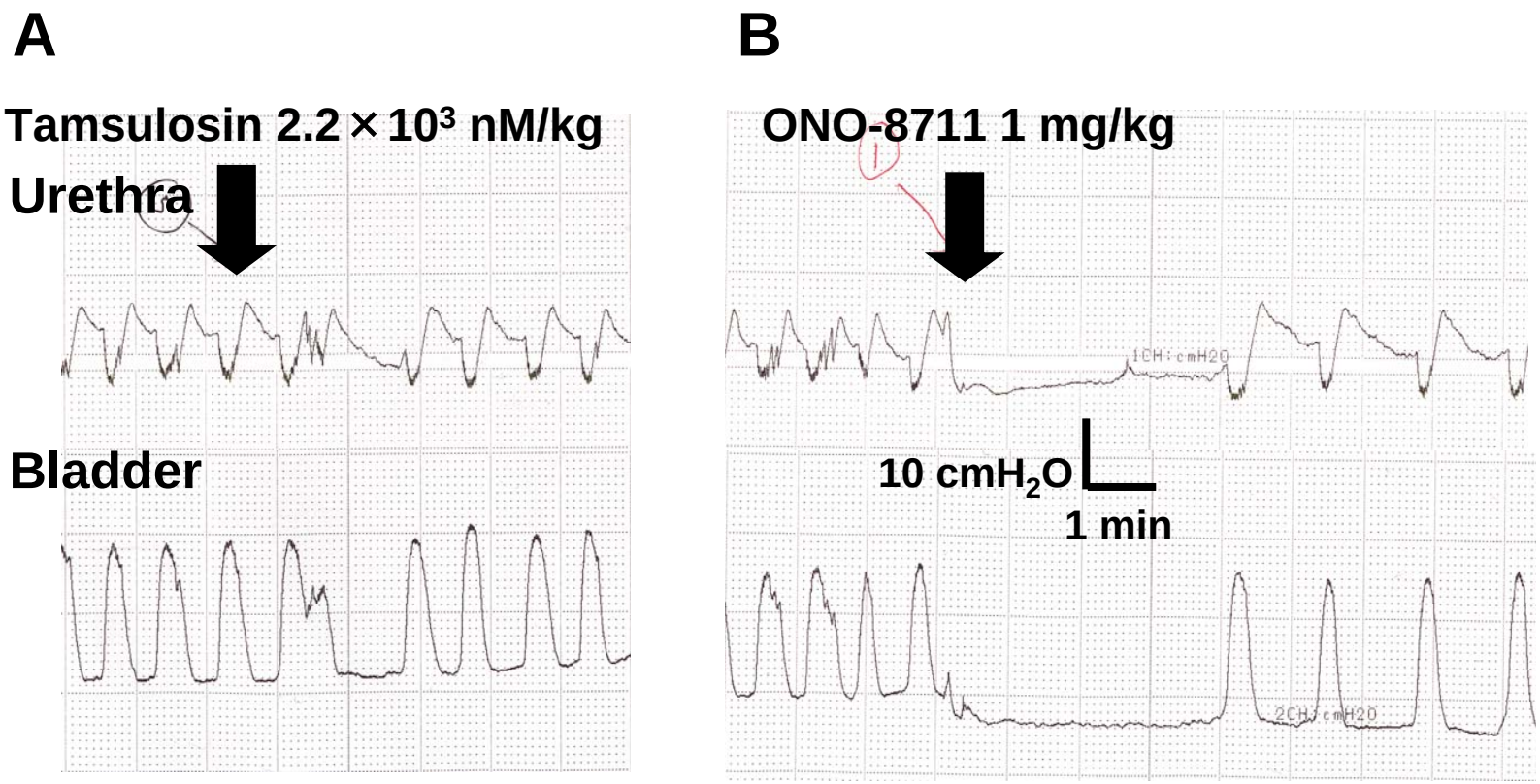

A
Tamsulosin 2.2×10³ nM/kg
Urethra
Bladder
B
ONO-8711 1 mg/kg
10 cmH2O
1 min

Fig. 6

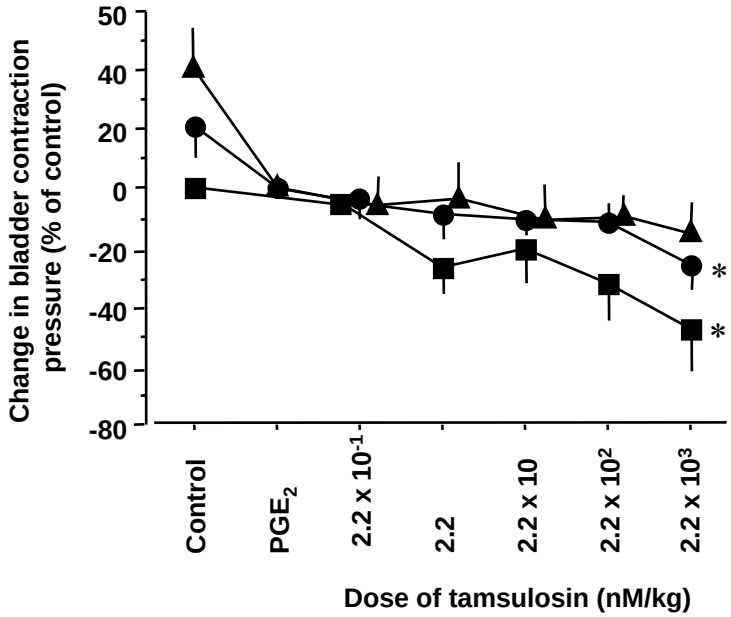
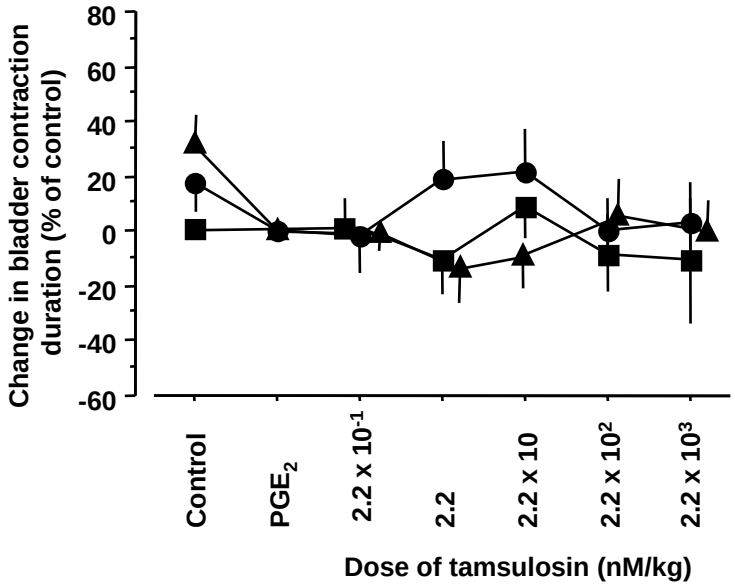

Change in bladder contraction pressure (% of control)
50
40
20
0
-20
-40
-60
-80
*
*
Control
PGE2
2.2 x 10-1
2.2
2.2 x 10
2.2 x 102
2.2 x 103
Dose of tamsulosin (nM/kg)

Fig. 7


Change in bladder contraction duration (% of control)
80
60
40
20
0
-20
-40
-60
Control
PGE2
2.2 x 10-1
2.2
2.2 x 10
2.2 x 102
2.2 x 103
Dose of tamsulosin (nM/kg)