Antimuscarinic Drug Inhibits Detrusor Overactivity Induced by Topical Application of Prostaglandin E2 to the Urethra With a Decrease in Urethral Pressure

ANTIMUSCARINIC DRUG INHIBITS DETRUSOR OVERACTIVITY INDUCED BY TOPICAL APPLICATION OF PROSTAGLANDIN E_2 TO THE URETHRA WITH A REDUCTION IN URETHRAL PRESSURE

OSAMU YOKOYAMA, YOSHIJI MIWA, NOBUYUKI OYAMA, YOSHITAKA AOKI, HIDEAKI ITO, AND HIRONOBU AKINO

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

Running head: antimuscarinic drug and urethra

Key words: antimuscarinic, urethra, detrusor overactivity, prostaglandin

Corresponding author:

Osamu Yokoyama

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

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

TEL +81-776-61-8396, FAX +81-776-61-8126

E-mail: oyoko@u-fukui.ac.jp

ABSTRACT

Purpose: Antimuscarinic drugs increase bladder capacity without prominent side effects such as urinary retention even when administered to patients with mild to moderate BOO. Some mechanisms might exist in the urethra to compensate for the emptying function of the detrusor after administration of antimuscarinic drugs. We investigated the influences of an antimuscarinic drug, propiverine, on urethral function.

Materials and Methods: Urethral pressure and rhythmic bladder pressure were simultaneously monitored in urethane-anesthetized female Sprague-Dawley rats. PGE_2 was continuously administered intravesically or intraurethrally to induce detrusor overactivity. Next, to eliminate the influence of bladder activity and to monitor urethral baseline pressure, isovolumetric pressure of the urethra was recorded after cystectomy and ligation of the external urethral meatus. Furthermore, the in vitro contractile responses of the urethral circular smooth muscle to field stimulation were examined in the presence of propiverine, tamsulosin, verapamil, ω-conotoxin, and atropine.

Results: The intravesical or intraurethral administration of PGE_2 significantly decreased bladder contraction interval (BCI) by 10.7% and 36.0%, respectively. The intraarterial administration of $2x10^2$ nM/kg propiverine significantly increased BCI in rats receiving intraurethral PGE_2 by 81.8%, but had no marked effect on rats receiving intravesical PGE_2. Significant decreases in urethral baseline pressure were found after propiverine administration. Field stimulation-induced contraction was inhibited by propiverine and verapamil, but not by tamsulosin, ω-conotoxin or atropine.

Conclusions: These results suggest that inhibitory effects of propiverine are more

prominent in rats with detrusor overactivity induced by intraurethral PGE_2 than those by intravesical PGE_2. Propiverine may compensate for detrusor function by decreasing urethral resistance in the voiding phase.

INTRODUCTION

The efficacy of the systemic administration of antimuscarinic drugs to decrease the symptoms of the overactive bladder is well documented, and thought to be mainly due to their pronounced effects on the muscarinic receptors of the detrusor muscle. However, antimuscarinic drugs increase bladder capacity without prominent side effects such as urinary retention when administered to women or even to men with OAB and BOO.[1] Some mechanisms might exist in the urethra to compensate for the emptying dysfunction of the detrusor after the administration of antimuscarinic drugs.

It has been shown that the innervation by fibers containing acetylcholinesterase is extensive in the normal human prostate gland.[2,3] This cholinergic innervation has been reported to innervate only the smooth muscle surrounding the ducts and acini of the normal human prostate or both its glandular and stromal tissues.[4,5] The location of these fibers suggests a role for acetylcholine in both contractility and secretion in the prostate gland. Acetylcholine caused contraction of prostatic smooth muscle from rabbits, pigs, rats, and guinea-pigs, but the response was less than that to α–adrenoceptor agonists.[6,7] Atropine has been reported to reduce contractions induced by field stimulation of nerves in prostate tissue isolated from guinea-pigs and rabbits.[6,7] Therefore, antimuscarinic drugs have the possibility to reduce urethral resistance by decreasing prostate muscle

tonus. This may be the underlying mechanism in men to compensate for incomplete emptying after the administration of antimuscarinic drugs. Nevertheless, no reports could be found addressing the influences of antimuscarinic drugs on the urethral smooth muscle, especially in women.

Antimuscarinic drugs act mainly during the storage phase, allowing an increase of the bladder capacity and decreasing urgency; therefore, they exert an inhibitory effect on bladder afferent nerves. We previously reported that a low dose of tolterodine, an antimuscarinic drug, exerted an inhibitory effect on C-fiber bladder afferents, improving bladder capacity in rats with cerebral infarction.[8] However, DO can be induced by both bladder and urethral stimulation. Previous studies in rats have demonstrated that the intravesical or intraurethral administration of PGE_2 resulted in detrusor overactivity.[9] If antimuscarinic drugs can act on the urethra, could the inhibitory effect on C-fiber afferents be dependent on the urethra? To determine whether antimuscarinic drugs can act on the C-fiber afferents within the bladder or urethral wall, it is necessary to compare the effect of the drug on DO induced by stimulation of the bladder wall with that induced by stimulation of the urethral wall. We studied the influence of intraarterial propiverine, an antimuscarinic drug, on DO induced by the intravesical or intraurethral administration of PGE_2.

MATERIALS AND METHODS

A total of forty female Sprague-Dawley rats weighing 215-258 g (mean = 235 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 RTX (0.3 mg/kg) 2 days prior to the 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 the 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.[9] The cone-shaped plug was fashioned from an 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.

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 two parameters, BCI and BCP were obtained from the micturition reflex measurements (fig. 1).

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). The effects of propiverine hydrochloride (Taiho Pharm Co., Ltd., Tokyo, Japan) on the intravesical or intraurethral PGE_2-stimulated micturition reflex were investigated at intraarterial doses of $2x10^2$ or $2x10^3$ nM/kg.

Urethral pressure measurement

To eliminate the influence of bladder activity and to monitor urethral baseline pressure, the isovolumetric pressure of the urethra was recorded after cystectomy and ligation of the external urethral meatus. The effects of propiverine (2x10 to $2x10^3$ nM/kg) on urethral baseline pressure were compared between the urethra filled with

PGE_2 or 0.1 M phosphate buffer (vehicle).

In vitro functional study

Circular smooth muscle strips were prepared from the middle part of the urethra. The urethra was cut into transverse circular preparations (width 1.5 mm, length 4 mm). Each segmental preparation was suspended vertically in an organ bath containing Krebs solution of the following composition (mmol/L); NaCl 111, KCl 5.90, $CaCl_2$ 2.50, $MgCl_2$ 1.20, NaH_2PO_4 1.20, $NaHCO_3$ 25.0, and Glucose 11.5. The Krebs solution was continuously bubbled with a mixture of 95% O_2 and 5% CO_2 at 37C, resulting in a pH of 7.4. The preparations were suspended between two L-formed hooks. One of the hooks was connected to a movable unit allowing adjustment of tension of 0.5 gm. Changes in muscle tension were measured by an isometric transducer (TB-612T, Nihon-Kohden Co., Ltd., Tokyo, Japan). Transmural EFS was performed by a field stimulator (SEN-7203, Nihon-Kohden Co., Ltd.) delivering square wave pulses of supramaximal voltage and 0.5 msec. duration at a frequency of 50 Hz in 3 sec. trains at 2 min. intervals. In order to study relaxant responses, the preparations were precontracted with the EFS. The contractile responses of the urethral circular smooth muscle to EFS were examined in the presence of propiverine, tamsulosin (α_1-blocker; Taiho Pharm Co., Ltd., Tokyo, Japan), verapamil (an inhibitor of L-type voltage-operated calcium channels; Sigma, St. Louis), ω-conotoxin (an inhibitor of N-type voltage-operated calcium channels; Sigma, St. Louis), and atropine (Sigma, St. Louis). Relaxant responses were expressed as a percentage of the response obtained before application of the test drug. When the test drug reduced the contraction, the

percentage inhibitory ratio was calculated. The negative logarithm of the drug concentration eliciting half maximum inhibition (IC_{50}) was determined by linear regression analysis.

Data analysis

Data are expressed as the mean ± standard error of the mean (SEM). Statistical comparisons were performed using one- or two-way 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

BCI was markedly reduced after the intravesical or intraurethral administration of PGE_2 in non-RTX rats (fig. 1), but was unchanged in RTX rats. The intravesical and intraurethral administration of PGE_2 decreased the BCI by 10.7% and 36.0%, respectively, with these ratios expressed as 0% in fig. 2 as baseline ratios for the next experiment. The bladder contraction pressure was not changed before and after the intravesical or intraurethral administration of PGE_2.

Effects of intraarterial propiverine on PGE_2-stimulated micturition reflex

The intraarterial administration of $2x10^2$ nM/kg propiverine significantly increased BCI in rats receiving intraurethral PGE_2 by 81.8% ($p < 0.05$ vs control), but had no marked effects on rats receiving intravesical PGE_2 (39.5%) or on rats receiving intraurethral 0.1 M phosphate buffer (30.0%)(fig. 2). A significant difference was found

in the changes in BCI between the rats receiving intraurethral and intravesical PGE_2 ($p < 0.05$). Propiverine significantly increased BCI at dose $2x10^3$ nM/kg in both the rats receiving intraurethral and intravesical PGE_2, whereas it had no effect on the rats receiving intraurethral 0.1 M phosphate buffer. Significant differences were found in the changes in BCI between the rats receiving intraurethral PGE_2 and those receiving intraurethral 0.1 M phosphate buffer, and between the rats receiving intravesical PGE_2 and those receiving intraurethral 0.1 M phosphate buffer (both; $p < 0.05$). Significant decreases in bladder contraction pressure were found after $2x10^3$ nM/kg propiverine administration in the three treatment groups ($p < 0.05$-0.01).

Effects of intraarterial propiverine on urethral baseline pressure

Urethral baseline pressure was compared between the urethra filled with PGE_2 and 0.1 M phosphate buffer (vehicle). A slight but significant decrease in urethral baseline pressure was found after $2x10^3$ nM/kg propiverine administration ($p < 0.05$, fig 3).

In vitro functional study

EFS induced contractions in the urethral circular smooth muscle at resting tension. A small tetorodotoxin ($1x10^{-6}$ mol/L) abolished EFS-induced contraction. These contractions were significantly inhibited by propiverine (IC_{50} = 1.16 x 10^{-5} ml/L) and verapamil (IC_{50} = 1.43 x 10^{-5} ml/L), but not by tamsulosin, atropine or ω-conotoxin.

DISCUSSION

The data in the present study showed that the intraarterial administration of propiverine was found to have an inhibitory effect on detrusor overactivity when the

micturition reflex was overdriven by intravesical or intraurethral PGE_2. The inhibitory effects of propiverine were more prominent in rats with detrusor overactivity induced by intraurethral PGE_2 than those induced by intravesical PGE_2. The effects of propiverine were accompanied by a decrease in urethral baseline pressure, which presumably depends on the calcium channel blocking effect of propiverine. These results support the hypothesis that propiverine improves detrusor overactivity by inhibition of bladder and urethral afferents.

Studies in rats and humans have demonstrated that the intravesical administration of PGE_2 results in detrusor overactivity.[10,11] 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. The excitatory influences of PGE_2 on the micturition reflex are attributable to the stimulation of C-fiber afferent nerves via the EP1 receptor.[9] In a previous study using the same model as the present one, the excitatory effects on the micturition reflex produced by the intravesical administration of PGE_2 were also seen in rats receiving intraurethral administration, but not in RTX-treated rats. The mechanism of these overactivities is unknown, but may be initiated by a PGE_2–mediated increase in bladder or urethral C-fiber afferent activity.[9] Pharmacological activation of urethral afferent nerves by intraurethral capsaicin elicited a biphasic change in micturition reflex,[12] initially decreasing bladder contraction interval within minutes, followed 15 to 30 min later by complete micturition reflex blockage. Barrington's second reflex, urethral detrusor facilitative reflex, is believed to exist in this animal model. In the present study, propiverine had an inhibitory effect on the intraurethral or intravesical

PGE_2-stimulated micturition reflex. These results have led us to hypothesize that propiverine exerts an inhibitory effect on C-fiber afferent nerves in the bladder and urethra. An antimuscarinic drug, tolterodine, has also been proven to improve detrusor overactivity caused by cerebral infarction through inhibition of the C-fiber bladder afferents.[8] Propiverine had the same inhibitory effects on detrusor overactivity in rats with cerebral infarction (unpublished data). Therefore, the underlying mechanism by which propiverine suppresses C-fiber urethral afferents remains to be clarified.

It has been reported that the longitudinal smooth muscle layer of the female urethra is continuous with the longitudinal layer of the detrusor, implying a possible role in bladder neck opening and urethral shortening at the onset of voiding.[12] The circular layer of the urethra is not continuous with the detrusor. It was suggested to be important for maintaining urethral closure and to be less sensitive to acetylcholine.[13] The circular muscles of the human urethra have been reported to show a minimum or no response to muscarinic stimulation in vitro.[14] Creed and Tulloch found that the increase in urethral pressure induced by pelvic nerve stimulation was resistant to α_1-blocker and to atropine.[15] Non-adrenergic and non-cholinergic contractions have been revealed in response to electrical stimulation of urethra isolated from rabbit, pig, and man, however, in the dog urethra an adrenergic contractions have been demonstrated.[16] In the present study of the rat urethra contraction response of the circular muscle to EFS was not inhibited by atropine or tamsulosin, meaning non-adrenergic and non-cholinergic contractions. Further studies are necessary to confirm whether the contraction depends on purinergic transmission or not. Furthermore, the contraction response to EFS was

not suppressed by ω-conotoxin (an inhibitor of N-type voltage-operated calcium channels), but was inhibited by propiverine and verapamil (an inhibitor of L-type voltage-operated calcium channels). The fact that, in the present study, propiverine inhibited the EFS-induced contractions of the circular muscle of the rat urethra may be explained by the blocking effect on the L-type voltage-operated calcium channel.

Functionally, both propiverine and oxybutynin have been shown to be modulators of voltage-operated calcium channels.[17] In addition to being a muscarinic receptor antagonist, propiverine has been reported to have an inhibitory effect on the L-type voltage-operated calcium channel.[18] The effects of propiverine on the intraurethral PGE_2-stimulated micturition reflex were considered to also be attributable to the action as an inhibitor of L-type voltage-operated calcium channels rather than to inhibition of the muscarinic receptor. In vivo and in vitro present studies revealed that propiverine had an inhibitory influence on urethral baseline pressure by the relaxant effect on the circular muscle of the urethra, and that the micturition reflex was then improved, when it had been overdriven by intraurethral PGE_2. Taken together, these findings suggest that propiverine exerts an inhibitory effect on C-fiber urethral afferent nerves by decreasing urethral tonus and thereby improving storage symptoms. However, using urethane-treated animal increases the risk that effects of antimuscarinic drug will be masked by urethane anesthesia, since antimuscarinic drug influences the bladder or urethral afferent nerve activity.[8] In order to really confirm C-fiber urethral afferent nerves, it is ideally necessary to record the activity from identified C-fibers.

Antimuscarinic drugs are widely used to treat OAB symptoms, but the potential role

of antimuscarinic drugs for LUTS secondary to BPH has not been explored extensively. The development of therapies for male LUTS avoid urinary retention, for which patients with BPH are at high risk.[19] Nevertheless, there are some reports suggesting that the inhibitory effect of antimuscarinic drugs on detrusor muscle contraction is unlikely to aggravate voiding dysfunction in men with OAB symptoms and possible BOO.[1,20] Although improvement in the urinary flow rate and a decrease in post-void residual volume were found, the underlying mechanisms to improve voiding dysfunction were not completely explained.[19] An antimuscarinic drug, atropine, reduces contractions induced by the field stimulation of nerves in prostate tissue isolated from guinea-pigs and rabbits.[6,7] An antimuscarinic drug, propiverine, has an effect on the L-type voltage-operated calcium channel, and may compensate for detrusor dysfunction by decreasing urethral resistance in the voiding phase. Antimuscarinic drugs have the possibility to reduce urethral resistance by decreasing prostatic and urethral muscle tonus. This is a hypothesis worthy of further study.

CONCLUSIONS: The data in the present study suggest that at a low dose, propiverine exerts a relaxant effect on the urethral smooth muscle, thereby improving detrusor overactivity caused by intraurethral PGE_2. Furthermore, this effect might diminish incomplete emptying by decreasing urethral resistance in patients with BOO.

REFERENCES

1. Abrams, P., Kaplan, S., De Koning Gans, H.J., Millard, R: Safety and tolerability of

tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. J Urol, **175**: 999, 2006

2. Dunzendorfer, U., Jonas, D., Weber, W.: The autonomic innervation of the human prostate. Histochemistry of acetylcholinesterase in the normal and pathologic states. Urol Res, **4**: 29, 1976

3. Chapple, C.R., Crowe, R., Gilpin, S.A., Gosling, J., Burnstock, G.: The innervation of the human prostate gland- the changes associated with benign enlargement. J Urol, **146**: 1637, 1991

4. Vaalasti, A., Hervonen, A.: Autonomic innervation of the human prostate. Invest Urol, **17**: 293, 1980

5. Higgins, J.R., Gosling, J.A.: Studies on the structure and intrinsic innervation of the normal human prostate. Prostate Suppl, **2**: 5, 1989

6. Najbar-Kaszkiel, A.T., Di, Iulio, J.L., Li, C.G., Rand, M.J.: Characterization of excitatory and inhibitory transmitter systems in prostate glands of rats, guinea pigs, rabbits and pigs. Eur J Pharmacol, **337**: 251, 1997

7. Lau, W.A.K., Pennefather, J.N.: Muscarinic receptor subtypes in the rat prostate gland. Eur J Pharmacol, **343**: 151, 1998.

8. Yokoyama, O., Yusup, A., Miwa, Y., Oyama, N., Aoki, Y., Akino, H.: Effects of tolterodine on an overactive bladder depend on suppression of C-fiber bladder afferent activity in rats. J Urol, **174**: 2032, 2005

9. Yokoyama, O., Yusup, A., Oyama, N., Aoki, Y., Miwa, Y., Akino, H.: Improvement in bladder storage function by tamsulosin depends on suppression of C-fiber urethral

afferent activity in rats. J Urol, **177**: 771, 2007

10. 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
11. 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
12. 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
13. Dass, N., McMurray, G., Greenland, J.E., Brading, A.F.: Morphological aspects of the female pig bladder neck and urethra: quantitative analysis using computer assisted 3-dimensional reconstructions. J Urol, **165**: 1294, 2001
14. Yamanishi, T., Chapple, C.R., Yasuda, K., Yoshida, K., Chess-Williams, R.: The role of M2 muscarinic receptor subtypes mediating contraction of the circular and longitudinal smooth muscle of the pig proximal urethra. J Urol, **168**: 308, 2002
15. Ek, A., Alm, P., Andersson, K.-E., Persson, C.G.: Adrenoceptor and cholinoceptor mediated responses of the isolated human urethra. Scand J Urol Nephrol, **11**:97, 1977
16. Creed, K.E., Tulloch, A.G.S.: The effect of pelvic nerve stimulation and some drugs

on the urethra and bladder of the dog. Br J Urol, **50**: 398, 1978

17. Hashimoto, S., Kigoshi, S., Muramatsu, I.: Neurogenic responses of urethra isolated from the dog. Eur J Pharmacol **213**: 117, 1992

18. Yono, M., Yoshida, M., Wada, Y., Kikukawa, Y., Takahashi, W., Inadome, A.: Pharmacological effects of tolterodine on human isolated urinary bladder. Eur J Pharmacol, **368**: 223, 1999

19. Wuest, M., Hecht, J., Christ, T., Braeter, M., Schoeberl, C., Hakenberg, O.W., et al: Pharmacodynamics of propiverine and three of its main metabolites on detrusor contraction. Br J Pharmacol, **145**: 608, 2005

20. Kaplan, S.A., Walmsley, K., Te, A.E.: Tolteridone extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol, **174**:2273, 2005

FIGURE REGENDS

Figure 1. 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. Intraarterial administration of $2x10^2$ nM/kg propiverine significantly increased bladder contraction interval (BCI). Bladder contraction pressure; BCP.

Figure 2. Effects of intraarterial propiverine ($2x10^2$, $2x10^3$ nM/kg) on bladder contraction interval (BCI)(A) and bladder contraction pressure (BCP)(B) in

urethane-anesthetized rats. The intravesical and intraurethral administration of PGE2 significantly reduced BCI (circles and squares, respectively). The BCI values after the intravesical or intraurethral administration of PGE_2 are expressed as 0%. Significant increases in BCI were recognized at 2 x 10^2 of propiverine in rats receiving intraurethral PGE_2 when compared to rats receiving intravesical PGE_2. No change in BCI was seen with increasing doses of propiverine in rats not receiving PGE_2 (triangles). * indicates value of $p < 0.05$, for indicated comparison. A high dose of propiverine (2 x 10^3 nM/kg) significantly decreased BCP when compared to the pre-administration value (control). # and ## indicate values of $p < 0.05$ and 0.01, respectively, vs control.

Figure 3. Effect of intraarterial propiverine on urethral baseline pressure in urethane-anesthetized rats with (circles) or without (triangles) the intraurethral administration of PGE_2. Note that propiverine decreased the urethral baseline pressure in rats with an intraurethral administration of PGE_2.. indicates value of $p < 0.05$.

Figure 4. Effects of compounds on the electrical field stimulation (EFS)-induced contraction of the urethral circular smooth muscle. This contraction was abolished by 1 μM tetrodotoxin (open circle). Note that propiverine (circles) and verapamil (triangles) inhibited contractions to EFS, but tamsulosin(inverted triangles), ω-conotoxin (squares) and atropine (diamonds) did not.

Fig. 1

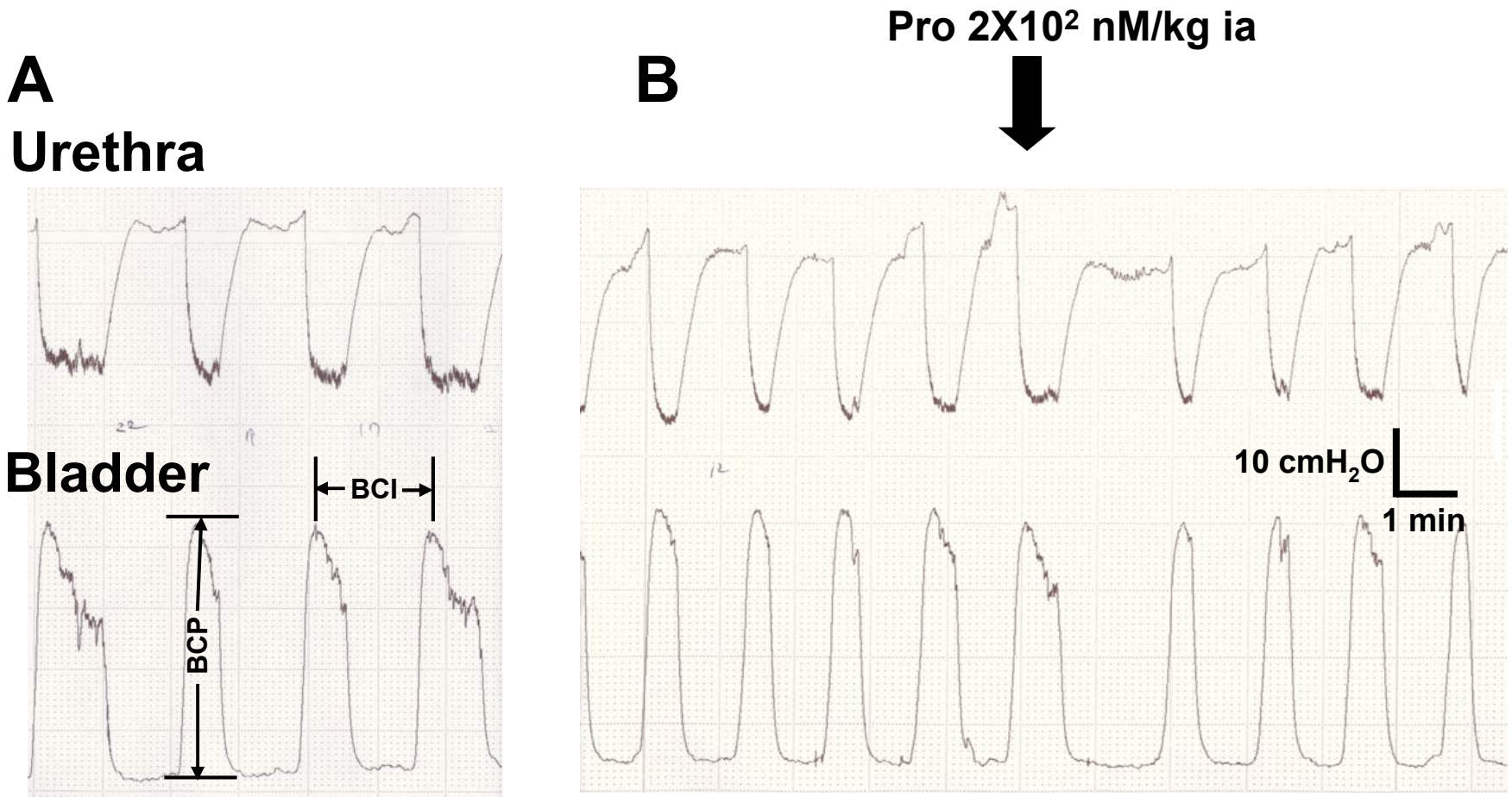


Fig. 2

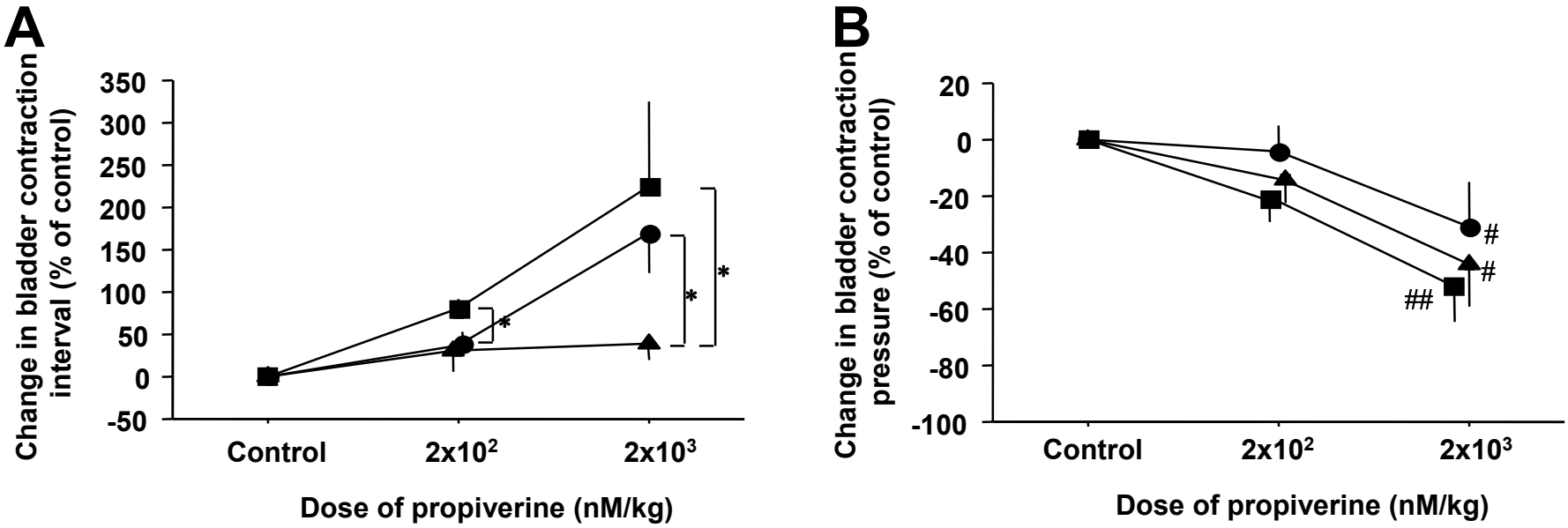

A
Change in bladder contraction interval (% of control)
350
300
250
200
150
100
50
0
-50
Control
2x10²
2x10³
Dose of propiverine (nM/kg)
*
*
*
B
Change in bladder contraction pressure (% of control)
20
0
-20
-40
-60
-80
-100
Control
2x10²
2x10³
Dose of propiverine (nM/kg)
#
#
##

Fig. 3

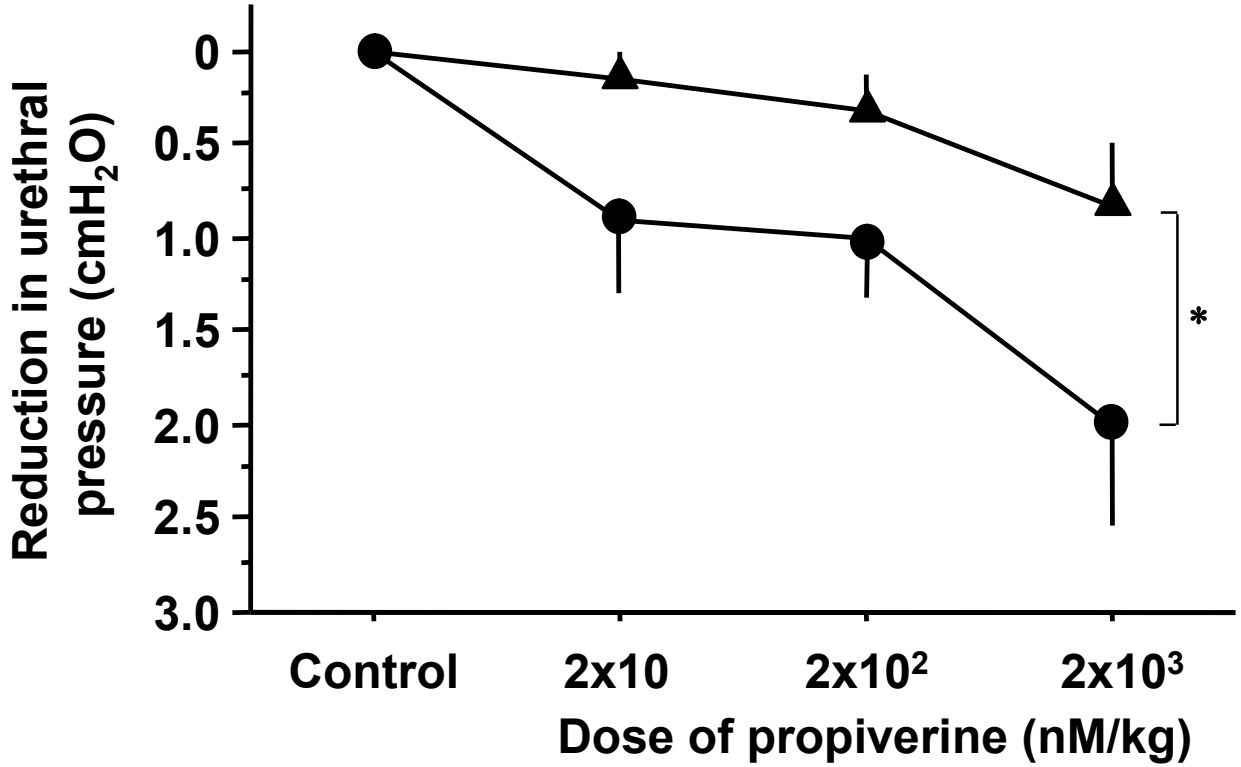
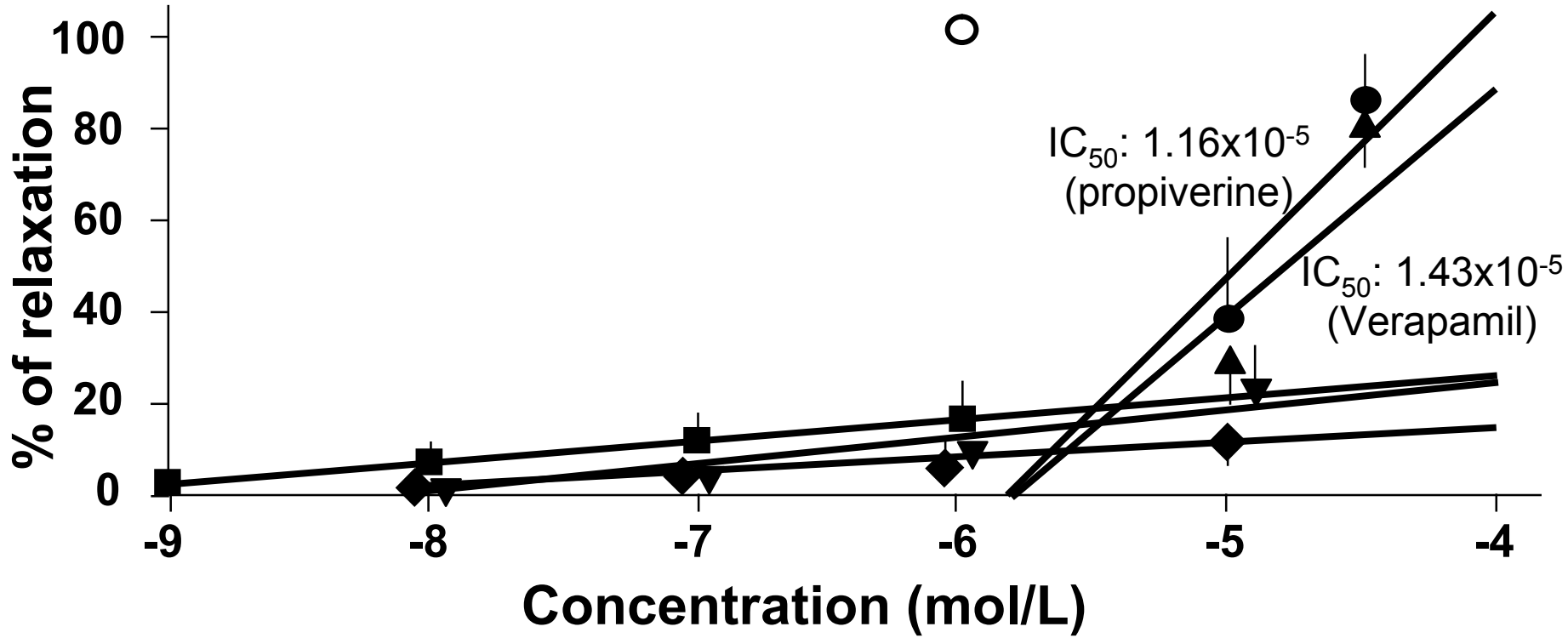

Reduction in urethral pressure (cmH_2O)
0
0.5
1.0
1.5
2.0
2.5
3.0
*
Control
2x10
$2x10^2$
$2x10^3$
Dose of propiverine (nM/kg)

Fig. 4


100
80
60
40
20
0
% of relaxation
-9
-8
-7
-6
-5
-4
Concentration (mol/L)
IC50: 1.16x10-5
(propiverine)
IC50: 1.43x10-5
(Verapamil)