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**Improvement of Bladder Storage Function by α 1-Blocker Depends on the
Suppression of C-fiber Afferent Activity in Rats**

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ABSTRACT

Aim: α 1-blockers improve voiding symptoms through the reduction of prostatic and urethral smooth muscle tone; however, the underlying mechanism of improvement of storage symptoms is not known. Using a rat model of detrusor overactivity caused by cerebral infarction (CI), we undertook the present study to determine whether the effect of an α 1-blocker, naftopidil, is dependent on the suppression of C-fiber afferents.

Methods: To induce desensitization of C-fiber bladder afferents, we injected resiniferatoxin (0.3 mg/kg, RTX) subcutaneously to female Sprague-Dawley rats 2 days prior to left middle cerebral artery occlusion (MCAO) (RTX-CI rats). As controls we used rats without RTX treatment (CI rats). MCAO and insertion of a polyethylene catheter through the bladder dome were performed under halothane anesthesia. We investigated the effects on cystometrography of intravenous, intracerebroventricular, or intrathecal administration of naftopidil in conscious CI rats.

Results: Bladder capacity (BC) was markedly reduced after MCAO in both RTX-CI and CI rats. Intravenous administration of naftopidil significantly increased BC in CI rats without an increase in residual volume, but it had no effects on BC in RTX-CI rats.

Intrathecal administration of naftopidil significantly increased BC in CI but not in RTX-CI rats.

Conclusion: These results suggest that naftopidil has an inhibitory effect on C-fiber afferents in the lumbosacral spinal cord, improving BC during the storage phase.

Abbreviations: CI, cerebral infarction; RTX, resiniferatoxin; MCAO, middle cerebral artery occlusion; BC, bladder capacity; BOO, bladder outlet obstruction; AR, adrenoceptors; i.v., intravenous; i.c.v., intracerebroventricular; i.t., intrathecal; ICA, internal carotid artery

Key words: C-fiber, α 1-blockers, detrusor overactivity, cerebral infarction, rat

INTRODUCTION

The voiding dysfunction accompanying bladder outlet obstruction (BOO) is due to mechanical compression induced by the enlarged prostate and to a dynamic component related to the contraction of the lower urinary tract caused by stimulated activity of the sympathetic nervous system [Shapiro et al., 1995]. The functional importance of α 1-adrenoceptors (α 1-ARs) in the sympathetic nerve terminals of the prostate has been

indicated, and dynamic obstruction has been shown to be mediated by $\alpha 1$ -AR stimulation. $\alpha 1$ -AR blockers are the most frequently prescribed therapeutic agents for elderly patients with voiding and storage symptoms. Currently, $\alpha 1$ -ARs are generally subdivided into $\alpha 1A$ -, $\alpha 1B$ -, and $\alpha 1D$ -AR subtypes [Bylund et al., 1994]. In the prostate gland, for example, the $\alpha 1A$ -AR subtype is predominantly expressed [Price et al., 1993; Yazawa et al., 1993], and contraction of the human prostate in response to $\alpha 1$ -AR stimulation is mediated by this subtype [Marshall et al., 1995]. The $\alpha 1D$ -AR subtype is expressed in the detrusor, peripheral ganglia, and spinal cord in humans and rats [Somogyi et al., 1995; Malloy et al., 1998; Smith et al., 1999; Hampel et al., 2002]. Recently, involvement of the $\alpha 1D$ -AR subtype in the storage symptoms has been indicated by some experimental findings [Hampel et al., 2002; Chen et al., 2005]. $\alpha 1$ -AR blockers with significant affinity for the $\alpha 1D$ -AR subtype are known to improve storage symptoms related to BOO; however, it is not clear why or how these agents relieve the overactive bladder [Sugaya et al., 2002]. $\alpha 1$ -AR blockers act during the storage phase, allowing an increase of the bladder capacity and decreasing urgency; therefore, they may exert an inhibitory effect on afferent nerves.

As an animal model of BOO, the rat with partial urethral obstruction reveals bladder hypertrophy, pre-micturition contraction, and increased bladder capacity [Malmgren et al., 1987; Igawa et al., 1994]. Pre-micturition contractions in the rat are spontaneous detrusor contractions during the storage phase that are not associated with micturition [Igawa et al., 1994]. The incidence of a positive ice water test mediated by C-fiber bladder afferents was significantly higher in subjects with BOO than in nonobstructed subjects [Chai et al., 1998]. These results indicate that increased activity of the afferent limb of the micturition reflex pathway, including C-fiber bladder afferents, is probably responsible for the development of detrusor overactivity in humans. Nevertheless, capsaicin-sensitive C-fiber afferents are not essential to induce pre-micturition contraction in rats with BOO [Tanaka et al., 2003]. Treatment with capsaicin prior to the creation of BOO did not decrease the frequency of pre-micturition contraction in the rat [Tanaka et al., 2003]. Detrusor overactivity in humans is likely to differ from pre-micturition contractions in rats with BOO. Therefore, it is not suitable to evaluate the effect of α 1-AR blockers on detrusor overactivity in the rat model with BOO. The α 1-AR blocker doxazosin did not markedly affect pre-micturition contraction or bladder

capacity [Ishizuka et al., 1996].

A rat model of detrusor overactivity due to cerebral infarction (CI) is widely known as a monitor tool for evaluating the usefulness of agents against bladder overactivity [Yokoyama et al., 1997]. To determine whether an α 1-AR blocker can act on C-fiber afferents, it is necessary to compare the effect of the drug on bladder overactivity between C-fiber-desensitized and C-fiber-normal rats. Using this model, we studied the influence of intravenous (i.v.), intracerebroventricular (i.c.v.), and intrathecal (i.t.) naftopidil [Takei et al., 1999], an α 1A- and α 1D-AR blocker, on detrusor overactivity caused by cerebral infarction in rats with or without pretreatment with RTX.

MATERIALS AND METHODS

Forty-eight female Sprague-Dawley rats, weighing 238-269 g (mean = 249 g), were used in this study. They were housed at a constant temperature ($23 \pm 2^\circ\text{C}$) and humidity (50-60%) under a regular 12-hour light/dark schedule (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. Before the experiment rats were trained to adapt to prolonged restraint.

Pretreatment with resiniferatoxin

To induce desensitization of C-fiber bladder afferents, resiniferatoxin (RTX; 0.3 mg/kg) was injected subcutaneously into female Sprague-Dawley rats 2 days prior to left middle cerebral artery occlusion (MCAO). RTX was dissolved in a vehicle of 10% ethanol and 90% saline. As controls we used rats without injection of RTX.

Cystometrography (CMG) in conscious rats

Surgical anesthesia was induced and maintained using 2% halothane. CMGs in conscious rats were performed according to previously published methods [Yokoyama et al., 1997]. The CMG catheter was passed through a small incision at the apex of the bladder dome. The rats were placed in a restraining cage (Ballman Cage, KN-326 Type 3; Natsume Seisakusho Co., Ltd., Tokyo, Japan) and allowed to recover from halothane anesthesia. The CMG catheter was connected to a pump (TE-311; Terumo Co. Ltd., Tokyo, Japan) for the continuous infusion of saline and to a pressure transducer (TP-200T; Nihon-Kohden Co., Ltd., Tokyo, Japan) by means of a polyethylene T-tube. Cystometric recording was achieved by infusing physiological saline at room

temperature into the bladder at a rate of 0.04 ml per minute and by collecting and measuring the saline voided from the urethral meatus to determine the voided volume. Evacuating the bladder through the cystometry catheter enabled us to measure the residual volume after the micturition reflex. The values of three cystometric parameters (bladder capacity, residual volume, and bladder contraction pressure) were obtained from each cystometry measurement. Bladder capacity was defined as the sum of the voided and residual volumes. Control cystometric recordings were performed 2 hours after surgical implantation of the cystometry catheter.

Induction of cerebral infarction in rats

After control cystometric recordings were made, surgical anesthesia was induced and maintained using 2% halothane. Left MCAO were performed according to previously published methods [Yokoyama et al., 1997].

Drug administration

For i.v. drug administration, the left jugular vein was cannulated (PE-10) immediately after MCA occlusion. Increasing doses of naftopidil ($2.6 \times 10^{-1} \sim 2.6 \times 10^3$ nM/kg) were administered. The dose of 2.6×10 nM/kg is almost equivalent to serum

dose in humans after oral administration of 25 mg naftopidil in pharmacokinetics study [Ohki et al., 1996].

For i.c.v. drug administration, the implantation of an injection tube into the right lateral ventricle was performed immediately after MCA occlusion. The rats were positioned in a stereotaxic frame, a scalp incision was made over the sagittal suture, and a hole (diameter about 1.0 mm) was drilled in the right parietal bone to expose the dural surface 1.0 mm lateral and 0 mm anterior from the bregma. A sterile stainless steel cannula (inside diameter: 0.3 mm, outside diameter: 0.6 mm, length: 10.5 mm) was lowered 5.3 mm ventrally from the skull surface with the end of a micromanipulator. By using a small screw placed in the skull as an anchor, the cannula was fixed to the skull with dental acrylic cement. Intracerebroventricular drug administration (5 μ l/rat) occurred while the rats were conscious.

For i.t. administration, the occipital crest of the skull was exposed and the atlanto-occipital membrane was incised at the midline with the tip of an 18-gauge needle. A catheter (PE-10) was inserted through the slit and passed caudally to the L6 level of the spinal cord. Single 5- μ l volumes of drug solutions were administered. At the

end of the experiment, a laminectomy was performed to verify the location of the cannula tip.

Effects of naftopidil on bladder activity

Two hours after MCAO, the effects of increasing doses of i.v., i.c.v., or i.t. naftopidil on cystometrography were investigated in conscious CI rats. Naftopidil was given to CI rats pretreated with RTX or to CI rats without injection of RTX (RTX-CI and CI rats, respectively) at 1-hour intervals. All rats were placed in a restraining cage.

Data analysis

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

RESULTS

Bladder capacity was markedly reduced 2 hours after MCAO in both RTX-CI and CI rats, and it remained consistently below half of the pre-occlusion capacity (Fig. 1). No significant differences were found in bladder capacity or bladder contraction pressure between RTX-CI and CI rats. No residual volume was recognized in either group.

Effects of i.v. administration of naftopidil

Intravenous naftopidil ($2.6 \times 10^{-1} \sim 2.6 \times 10^3$ nM/kg) significantly increased bladder capacity in CI rats ($p < 0.01$) without any significant change in bladder contraction pressure or increase in residual volume (Fig. 2, 3). However, naftopidil had no effects on bladder capacity in RTX-CI rats (Fig. 3, 4). Significant differences were recognized in changes in bladder capacity between RTX-CI and CI rats ($2.6 \times 10^{-1} \sim 2.6 \times 10^3$ nM/kg; $p < 0.01 \sim 0.05$).

Effects of i.c.v. administration of naftopidil

Intracerebroventricular naftopidil did not elicit detectable changes in bladder capacity or bladder contraction pressure in CI rats (Fig. 5). A high dose (1.3×10 nmol) of naftopidil increased residual volume.

Effects of i.t. administration of naftopidil

Intrathecal naftopidil ($1.3 \times 10^{-3} \sim 1.3 \times 10^{-1}$ nmol) significantly increased bladder capacity in CI rats ($p < 0.01 \sim 0.05$; Fig. 6). A high dose (1.3×10^{-1} nmol) of naftopidil increased residual volume without significance. On the contrary, intrathecal naftopidil did not change any parameters in RTX-CI rats (Fig. 6, 7).

DISCUSSION

The data in the present study showed that intravenous or intrathecal naftopidil enlarged the bladder without decreasing bladder contraction pressure or increasing residual volume in C-fiber-intact CI rats. In contrast, naftopidil did not enlarge the bladder in C-fiber-desensitized CI rats, supporting the hypothesis that this $\alpha 1$ -AR blocker improves detrusor overactivity by inhibition of the C-fiber afferent. This effect might depend on C-fiber afferent effects in the spinal cord rather than in the brain.

The slow development of detrusor overactivity following spinal cord injury is mediated by a reorganization of reflex connections [de Groat et al., 1990]. The afferent limb of the micturition reflex consists of C fibers in chronic spinal cats, which also

seems to be true in humans with spinal cord injury [Geirsson et al., 1995]. In patients with suprapontine lesions, such as those resulting from cerebrovascular accidents, dementia and Parkinson's disease, cortical or diencephalic-mediated timing of the on-off switching mechanism is impaired, leading to detrusor overactivity [Bosch, 1999]. Detrusor overactivity in rats with cerebral infarction may be explained by impairment of this suprapontine regulatory system. C-fiber bladder afferents are not related to the development of detrusor overactivity caused by CI. Therefore, detrusor overactivity was recognized in C-fiber-desensitized rats as well as in C-fiber-intact rats in the present study.

There are a few clinical reports concerning the usefulness of $\alpha 1$ -AR blockers on detrusor overactivity caused by neurological diseases [Jensen, 1981; Swierzewski et al., 1994; Yasuda et al., 1996]. Prazosin, a non-selective $\alpha 1$ -AR blocker, has been reported to be a valuable tool for neurogenic bladder [Jensen, 1981]. This agent diminished uninhibited detrusor contraction and increased bladder capacity. Terazosin has been shown to work to increase bladder capacity in spinal cord injured patients with detrusor overactivity [Swierzewski et al., 1994]. Urapidil has also been shown to be effective for

decreasing detrusor overactivity and daytime urinary frequency [Yasuda et al., 1996]. At present no definitive conclusions can be drawn on the efficacy of $\alpha 1$ -AR blockers in the treatment of neurogenic bladder. The present study provides further basic information about an $\alpha 1$ -AR blocker available for neurogenic storage dysfunction.

The smooth muscle contraction in infravesical part of the human lower urinary tract, and in particular the prostate are mediated largely, if not exclusively, by the $\alpha 1A$ -AR subtype [Price et al., 1993; Yazawa and Honda et al., 1993; Marshall et al., 1995]. However, which subtype is related to storage symptoms and how $\alpha 1$ -AR blockers work to improve detrusor overactivity remain a topic of controversy. In studies with $\alpha 1d$ -knockout mice, the $\alpha 1D$ -AR subtype has been suggested to play a significant role in regulating bladder function and it is likely to contribute to the development of storage symptoms [Chen et al., 2005]. Subtype analysis carried out in men indicated that the $\alpha 1a$ - and $1d$ -AR mRNAs in the detrusor were expressed at a superimposable low density [Sigala et al., 2004]. In the trigone, the most expressed subtype was the $\alpha 1a$ -AR. Studies on human normal and obstructed bladders did not show any differences in term of $\alpha 1$ -AR subtype mRNA expression and function [Nomiya and Yamaguchi et al.,

2003], suggesting that in patients with BOO, the detrusor overactivity involving α 1-ARs could be mediated by extra-bladder localization of these receptors. The α 1d-AR subtype is expressed in the detrusor, peripheral ganglia, and spinal cord in humans and rats [Somogyi et al., 1995; Malloy et al., 1998; Smith et al., 1999; Hampel et al., 2002]. α 1d-AR was the predominant receptor subtype (present at twice the level of the other α 1-AR subtypes) in sacral ventral motor neurons and autonomic parasympathetic pathways [Smith et al., 1999]. Sugaya et al [2002] reported that intrathecal injection of naftopidil, an α 1A- and α 1D-AR blocker (a relatively selective α 1D-AR subtype) transiently abolished isovolumetric bladder contraction, although the interval and amplitude were unchanged after the reappearance of contractions in urethane-anesthetized rats. They suggested that naftopidil blocked the spinal afferent limb of the micturition reflex. The present study also revealed the inhibitory effect of intrathecal naftopidil on the micturition reflex of conscious rats. Bladder contraction pressure did not decrease after a high dose of naftopidil, meaning that this agent could not block descending efferent signal to the lower urinary tract at the level of the lumbosacral cord.

The distribution patterns of mRNA encoding the α 1a-, 1b and 1d-AR subtypes were determined by in situ hybridization in the rat brain [Day et al., 1997]. The expression pattern of α 1a mRNA was found to be widespread throughout the rat central nervous system. Supraspinal α 1-ARs are involved in the control of micturition reflex [Bao et al., 2002]. I.c.v. administration of nonselective or selective α 1A-AR blocker has been reported to produce an inhibitory effect on micturition reflex, whereas α 1B- and 1D-AR blockers have no effect. These findings suggest that central α 1A-AR has an excitatory influence on the bladder activity. In the present study residual volume increased after a high dose of naftopidil, meaning that this agent could suppress micturition reflex at the supraspinal level via α 1A-AR.

Vanilloid (capsaicin) receptors have been reported to exist in the brain stem (sensory nuclei), dorsal horn, dorsal root, and trigeminal and nodose ganglia other than peripheral sensory nerves (C-fiber afferents) [Szallasi et al., 1995]. RTX, which has a structure similar to that of capsaicin and acts as an ultra-potent capsaicin analogue, is highly specific for small-diameter sensory neurons, notably those with C-fibers. A large dose of RTX produces long-lasting but reversible suppression (desensitization) of the

activity of C-fibers. RTX, as well as capsaicin, has been used as a valuable tool to investigate the role of C-fiber afferents in the micturition reflex or nociceptive pathway [Tanaka et al., 2003]. Subcutaneous (systemic) RTX treatment depletes vanilloid-binding sites from the brain stem, spinal cord, and peripheral nerves. Therefore, the inhibitory effect of intravenous naftopidil on the overactive bladder does not necessarily depend on the suppression of C-fiber bladder afferents. However, in the present study intravenous and intrathecal administration of naftopidil improved the detrusor overactivity in CI rats but had no effect on RTX-CI rats, indicating that this $\alpha 1$ -AR blocker improves detrusor overactivity by inhibiting C-fiber-mediated sensory input from the lower urinary tract at the lumbosacral spine. To our knowledge, the possibility that systemic (oral or intravenous) administration of $\alpha 1$ -AR blockers could exert these therapeutic effects via suppression of C-fiber afferents in the spine has never been proven.

CONCLUSIONS

The present study demonstrates that the $\alpha 1$ -AR blocker naftopidil enlarges the

bladder via suppression of C-fiber afferents in the lumbosacral spine. This result may explain the clinical findings that α 1-AR blockers are effective for treating storage symptoms.

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FIGURE LEGENDS

Figure 1. Mean influence \pm SEM of left middle cerebral artery occlusion (MCAO) on bladder capacity in rats without pretreatment (A) or with pretreatment with

resiniferetoxin (B) 2 hours after occlusion. Double asterisks indicate $p < 0.01$ vs. bladder capacity before MCAO.

Figure 2. Representative cystometrogram showing the effects of intravenous administration of naftopidil ($2.6, 2.6 \times 10^2$ nM/kg) in cerebral infarcted rats. The bladder contraction interval decreased after cerebral infarction. Naftopidil increased the bladder contraction interval.

Figure 3. Log dose-response curves of mean effects \pm SEM on bladder capacity (A) and bladder contraction pressure (B), expressed as percent change after intravenous administration of increasing naftopidil doses of 2.6×10^{-1} to 2.6×10^3 nM in 6 cerebral infarcted (CI) rats without pretreatment (squares) or with pretreatment with resiniferetoxin (triangles). Single and double asterisks indicate $p < 0.05$ and $p < 0.01$, respectively, versus CI rats with pretreatment with resiniferetoxin (triangles).

Figure 4. Representative cystometrogram showing the effects of intravenous administration of naftopidil ($2.6, 2.6 \times 10^2$ nM/kg) in cerebral infarcted rats pretreated with resiniferetoxin. The bladder contraction interval decreased after cerebral infarction. Naftopidil did not increase the bladder contraction interval.

Figure 5. Log dose-response curves of mean effects \pm SEM on bladder capacity (A), bladder contraction pressure (B), and residual volume (C), expressed as percent change after intracerebroventricular administration of increasing naftopidil doses of 1.3×10^{-2} to 1.3×10 nmol in 6 cerebral infarcted rats without pretreatment (squares) or with pretreatment with resiniferetoxin (triangles). A high dose (1.3×10 nmol) of naftopidil increased residual volume. Double asterisks indicate $p < 0.01$ versus CI rats with pretreatment with resiniferetoxin.

Figure 6. Log dose-response curves of mean effects \pm SEM on bladder capacity (A), bladder contraction pressure (B), and residual volume (C), expressed as percent change after intrathecal administration of increasing naftopidil doses of 1.3×10^{-3} to 1.3×10^{-1} nmol in 6 cerebral infarcted (CI) rats without pretreatment (squares) or with pretreatment with resiniferetoxin (triangles). Single and double asterisks indicate $p < 0.05$ and $p < 0.01$, respectively, versus CI rats with pretreatment with resiniferetoxin.

Figure 7. Representative cystometrogram showing the effects of intrathecal administration of naftopidil (1.3×10^{-2} , 1.3×10^{-1} nmol) in cerebral infarcted rats pretreated with resiniferetoxin. The bladder contraction interval decreased after cerebral

infarction. Naftopidil did not increase the bladder contraction interval.