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Effects of Spinal and Peripheral Injection of α1A or α1D Adrenoceptor Antagonists on Bladder Activity in Rat Models with or without Bladder Outlet Obstruction

Jae Heon Kim, Ji Sung Shim, Seung Chul Kang[1], Kang Soo Shim[2], Jae Young Park[1], Du Geon Moon[1], Jeong Gu Lee[1], Jae Hyun Bae[1]

Department of Urology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan;
[1]Department of Urology, Korea University College of Medicine, Seoul;
[2]Department of Urology, Andong Hospital, Andong, Korea

Purpose: Antagonists of α1-adrenergic receptors (α1ARs) relax prostate smooth muscle and relieve voiding and storage symptoms. Recently, increased expression of α1ARs with change of its subtype expression has been proved in bladder outlet obstruction (BOO). To search for the evidence of changes in α1ARs subtype expression and activity in the peripheral and spinal routes, the effects of spinal and peripheral administration of tamsulosin (an α1A/D-selective AR), naftopidil (an α1A/D-selective AR), and doxazosin (non-selective AR) on bladder activity were investigated in a rat model with or without BOO.
Methods: A total of 65 female Sprague-Dawley rats were divided into the BOO surgery group (n=47) and the sham surgery group (n=18). After 6 weeks, cystometry was assessed before and after intrathecal and intra-arterial administrations of tamsulosin, naftopidil, and doxazosin.
Results: After intra-arterial administrations of all three drugs, bladder capacity (BC) was increased and maximal intravesical pressure (Pmax) was decreased in both BOO and the sham rat models ($P<0.05$). After intrathecal administration of all three drugs, BC was increased and Pmax was decreased in only the BOO group. The episodes of involuntary contraction in the BOO rat models were decreased by intra-arterial administration ($P=0.031$). The increase of BC after intrathercal and intra-arterial administrations of α1ARs was significantly greater in the BOO group than in the sham group ($P=0.023$, $P=0.041$). In the BOO group, the increase of BC and decrease in Pmax were greater by intra-arterial administration than by intrathecal administration ($P=0.035$). There were no significant differences of the degrees of changes in the cystometric parameters among the three different α1ARs.
Conclusions: Up-regulations of the α1ARs in BOO were observed by the greater increases of BC after α1AR antagonist administrations in the BOO group than in the sham group. However, there were no subtype differences of the α1ARs in functional parameters of bladder activity. In addition, α1ARs also act on the lumbosacral cord which implies that the sensitivity of α1ARs is increased in pathologic models such as BOO. Further evaluation including differential expression of α1ARs in BOO models are need.

Keywords: Urinary bladder; Urinary bladder neck obstruction; Adrenergic alpha-antagonists; Rats

INTRODUCTION

Bladder outlet obstruction (BOO) is a common disease among aged males, that usually caused by benign prostate hyperplasia (BPH), and leads to voiding and storage dysfunction. In particular, storage symptoms such as frequency, nocturia, and urgency are bothersome problems and have a significant impact on quality of life [1].

Corresponding author: Jae Hyun Bae
Department of Urology, Korea University Ansan Hospital, Korea University College of Medicine, 516 Gojan-dong, Danwon-gu, Ansan 425-707, Korea
Tel: +82-31-412-5190 / Fax: +82-31-412-5194
E-mail: urobae@genetherapy.or.kr
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Currently α1 adrenergic receptor (α1AR) antagonists are considered the first-line drug treatment for BPH. Alpha-1ARs are generally subdivided into α1A, α1B, and α1D AR subtypes [2]. Highly selective α1ARs are effective for the treatment of BOO, but they do not appear to relieve storage symptoms. Because non-subtype-selective α1AR antagonists have been shown to relieve voiding and storage symptoms, it is logical to conclude that another distinct (non α1A) subtype mediates storage responses. A number of experimental studies have shown the expression of the α1D AR subtype in the detrusor, urothelium, prostate, peripheral ganglia and spinal cord in humans and rats [3,4], which suggests the involvement of the α1D AR subtype in storage dysfunction and related storage symptoms [5]. It has also been reported that the α1D AR in the bladder trigone, body, and dome markedly increase, and weight and overactivity also increase, after incomplete urethral obstruction produced for 6 weeks in female rats [6].

Tamsulosin and naftopidil are well-known α1A/D-selective ARs, but their receptor selectivity is quite different that their affinity to α1A or α1D AR is dissimilar [7]. Most of experimental studies of BOO models have focused on tamsulosin and other non-selective ARs, and experiments using naftopidil in BOO models are scarce.

One of the important motives of this study was to investigate the evidence for changes in α1AR subtype expression and activity in the peripheral and spinal routes. We investigated the effects of spinal and peripheral administraion of tamsulosin (an α1A/D-selective AR), naftopidil (an α1A/D-selective AR), and doxazosin (non-selective AR) on bladder activity in a rat model with or without BOO.

MATERIALS AND METHODS

Experimental Design

At 12 to 14 weeks of age, female Sprague-Dawley rats weighing 180 to 210 g at acquisition underwent partial BOO (BOO rats; n=47) or sham surgery (sham group; n=18). After 6 weeks, a polyethylene tube was inserted for cystometry, and an intrathecal catheter and intra-arterial catheter were inserted at the same time. Cystometry was assessed before and after intrathecal and intra-arterial administration of α1ARs antagonists (tamsulosin, naftopidil, and doxazosin) (Fig. 1). Drug administration was done in the middle of the micturition cycle after establishing a constant contractile activity. The effects of drugs on the cystometric parameters were monitored more than 60 minutes.

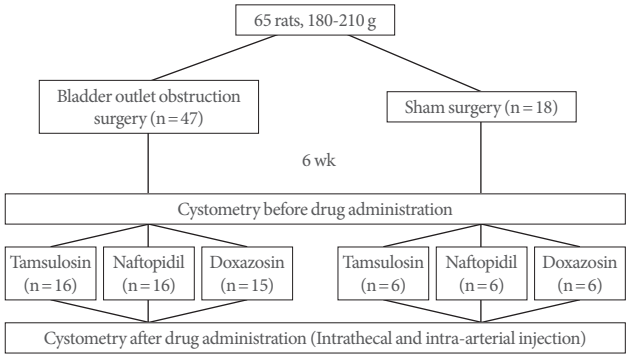

Fig. 1. Experimental design.

Creation of BOO

Female Sprague-Dawley rats were anesthetized with intraperitoneal ketamine (80 mg/kg; Ketamine, Yuhan, Seoul, Korea) and xylazine (10 mg/kg; Rompun,, Bayer Korea Ltd., Seoul, Korea). Surgical creation was performed by using sterile techniques. Through an abdominal incision, the bladder neck and the urethra were introduced without damaging the bladder. A 3-0 silk suture was placed around the urethra with a polyethylene tube (outside diameter: 1.09 mm) placed on the ventral side of the urethra. Subsequently, the urethra and tube were ligated loosely to avoid urethral compression and the tube was removed with a securing suture. The bladder was returned to the normal position in the abdomen, and the incision was closed.

Sham surgeries were performed in identical fashion in 18 rats except for the urethral ligatures. After these steps, the bladder was returned to its normal position in the abdomen, and the incision was closed.

Intrathecal Catheter Implantation

Intrathecal catheters were implanted at the same time as the bladder catheters for cystometry after anesthesia with intraperitoneal ketamine and xylazine. A polyethylene catheter (PE-10) was inserted into the subarachnoid space at the level of the L6-S1 spinal cord segments for intrathecal administration of drugs as described previously [8]. The injection sites in the spinal cord and the extent of dye distribution were confirmed by injection of dye (1% methylene blue) in every animal at the end of the procedure.

Intra-Arterial Catheter Implantation

The femoral artery was exposed through an inguinal incision, and a PE-10 tube filled with heparinized saline (30 IU/mL) was inserted and advanced proximally to the abdominal aortic bi-

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furcation. The catheter was tunneled subcutaneously and an orifice was made on the ventral skin of the rat.

Functional Evaluation of Cystometry

The abdomen was opened through a midline incision, and a PE-160 polyethylene tube with double lumen catheter was inserted into the bladder dome. A PE-150 tube was implanted into the bladder through the dome and connected to both a micro-injection pump (Harvard infusion pump) for continuous saline infusion and a polygraph (0.25 mm/sec) to monitor changes in intravesical pressure via a pressure transducer (P-23XL, Gilson Inc., Middleton, WI, USA). Saline (normal temperature) was infused into the bladder at a constant rate of 0.1 mL/min to induce a micturition reflex. After an equilibration period, three reproducible micturition cycles were recorded before drug administration and were used as baseline values. After a stabilization period of at least 30 minutes, cystometric recording was used to evaluate the cystometric parameters.

The cystometric parameters analyzed were bladder capacity (BC), maximal bladder pressure, and involuntary contraction. Bladder capacity was defined as the highest capacity until the initiation of the micturition reflex. Maximal vesical pressure (Pmax) was defined as the highest pressure from baseline bladder pressure. Involuntary contraction was defined as as spontaneous detrusor contractions with an amplitude of 4 cm water or more that were not associated with during the bladder filling state [9]. Involuntary contraction was observed in 44 rats among BOO group and in one rat in sham group.

The three micturition cycles showing the most pronounced changes (increase or decrease) after administration of the drugs were analyzed and compared with the baseline values.

Drugs and Administration

Doxazosin (Pfizer Central Research, Sandwich, UK), tamsulosin (Astellas Pharm Inc., Ibaraki, Japan), and naftopidil (Asahi Kasei Co., Tokyo, Japan) were used. After establishing constant bladder contractile activity and accompanying micturition during the equilibration period, drugs were administered in the middle of the micturition cycle. Stock solutions of all drugs were made in distilled water. All drugs were administered carefully at an interval of 30 seconds to minimize volume effects. To assess the effects of solvents, normal saline was administered before drug administration. Drugs were administered intrathecally through the spinal catheter in a volume of 20 μL for 20 seconds and intra-arterially in a volume of 0.2 mL/100 g. All drugs were delivered by intrathecally and intra-arterially with the concentration of 1.0 μmol/L [10].

Statistical Analysis

Parametric tests were conducted because the data were shown to be normally distributed. The results are given as mean values ± standard errors. For comparisons between values obtained before and after drug administration, Student's paired t-tests were used. One-way analysis of variance was used for comparisons among the drugs. SPSS ver. 18.0 (IBM, New York, NY, USA) was used for statistical processing and differences were considered to be significant when $P < 0.05$.

RESULTS

Bladder Weight

The mean bladder weight of the rats that underwent BOO surgery was significantly greater than that of the sham rats (Fig. 2). An approximately 1.7 to 2.8-fold increase in bladder weight was observed. There were no significant differences in bladder weight among the drug administration group both in BOO and sham group.

Effects of Intrathecal and Intra-Arterial Administration of α1AR Antagonists on Bladder Activity in the Sham Surgery Group

After intra-arterial administration of all types of α1ARs antago-

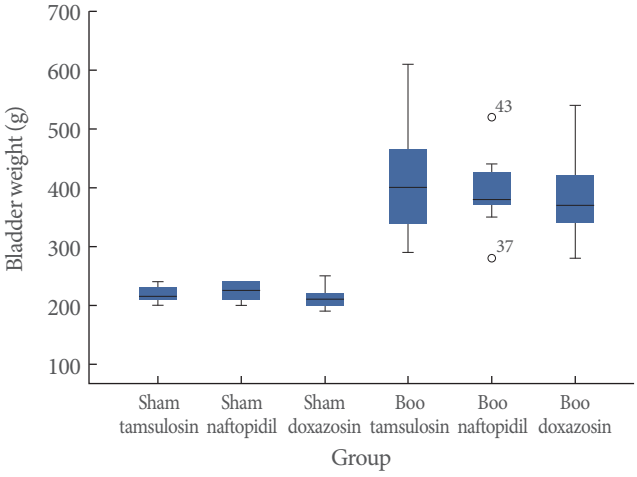

Fig. 2. Box-plot of mean bladder weight. The bladder weight of the bladder outlet obstruction (BOO) group was significantly greater than that of the sham group ($P < 0.05$). There were no significant differences among the drug administration subgroups in the BOO or sham group ($P > 0.05$).

Table 1. Changes in functional parameters before and after administration of α-adrenoceptor antagonists in rats

Variable	Group	Route	Before administration	After administration	P-value[a)]
BC (mL)	BOO	Intra-arterial	0.91 ± 0.56	1.09 ± 0.67	0.021
		Intrathecal	0.38 ± 0.15	0.41 ± 0.22	0.041
	Sham group	Intra-arterial	1.04 ± 0.98	1.51 ± 1.81	0.031
		Intrathecal	0.66 ± 0.30	0.85 ± 0.41	> 0.05
Pmax (mmHg)	BOO	Intra-arterial	22.75 ± 12.26	19.64 ± 11.88	0.012
		Intrathecal	20.42 ± 6.70	18.04 ± 6.15	0.015
	Sham group	Intra-arterial	20.00 ± 17.06	16.44 ± 14.50	0.022
		Intrathecal	16.93 ± 13.09	14.41 ± 13.01	> 0.05
Involuntary contraction (time/min)	BOO	Intra-arterial	0.68 ± 1.19	0.50 ± 0.89	0.031
		Intrathecal	0.35 ± 0.41	0.32 ± 0.40	> 0.05

Values are presented as mean ± standard deviation.
BC, bladder capacity; Pmax, maximal intravesical pressure; BOO, bladder outlet obstruction.
[a)]Statistically analyzed by paired t-test.

Table 2. Comparison of bladder activity after intrathecal and after intra-arterial administration of α1ARs antagonists

		Intrathecal administration	Intra-arterial administration	P-value[a)]
Δ BC (mL)	BOO	0.19 ± 0.16	0.46 ± 0.92	0.035
	Sham group	0.04 ± 0.09	0.18 ± 0.22	> 0.05
Δ Pmax (mmHg)	BOO	2.52 ± 2.41	3.55 ± 3.50	0.025
	Sham group	2.38 ± 2.08	3.11 ± 2.15	> 0.05

Values are presented as mean ± standard deviation.
Δ BC, differentials of bladder capacity; Δ Pmax, differentials maximal intravesical pressure; BOO, bladder outlet obstruction.
[a)]Statistically analyzed by paired t-test.

nists, BC was increased and maximal Pmax was decreased with statistical difference (P = 0.031, P = 0.022). After intrathecal administration of all types of α1AR antagonists, BC and Pmax showed no siginificant difference compared with baseline values (Table 1).

Effects of Intrathecal and Intra-Arterial Administration of α1ARs Antagonists on Bladder Activity in the BOO Group

After intra-arterial administration of all types of α1AR antagonists, BC was increased and Pmax was decreased with statistical difference (P = 0.021, P = 0.012). After intrathecal administration of all types of α1ARs antagonists, BC was increased and Pmax was decreased with statistical difference (P = 0.041, P = 0.015). The episodes of involuntary contraction in the BOO rat models were decreased by intra-arterial administration (P = 0.031; Table 1).

Comparison of Bladder Activity after Intrathecal and after Intra-Arterial Administration of α1AR Antagonists

In the BOO group, the increase of BC and decrease of Pmax were greater with intra-arterial administration than with intrathecal administration (P = 0.035, P = 0.025). In the sham group there were no significant differences between intrathecal and intra-arterial administration (Table 2).

Comparison of Bladder Activity after Intrathecal and Intra-Arterial Administration of α1ARs Antagonists between the Sham and BOO Groups

Differentials of BC (Δ BC) before and after administration of α1ARs antagonists showed a greater increase in the BOO group than in the sham group (P = 0.041, P = 0.023). Differentials of maximal intravesical pressure (Δ Pmax) before and after administrations of α1AR antagonists showed no differences in the BOO group compared with sham group (P > 0.05; Table 3).

Comparison of Bladder Activity after Intrathecal and Intra-Arterial Administration of α1ARs among Tamsulosin, Naftopidil, and Doxazosin

Differentials of Δ BC, Δ Pmax, and Δ involuntary contractions showed no significant differences among the tamsulosin, naftopidil, and doxazosin administration groups in the BOO group (Table 4). Differentials of Δ BC, Δ Pmax, Δ involuntary contractions also did not differ significantly among tamsulosin, naftopidil, and doxazosin administration groups in the sham group.

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Table 3. Comparison of BC and Pmax between the BOO and sham groups

	Sham group	BOO	P-value[a]
Δ BC (mL)			
Intra-arterial	0.18 ± 0.22	0.46 ± 0.92	0.041
Intrathecal	0.04 ± 0.09	0.19 ± 0.16	0.023
Δ Pmax (mmHg)			
Intra-arterial	3.11 ± 2.15	3.55 ± 3.50	> 0.05
Intrathecal	2.38 ± 2.08	2.52 ± 2.41	> 0.05

Values are presented as mean ± standard deviation.
Δ BC, differentials of BC bladder capacity; Δ Pmax, differentials of maximal intravesical pressure; BOO, bladder outlet obstruction.
[a]Statistically analyzed by paired t-test.

Table 4. Comparison of the parameters among the drug treatment goups in BOO rats

	Tamsulosin	Naftopidil	Doxazosin	P-value[a]
Δ BC (mL)				
Intra-arterial	0.70 ± 1.48	0.40 ± 0.47	0.26 ± 0.23	> 0.05
Intrathecal	0.15 ± 1.09	0.20 ± 0.23	0.22 ± 0.04	> 0.05
Δ Pmax (mmHg)				
Intra-arterial	5.19 ± 3.35	1.85 ± 1.44	4.64 ± 5.29	> 0.05
Intrathecal	2.11 ± 1.77	3.35 ± 3.28	2.16 ± 2.11	> 0.05
Δ Involuntary contraction (time/min)				
Intra-arterial	0.09 ± 0.23	0.37 ± 0.69	0.08 ± 0.17	> 0.05
Intrathecal	0.03 ± 0.08	0.04 ± 0.15	0.02 ± 0.15	> 0.05

Values are presented as mean ± standard deviation.
Δ BC, differentials of bladder capacity; Δ Pmax, differentials of maximal intravesical pressure; BOO, bladder outlet obstruction.
[a]Statistically analyzed by one-way analysis of variance.

DISCUSSION

Many reports have stated that α-blockers have pharmacologic and clinical effects in the treatment of voiding and storage symptoms in BPH; however the pathogenic mechanism and treatment of storage symptoms are not clearly understood. It is clear that the most reasonable explanation for the limited role of α-blockers is the up-regulation of the α1ARs, with changes in their subtypes, and α1AR-mediated bladder afferent activation [11]. In our study, we tried to investigate on the up-regulation of α1ARs and its subtype change, and spinal and peripheral α1AR antagonism on bladder activity.

The composition of human α1ARs measured quantitatively by mRNA is follows: α1A, 6 to 74%; α1B, 1 to 6%; and α1D, 25 to 31% [12]. Weinberg et al. [13] reported similar results. Malloy et al. [3], however, investigated the expression of α1receptor mRNA in the human bladder detrusor muscle, and revealed the distribution of subtypes of α1 receptors to be 34% α1A, and 66% α1D. Hampel et al. [14] showed that there was a change in α1AR subtype expression from α1A to α1D AR in detrusor muscle in rats with BOO. However, it remains to be elucidated whether α1ARs (mainly α1D) in the detrusor muscle are responsible for detrusor overactivity [15]. A shift from α1A AR to α1D AR and de novo α1D AR protein expression is predominant in BOO rat models, particularly in bladders with a mass more than 5-fold the mean of sham bladder masses [14].

Although the changes in AR subtypes are important, α1AR-mediated bladder afferent activation is another important mechanism for understanding overactivity in BOO experimental models. Recently, it was reported that α1AR antogonists are effective in the treatment of storage symptoms [16]. This suggests that not only the α1D AR but also the α1A AR may have an important role in the development of storage symptoms. With regard to the mechanisms of α1AR antagonists in the improvement of storage symptoms, recent attention has focused on the possibility that α1AR antagonists may inhibit afferent nerves from the lower urinary tract [16].

With regard to α1AR-mediated bladder afferent activation, the expression of α1ARs in the urothelium has been well documented. Up-regulation of these receptors can trigger the release of a number of mediators including ATP and nitric oxide, which may modulate bladder afferent nerve activity [17]. Alpha 1 ARs located in the bladder urothelium, primary sensory nerve, and bladder vessel, are involved in afferent signaling. It is suggested that α1AR antagonists may decrease bladder afferent activity by blocking α1ARs in these sites, thereby reducing the storage dysfunction associated with BOO [18].

In our study, intra-arterial administration of α1AR antagonists showed that BC was increased and Pmax was decreased in both BOO and sham group. But after intrathecal administration of α1AR antagonists, BC was increased and Pmax was decreased in only BOO group. Involuntary contraction was decreased only after intra-arterial administration of α1AR antagonists in the BOO group. These results may reflect the inhibition of the micturition reflex not only at a spinal but also at the peripheral level, and in pathologic models spinal receptor sensitivity is more increased than in normal models [10].

The most prominent feature of our study is that we directly compared the bladder activity among tamsulosin, naftopidil

and doxazosin treatment groups. Before the emergence of naftopidil, there was no α1A/D-selective AR, and most studies have used tamsulosin. Naftopidil and tamsulosin are α1 blockers of the same category in that they have antagonistic action on both α 1A and α1D receptors, but they have an affinity contrary to each other [7]. Naftopidil has an affinity to α1D AR about 3.1 times as high as the affinity to α1A AR. The affinity of tamsulosin, which is commonly used as an α1 blocker, has an affinity to α1A AR about 3.3 times as high as the affinity to α1D AR [7].

In our study, the increase of BC after intrathercal and intra-arterial administrations of α1ARs was significantly greater in the BOO than in sham rat models but there were no significant differences in the degrees of the changes in the cystometric parameters among the three different α1ARs antagonists. To our knowledge, there have been no experimental reports comparing bladder activity among tamsulosin, naftopidil and doxazosin treatment groups.

Although our method is not direct, such as detecting receptor expression for evidence of the up-regulation of α1ARs and changes in subtype expression, our experiment has yield a definite results on functional study by intrathecal and intra-arterial administration of each α1ARs. The most ideal method of detecting the up-regulation of α1ARs and changes in subtype expression is to use the robust method of quantitative competitive reverse transcriptase-polymerase chain reaction [19]. However, the localization of bladder α1ARs is not a simple method because of low sensitivity [20].

Our study had some limitations. First, cystometry was not performed with the rats in a conscious state and voiding behavior was not investigated before and after BOO surgery. It is better to perform the experiments without than with anesthesia because it has been reported that anesthesia affects urinary function [21]. Although we did not collect voiding behavior data, analysis of bladder weights indicated that our surgical procedure for the BOO model resulted in changes approximating detrusor hypertrophy in clinical BOO. Second, spinal and peripheral bolus injections of α1AR antagonists are not a natural treatment model. Third, drug uroselectivity is different in rats than in other species (rabbits, dogs and humans) [22, 23].

In conclusion, our study implies that both central and peripheral effects of a and a1-adrenoceptor antagonists may contribute to the increase BC and the decrease in the Pmax after intrathecal and intra-arterial administration, but the exact role of detrusor α1ARs in the bladder overactivity after BOO remains to be completely elucidated. The present study demonstrates that tamsulosin, naftopidil, and doxazosin increase BC and decrease maximal bladder pressure in BOO models. Future study must be performed examining the definite role of α1ARs and their subtypes and α1AR-mediated bladder afferent activation to elucidate the pathologic mechanism of storage symptoms in BOO.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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