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Effect of α1D-adrenoceptor blocker for the reduction of ureteral contractions

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Purpose: Urolithiasis is a common urinary tract disease with growing prevalence. Alpha1-adrenoceptors (α1-ARs) are abundant in ureteral smooth muscle, distributed with different α1-AR subtypes. α1D-AR is the most widely distributed in the ureter. However, the effect of α1D-AR blockade on ureteric contraction remains unknown.

Materials and Methods: We dissected smooth muscle tissues (3 mm×3 mm) from the rat bladder and human ureter, tied silk strips on both tissue ends, and measured contraction in an organ bath chamber. Contraction activity in ureteral smooth muscle cells (USMCs) was immunocytochemically examined using primary rat and human USMC cultures.

Results: Using the organ bath system, we determined the inhibitory effects of silodosin, tamsulosin, and naftopidil. Naftopidil significantly decreased contractility of rat bladder tissue; similar results were observed in human ureteral tissue. To confirm *ex vivo* experimental results *in vitro*, we examined the phosphorylation of myosin light chain (MLC), a marker of contractility, in a primary human USMC culture. The examined drugs decreased phospho-MLC levels in human USMCs; however, naftopidil profoundly increased MLC dephosphorylation.

Conclusions: We studied the effects of naftopidil, an α1D-AR inhibitor, on the ureter. Compared with alpha-blockers, naftopidil significantly relaxed ureteral smooth muscle. Therefore, naftopidil could be an effective therapy for patients with ureteral stones.

Keywords: Alpha-adrenergic receptor; Smooth muscle; Ureter

INTRODUCTION

Urolithiasis is one of the most common symptoms of urological diseases, and its growing prevalence can be attributed to a westernized lifestyle, obesity, global warming, and an aging society [1,2]. Sharp flank pain due to hydronephrosis, ureteral spasm, nausea, and disturbance of intestinal motility are major causes of underlying discomfort in patients with urolithiasis. If the urolithiasis is small or located at the distal end of the ureter, with no clinical evidence of infection and pain, conservative medical expulsive therapy (MET) may promote spontaneous expulsion of ureteral stones [3,4]. Adrenergic nerve fibers, similarly distributed in the urinary tract of animals, including humans, are most abundant in the distal ureter and are present in the muscle layer, perivascular networks, and submucosal layer [5,6].

Alpha1-adrenoceptors (α1-ARs) are conserved in the ureters of both animals and humans. Reportedly, ureteral smooth muscle α1-ARs are denser than other adrenoceptors, and a homogeneous distribution of different α1-AR subtypes

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has been noted in the human ureter [7]. In several clinical reports, α1-AR antagonists, including alfuzosin, doxazosin, tamsulosin, silodosin, and naftopidil, were shown to inhibit ureteral contraction [8,9]. Based on the findings of a randomized controlled study, α1-AR antagonists can be used to promote the spontaneous excretion of ureteral stones in patients. In contrast, a recent study has shown that tamsulosin, which exhibits α1A-AR and α1D-AR selectivity, is ineffective for MET therapy [10]. Tamsulosin is an α1A-AR and α1D-AR antagonist, silodosin is an α1AR antagonist, and naftopidil is more selective toward α1D-AR [11,12]. Among the α1ARs, the α1D-AR subtype is the most widely distributed in the ureter [13]. However, the effect of α1D-AR blockade on ureteric contractions has not been investigated.

In the present study, we examined the effects of naftopidil on the rat bladder and ureter, known to exhibit similar contractility to human ureters. In addition to the rat bladder and ureter, we examined the contractions inhibited by naftopidil in the human ureter. We also compared the effects of naftopidil with those of tamsulosin and silodosin on ureteral contraction.

MATERIALS AND METHODS

1. Animals

Eight-week-old male Sprague–Dawley rats (n=6) were purchased from Orient Bio (Seongnam, Korea). The rats were acclimatized for one week under controlled room temperature in standard cages. The rats were sacrificed by carbon dioxide asphyxia, and ureters and bladders were immediately harvested, placed in cold Krebs solution, and transferred to the laboratory for experiments. All experimental procedures were performed in accordance with the institutional guidelines approved by the Hanyang University Institutional Animal Care and Use Committee (approval no. 2020-0213A). All procedures related to the *in vivo* experiments and animal care were carried out in accordance with the approved guidelines. The study is compliant with the ARRIVE guideline 2.0.

2. Human tissues

Normal ureters were obtained from patients who underwent donor and radical nephrectomy. Patients consented to participate by signing the appropriate informed consent paperwork. The reasons and purpose for the research and ureter tissue harvesting were explained to all patients, who provided informed consent prior to the surgery. This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Hanyang University Hospital (no. HYUH 2017-08-033-011). All methods were performed in accordance with the relevant guidelines, regulations by including a statement. Ten ureteral tissue specimens were obtained during surgery and promptly placed in cold Krebs solution. The tissue specimens were instantly transported to the laboratory bench, typically requiring less than 5 minutes, and used for ureter contraction experiments in an organ bath chamber. After organ bath examination, parts of the tissues were fixed for immunocytochemistry.

3. Isolation and primary culture of ureteral smooth muscle cells

Given that ureteral smooth muscle cells (USMCs) cannot be obtained commercially, we cultured USMCs from rats and patient ureters using a *de novo* technique [14]. Briefly, the ureters harvested from patients and rats were immediately placed in cold Krebs solution, cut into 5 mm sections, and incubated on a plate containing trypsin. After centrifugation at 1,000 rpm for 3 minutes, the cells were resuspended in media mixed with SmGM2 complete media and trypsin at a ratio of 10:1 and seeded on collagen-coated plates. The medium was carefully replaced by complete medium every 2 to 3 days and used for experimentation after 7 to 10 days.

4. Drugs and solutions

Krebs solution was obtained from Sigma Aldrich (St. Louis, MO, USA). Silodosin (Recordati, Milan, Italy), tamsulosin (Cayman, Ann Arbor, MI, USA), and naftopidil (Cayman) were procured and used. Silodosin and tamsulosin were dissolved in ethanol and naftopidil in methanol (Merck, Kenilworth, NJ, USA) and stored as stock solutions: silodosin (1 mM), tamsulosin (400 nM), and naftopidil (200 μM) [15-17].

5. Organ bath system

The organ bath system was used as described by Jespersen et al. [18]. A recirculating heated water bath preheated the tissue bath system to 37℃ and was connected to 95% O_2 and 5% CO_2 medical-grade gases. The force transducer was connected to a data acquisition system. The isolated bladder or ureteral tissue was immediately transferred to the laboratory and incised in luminal and longitudinal directions (3 mm×3 mm; rat bladder and human ureter and 1 mm×3 mm; rat ureter), respectively. After maintaining tension by fixing both ends with silk threads, the isolated tissue was equilibrated for approximately 60 minutes. By changing the concentration of the three drugs, the degree of contraction for each drug and the concentration were comparatively analyzed. Electrical stimulation was used to determine the de-

gree of contraction. The contraction strength and frequency were recorded using a force transducer and data acquisition system.

6. Immunocytochemistry

Briefly, cells were seeded in 12-well plates containing coated coverslips and treated with relevant drugs for 24 hours. The coverslips with attached drug-treated cells were washed with phosphate-buffered saline (PBS) and fixed with 4% paraformaldehyde solution at room temperature for 30 minutes. The cells were incubated with 0.1% Triton X-100 at room temperature for 5 minutes and then blocked with 1% goat serum/PBS for 30 minutes at room temperature. Next, the cells were incubated for 30 minutes in a dilution (1:800) of the primary phosphor-myosin light chain (MLC) antibody (#95777, Cell Signaling Technology, Danvers, MA, USA) in 1% goat serum and washed with PBS. Subsequently, the fluorescein isothiocyanate-conjugated secondary antibody was added to the cells and incubated for 30 minutes. After adding Hoechst stain for nuclear staining, the cells were washed and mounted. Images were captured using a fluorescence microscope (Leica, Wetzlar, Germany) at 200× magnification.

7. Statistics

In vivo and *in vitro* data were analyzed using GraphPad Prism 7.0 (GraphPad, San Diego, CA, USA). Comparisons between groups were performed using one-way ANOVA, followed by Tukey's post-hoc test. Statistical significance was set at $p<0.05$. All group numbers and important values are described in figure legends or results.

RESULTS

1. *Ex vivo* effects of α1-AR antagonists on the ureter and bladder of the human and rat

To directly measure the effects of the three drugs on ureteral contractility, we used an organ bath system as a bench-top *ex vivo* system (Fig. 1A). It is known that the mechanism of the muscle contractility for the bladder is similar to that of ureter [14,19]; hence, we tested contraction using the rat bladder. First, untreated rat bladder tissue was electrically stimulated. We observed that naftopidil significantly reduced the intensity and frequency of rat bladder contractions induced by electrical stimulation (Fig. 1B). The naftopidil-induced reduction in contraction was observed in all experimental rats. In contrast, although silodosin or tamsulosin decreased contraction, this was not a common response in all animals, and the magnitude was less than that of naftopidil. To confirm that results derived using the rat bladder were consistent with those in the rat ureter, we examined the effect of the drugs on the rat ureter. In the rat ureter, naftopidil exhibited superior inhibitory effects on strength and frequency of contraction compared to other examined drugs (Fig. 1C).

To determine whether the superiority of naftopidil identified in rats could be applied to patients, we collected ureteral tissues from 10 patients and examined them using an organ bath system. In most patients, ureteral contractions were reduced upon administering all α1-AR antagonists; however, naftopidil showed superior inhibition of ureteral contractions (Fig. 2). Accordingly, we confirmed that naftopidil exhibited greater inhibitory effects than silodosin and tamsulosin on the strength and frequency of contraction mediated by experimentally induced electrical stimulation, as well as on inherent self-contraction (Fig. 3).

2. *In vitro* relaxation induced by naftopidil

The physiological response of ureteral contraction can be quantified by assessing the phosphorylation of the MLC [20,21]. As MLC dephosphorylation is mediated by drug-induced relaxation, we measured the level of phospho-MLC in primary cultured USMCs of rats and humans using immunocytochemistry. To investigate differences in contractile inhibition according to the contractile function of each drug, we performed serial dilutions based on the final concentration (silodosin; 50 ng/mL, tamsulosin; 12 ng/mL, naftopidil; 86 ng/mL). All three drugs inhibited contractions in isolated rat and human ureters in a concentration-dependent manner (Fig. 4A, B).

To compare the reduction effect induced by each drug at the recommended concentration, we measured contractile activity in primary cultured USMCs of rats and humans and found that naftopidil showed the most potent effect (Fig. 4C, D). Collectively, these results suggested that the α1D-AR subtype, among the α1-ARs, plays a more critical role in mediating ureteral contraction than the α1A-AR subtype.

DISCUSSION

To the best of our knowledge, this is the first study to compare the efficacy of α1A-AR and α1D-AR inhibitors in the ureter. The inhibitory ratio of actual contraction was measured in an organ bath system using rat bladder and ureteral tissues, as well as human ureteral tissue. In addition to *ex vivo* experiments, we examined primary cultures of USMCs and the expression of phospho-MLC *in vitro*. Collectively, our results confirmed that targeting α1D-AR, which is most widely distributed in the ureter, is more effective than

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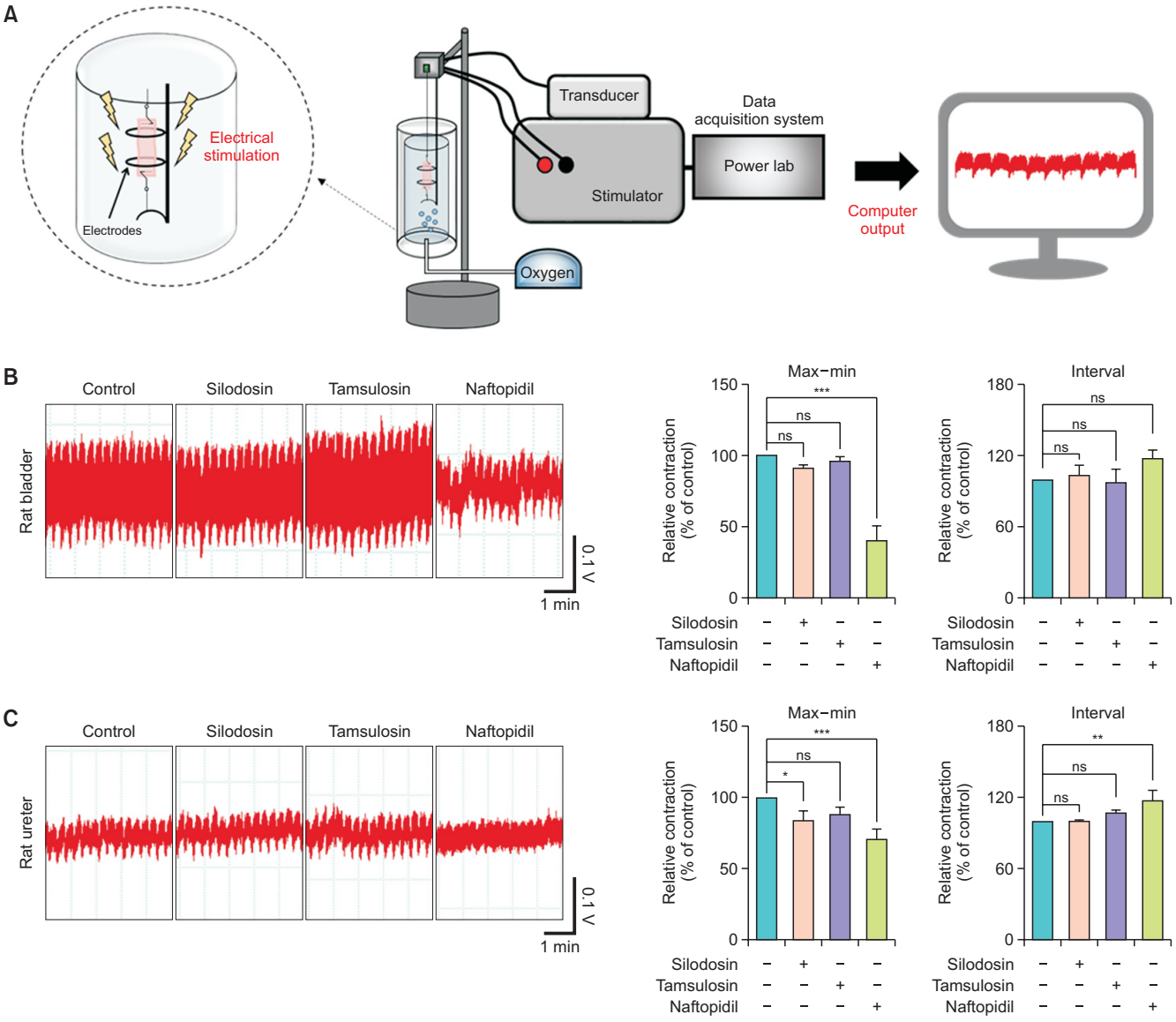

Fig. 1. *Ex vivo* effects of alpha1-adrenoceptor antagonists on the rat bladder and ureter. (A) A schematic diagram of the organ bath system. Representative images and graphs for ureteral contraction recordings after administration of silodosin, tamsulosin, and naftopidil to bladder (B) and ureter (C) of rats (n=3). *p<0.05, **p<0.01, ***p<0.001.

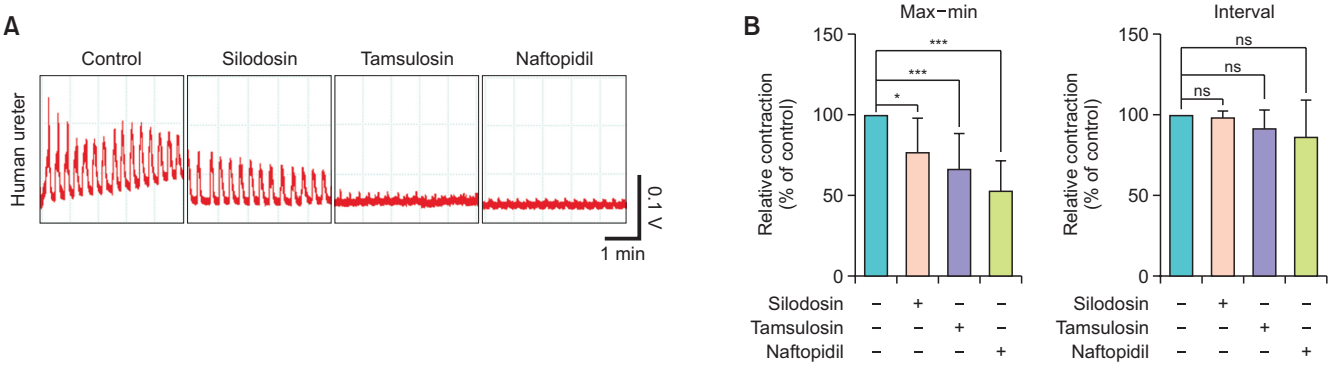

Fig. 2. *Ex vivo* effects of alpha1-adrenoceptor antagonists on the human ureter. Representative images (A) and graphs (B) presenting ureteral contraction recordings after administration of silodosin, tamsulosin, and naftopidil to the human ureter (n=10). *p<0.05, ***p<0.001.

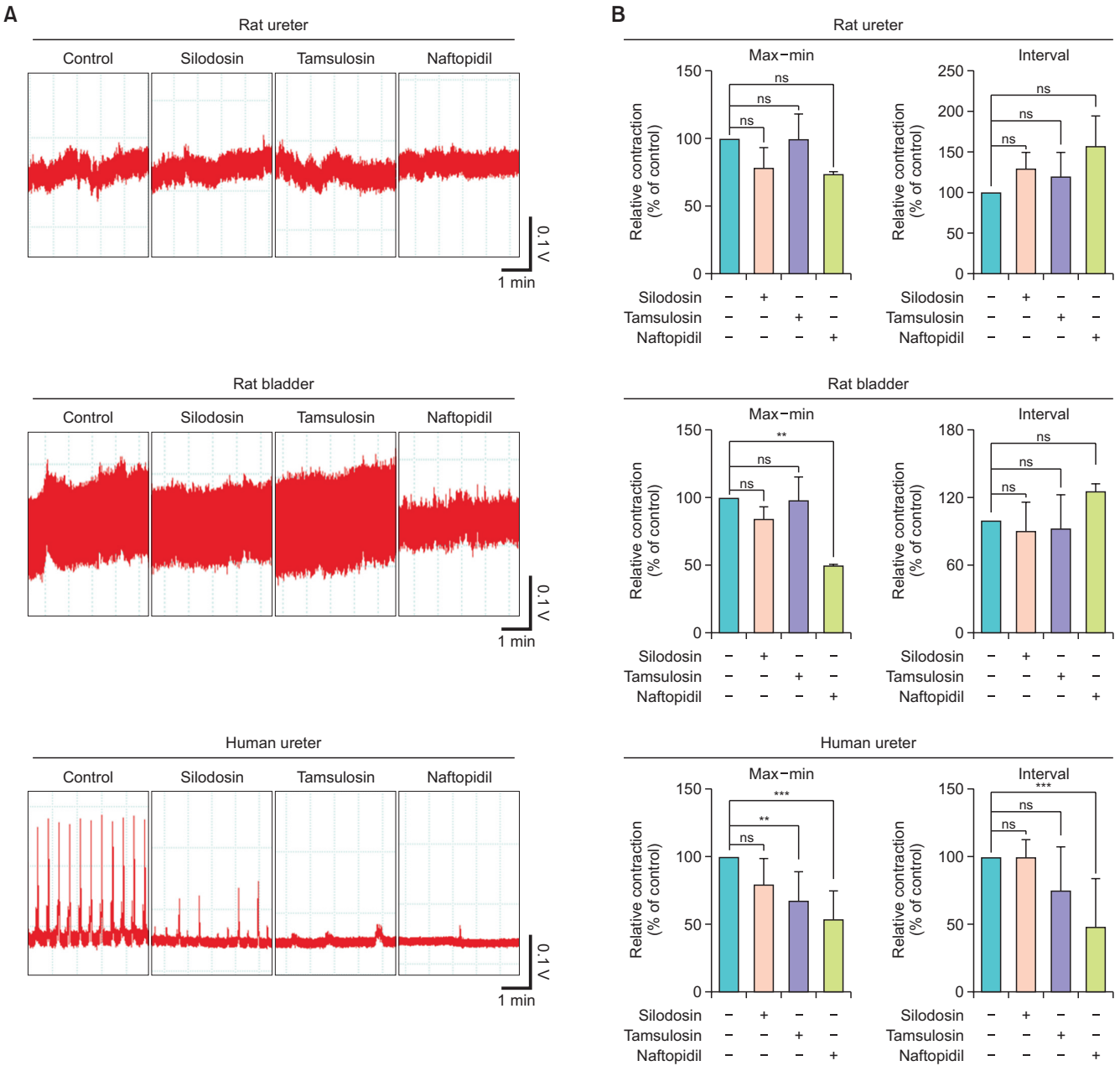

Fig. 3. Alpha1-adrenoceptor antagonists inhibit self-contraction of bladder and ureteral tissues. Representative images (A) and graphs (B) for ureteral contraction recordings after administration of silodosin, tamsulosin, and naftopidil to human ureter and rat bladder and ureter. **p<0.01, ***p<0.001.

targeting α1A-ARs (Fig. 5A).

Tamsulosin, prescribed to treat benign prostatic hyperplasia, is also used for stone expulsion [22,23] during MET. Several studies have indicated that silodosin and tamsulosin effectively enhance the spontaneous expulsion of ureteric stones [24-27]. However, Itoh et al. [13] have reported that α1D subtype mRNA was highly expressed throughout the ureter, including upper, mid, and lower ureter, accounting for approximately 54% of the total AR mRNA. Therefore, the authors suggested the use of α1D-AR antagonists for conservative expulsive therapy of distal ureteral stones in the region of high α1D subtype distribution [13]. Our data showed that silodosin and tamsulosin presented an overall benefit in ureteral smooth muscle relaxation; however, naftopidil afforded superior effects on ureteral smooth muscle relaxation, which is probably expected as the α1D subtype is the most dominant AR in the ureter.

This study is the first report to indicate that a specific α1D-AR antagonist may afford significant clues to clarify the complex mechanism between ureteral contractility and tone of ureteral smooth muscle. Our results suggest that a pharmacological approach that selectively blocks α1D-AR

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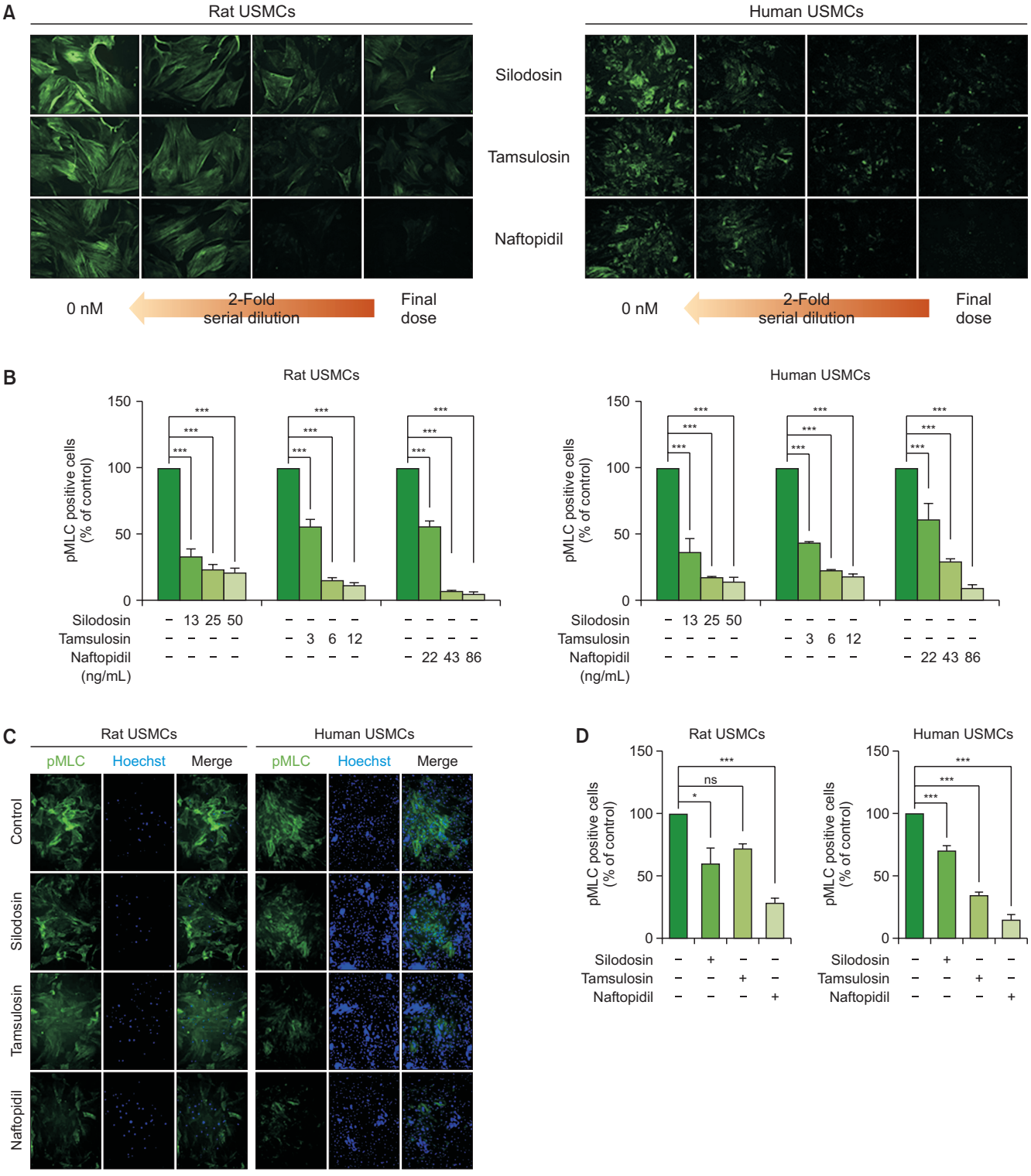

Fig. 4. In human and rat ureteral smooth muscle cells (USMCs), contraction activity was significantly reduced by naftopidil. For rats and humans, silodosin-, tamsulosin-, and naftopidil-treated USMCs were fixed. Fixed USMCs were stained with anti-phospho-myosin light chain (pMLC, green) and observed using fluorescence microscopy to measure relaxation. Representative images (A) and graphs (B) of the positive pMLC areas in rat and human USMCs. Representative images (C) and graphs (D) for silodosin-, tamsulosin-, and naftopidil-treated rat and human USMCs stained with anti-pMLC (green) and Hoechst (blue). *p<0.05, ***p<0.001.

activity may be a better treatment strategy than inhibiting other α1 subtypes for patients with urolithiasis. Kumar et al. [28] have compared the efficacy of the α1D-receptor antagonist naftopidil and the α1A/D-receptor antagonist tamsulosin in managing distal ureteral stones. The authors reported that the stone expulsion rate in the naftopidil group (87.5%)

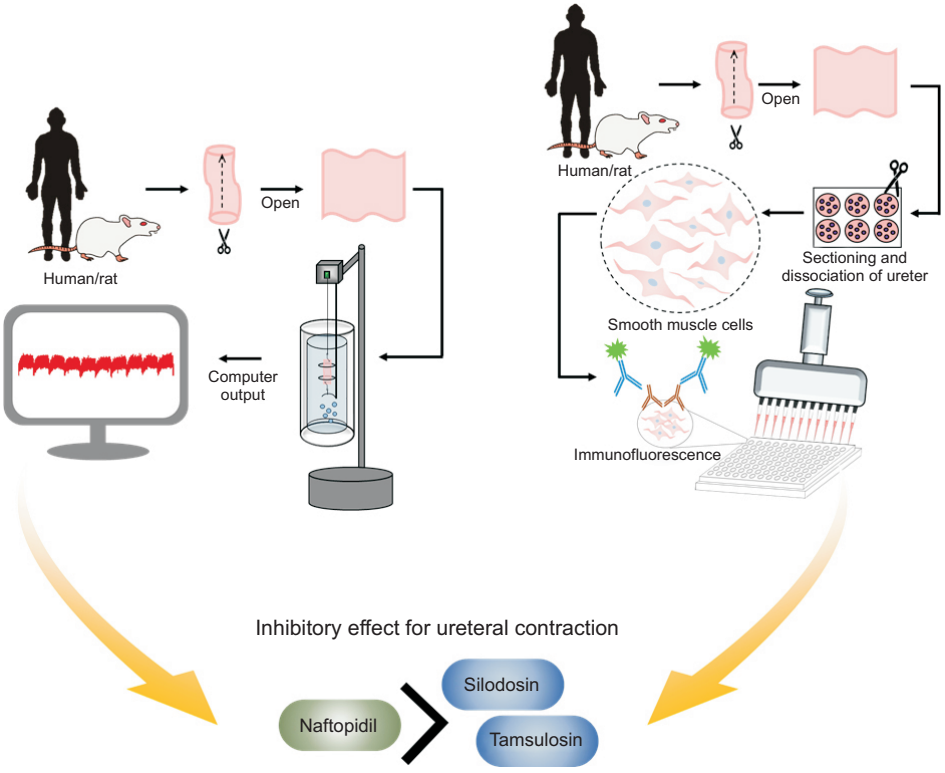

Fig. 5. Graphical summary of *in vitro* relaxation induced by alpha1D-adrenoceptor antagonists.

was higher than that in the tamsulosin group (70%, p=0.056). In contrast, no difference in the stone expulsion rate between naftopidil and tamsulosin groups was observed in another report. In addition, several studies have reported that the affinity of naftopidil is not superior to that of α1D-AR compared to other subunits and that the uroselectivity of silodosin and tamsulosin is controversial. However, since these studies were not conducted in organs or cells related to actual ureteral contraction, further study is needed in models related to the actual environment [29,30]. Hence, we believe that large-scale clinical trials are required to establish the superior drug for MET. The development of more potent α1D-AR inhibitors is also required. As the number of patients with urolithiasis continues to grow for several reasons, primary objectives of drug therapy include decreasing patient-reported pain, induction of spontaneous stone passage, and reducing the recurrence rate of urolithiasis.

To study changes in ureteral contractile force induced by drugs, we used the organ bath system to measure substantial contractile capacity, and we observed phospho-MLC expression to visualize the activation of USMCs involved in contraction. Most researchers utilize phospho-MLC, as it is practically the only marker indicating USMC contraction *in vitro*. Although we also used phospho-MLC to verify drug-induced changes in contraction, ureteral contractions occur through diverse combined actions *in vivo*. To overcome this limitation, it is necessary to discover novel markers by examining regulatory factors altered simultaneously by employing RNA sequencing or protein arrays in drug-treated tissues.

CONCLUSIONS

In the present study, we observed that naftopidil effectively inhibited the contraction of ureteral smooth muscles. Although other α1-AR antagonists also inhibited contraction, naftopidil showed a superior inhibitory effect compared to other drugs. These results suggest that the outstanding therapeutic effect of naftopidil can be expected in patients with urolithiasis, and targeting α1D-AR may be a pharmacological strategy for promoting MET.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Seong Hwi Hong and Young Eun Yoon. Data acquisition: Seong Hwi Hong and Eun Bi Jang. Statistical analysis: Seong Hwi Hong and Eun Bi Jang. Data analysis and interpretation: all authors. Drafting of the manuscript: Seong Hwi Hong and Young Eun Yoon. Critical revision of the manuscript: Seong Hwi Hong and Young Eun Yoon. Obtaining funding: Young Eun Yoon. Administrative, technical, or material support: Seong Hwi Hong and Eun Bi Jang. Supervision: Young Eun Yoon. Approval of the final manuscript: all authors.

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