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Uroselectivity in Male Dogs of Silodosin (KMD-3213), A Novel Drug for the Obstructive Component of Benign Prostatic Hyperplasia

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Aims: Our main aim was to compare the prostatic selectivity of silodosin with that of other α_1-adrenoceptor (AR) antagonists. **Methods:** We examined uroselectivities in two sets of experiments namely, in vitro and in vivo functional studies using male dogs. In the in vitro study, after evaluating the inhibitory effects of silodosin on noradrenaline (NA)-induced contractions in the isolated prostate and isolated carotid artery using the Magnus method, we calculated prostatic selectivity. In the in vivo study, we examined the effects of drugs on the hypogastric nerve stimulation (HNS)-induced increase in intraurethral pressure (IUP) and on blood pressure. The uroselectivity of silodosin was compared with those of tamsulosin and naftopidil. **Results:** In vitro, all drugs antagonized NA-induced contraction in both prostate and carotid artery. The prostatic selectivity of silodosin (79.4) was much higher than those of tamsulosin (1.78), naftopidil (0.55), BMY 7378 (0.115), and prazosin (0.01). In vivo, intravenously (i.v.) administered silodosin dose-dependently inhibited the HNS-induced increase in IUP with much less hypotensive effect than either tamsulosin or naftopidil, the uroselectivity (ED_{15}/ID_{50}) of silodosin (237) being significantly higher than those of tamsulosin (1.21) and naftopidil (2.65). **Conclusions:** Our results clearly demonstrate that silodosin is a potent and highly selective α_{1A}-AR antagonist. A selective α_{1A}-AR antagonist such as silodosin may have good potential as a less-hypotensive drug for the treatment of urinary dysfunction in benign prostatic hyperplasia patients. *Neurourol. Urodynam. 25:792–799, 2006.*

Key words: α_{1A}-adrenoceptor subtype; dog; silodosin (KMD-3213); uroselectivity

INTRODUCTION

Lower urinary tract symptoms (LUTS) are classified broadly into irritative (storage), obstructive (voiding), and post-micturition symptoms, such as slow stream, urgency, frequency, and nocturia [AUA Practice Guidelines Committee, 2003]. Benign prostatic hyperplasia (BPH) is an age-related and typical disorder of the LUTS characterized by a progressive enlargement of prostatic tissue that results in a voiding dysfunction caused by obstruction of the proximal urethra. The voiding dysfunction accompanying BPH is generally considered to consist of two components: a static component (related to prostatic mass) and a dynamic component [related to contraction of prostatic and urethral smooth muscle, mediated mainly via an α_1-adrenoceptor (AR) and caused by increased activity in the sympathetic nervous system].

Animal models that emulate human BPH symptoms are helpful for the development of new drugs. Male dogs are reported to be the only familiar animal model for human BPH (a) because spontaneous BPH occurs in both species with aging [Brendler et al., 1983; Johnston et al., 2000] and (b) because the α_{1A}-AR subtype—which mediates contraction of the prostate in response to noradrenaline [Marshall et al., 1995]—is predominant in the lower urinary tract (LUT) of both species [Price et al., 1993; Goetz et al., 1994; Nasu et al., 1996, 1998]. Hence, evaluation of drugs using dogs should be a useful way of examining their potential as therapeutic agents in the treatment of the dysuria that accompanies human BPH.

At present, α_1-AR antagonists are used as first-line pharmacotherapy for the voiding dysfunction associated with BPH. Initially, subtype-nonselective α_1-AR antagonists such as prazosin, which was originally developed for hypertension, were used. However, although this drug is effective it may cause adverse effects (such as orthostatic hypotension, dizziness, and first-dose phenomenon) because of the existence of α_1-ARs in the vasculature [Lepor, 1993; Monda and Oesterling,

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1993]. Concerning the α_1-AR subtypes present in the vasculature, the participation of α_{1B}-AR in the regulation of blood pressure (BP) has been indicated by various experiments on α_{1B}-AR in knockout mice [Cavalli et al., 1997], spontaneously hypertensive rats [Hancock et al., 2002], and conscious dogs [Brune et al., 2002]. These findings suggested that a low affinity drug for α_{1B}-AR might have fewer side effects related to hypotension.

As an improvement on subtype-nonselective drugs, tamsulosin, an antagonist with a higher selectivity for α_{1A}- versus α_{1B}-AR, was developed. This drug is characterized by an enhanced selectivity for the LUT, and it is better tolerated clinically. An antagonist with comparative selectivity for α_{1D}-AR versus α_{1A}- and α_{1B}-ARs, naftopidil, is also used clinically because α_{1D}-AR are related to the irritative symptoms induced by the bladder-outlet obstruction that can be secondary to BPH [Malloy et al., 1998; Hampel et al., 2002]. However, selectivity for α_{1A}-AR is not particularly high for these drugs, and doses high enough to provide sufficient improvement in dysuria could not be used without adverse events. Furthermore, to our knowledge the functional roles of α_{1D}-AR remain unclear. Against this background, we hypothesized that a strongly α_{1A}-AR-selective, in fact prostate-selective, antagonist would be useful as a therapeutic drug providing sufficient improvement in dysuria without provoking hypotension.

It has been reported that silodosin is a selective α_{1A}-AR antagonist [Shibata et al., 1995; Tatemichi et al., 2006] displaying at least approximately 160- and 50-fold higher affinities for human α_{1A}-AR versus α_{1B}- and α_{1D}-AR, respectively, in radioligand-binding studies (Fig. 1). Moreover, as an antagonist silodosin is selective for the human prostate (pK_B value, 9.64) versus the human mesenteric artery (pA_2 value, 7.47) [Murata et al., 2000].

In the present in vitro and in vivo studies, we evaluated the effects of silodosin on the LUT and cardiovascular system using male dogs, and we determined its prostatic selectivity.

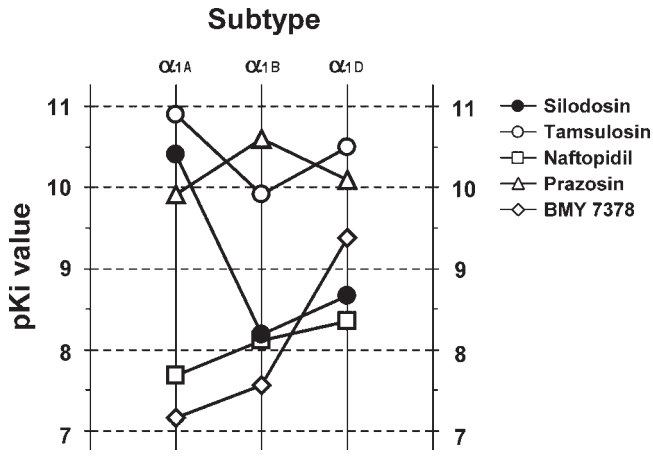

Fig. 1. Diagrammatic comparison of the affinities of various α_1-AR antagonists for recombinant human α_1-AR subtypes. Data was taken and modified from Tatemichi et al. [2006].

In the in vitro experiment, we evaluated the antagonistic effects of silodosin and other α_1-AR antagonists in dog isolated prostate and carotid artery, tissues that are predominantly regulated by the α_{1A}- [Goetz et al., 1994] and α_{1B}-AR subtypes [Muramatsu et al., 1991], respectively. In the in vivo experiment, we used anesthetized dogs to study the effects of silodosin on the hypogastric nerve stimulation (HNS)-induced increase in IUP, and on BP and heart rate (HR). In addition, in view of the differences in their modes of action-based on their selectivity profiles toward α_1-AR subtypes—silodosin was compared with tamsulosin ($\alpha_{1A/1D}$-AR antagonist) and naftopidil (α_{1D}-AR antagonist), two clinically used agents.

MATERIALS AND METHODS

This study was conducted according to guidelines approved by the Laboratory Animal Committee of Kissei Pharmaceutical Co., Ltd., and it conformed to current Japanese Law. Male beagle dogs (Nihon Nosan Corporation, Yokohama, Japan; LSG, Tokyo, Japan; Oriental Yeast, Tokyo, Japan) were maintained under a 12-hr light/12-hr dark cycle with free access to water and standard laboratory food until the day of the experiment.

Drugs

Silodosin (KMD-3213: (—)-1-(3-hydroxypropyl)-5-[(2*R*)-2-({2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-2,3-dihydro-1*H*-indole-7-carboxamide), tamsulosin hydrochloride, and naftopidil were synthesized by Kissei Pharmaceutical Co., Ltd. (Matsumoto, Japan). Prazosin hydrochloride, BMY 7378 dihydrochloride, desipramine hydrochloride, (±)-propranolol hydrochloride, corticosterone, yohimbine hydrochloride, and (−)-noradrenaline bitartrate (NA) were purchased from Sigma (St. Louis, MO). For the in vitro study, silodosin was dissolved in dimethylsulfoxide (DMSO), then diluted with Hartmann's solution of the following composition (w/v %): NaCl 0.6, KCl 0.03, $CaCl_2$ 0.02, and lactic acid 0.31. The other agents were dissolved in DMSO and diluted with physiological saline or distilled water (except NA, which was dissolved in physiological saline). For the in vivo experiments, silodosin was dissolved in Hartmann's solution containing hydrobromide at a twofold equivalent of the silodosin. Tamsulosin hydrochloride was dissolved in physiological saline. Naftopidil was dissolved in 0.1 mol/L phosphate-buffer solution, and diluted with distilled water.

Isolated Prostate And Carotid Artery Tissue Studies

The prostate gland and bilateral common carotid arteries were removed from male beagle dogs weighing 9.6−14.8 kg after euthanasia (via an overdose of sodium pentobarbital through the cephalic vein). After removal of connective tissue and fat, endothelial cells were removed from the carotid artery by rubbing with filter paper. Isolated prostates were cut into

strips (15 × 3 mm) and carotid arteries were cut helically (10 × 2 mm). Tissues were suspended in an organ bath filled with 10 ml Krebs–Henseleit solution of the following composition (mmol/L): NaCl 118.1, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0, and glucose 11.1. Baths were maintained at 37°C and constantly gassed with 95% O_2/5% CO_2, and the preparations were allowed to equilibrate under a resting tension of 0.5 g for prostate and 1 g for carotid artery for at least 1 hr before the start of the experiment. Desipramine (1×10^{-7} mol/L), corticosterone (1×10^{-5} mol/L), yohimbine (1×10^{-7} mol/L), and (±)-propranolol (1×10^{-6} mol/L) were present throughout the experiments to block neural uptake of NA, extraneural uptake of NA, α_2-AR-induced and β-AR-induced responses, respectively. The tensions developed were measured through an isometric force-displacement transducer (Type 45196A; NEC San-ei, Tokyo, Japan). Cumulative concentration-response curves, which were constructed for all tissues by cumulative addition of NA at concentrations of 1×10^{-8} to 1×10^{-3} mol/L in half-log increments, were obtained three times from one and the same strip. After the second control curve had been obtained, each strip was incubated with a certain concentration of test drug. This incubation was begun 1 hr before and continued during the construction of the subsequent experimental curve.

Hypogastric Nerve Stimulation (HNS)-Induced Intraurethral Pressure (IUP), and Blood Pressure (BP) and Heart Rate (HR)

Male beagle dogs weighing 9.5–16.4 kg were anesthetized with intravenously (i.v.) administered sodium pentobarbital (30 mg/kg), and anesthesia was maintained using a continuous i.v. infusion of the same drug (2–4 mg/kg/hr). After intratracheal intubation, respiration was controlled using a respirator (SN-480-3; Shinano Seisakusho, Tokyo, Japan; volume 20 ml/kg, frequency 20 times/min). The test drugs and a drip infusion of glucose-electrolyte solution were given through a cannula placed in the right cephalic vein.

The penis was then dissected from the abdominal wall, and the bladder and prostate were exposed through a midline incision. To prevent filling of the bladder, the ureters were cannulated bilaterally and urine from the kidney was drained. The bladder neck (immediately above the prostate) was ligated to prevent any interaction between IUP and intravesical pressure. A pressure transducer (CTO-1: 6 Fr.; Gaeltec, Dunvegan, Scotland, UK) was inserted through the urethral meatus in a retrograde fashion, the pressure-sensor of the catheter being located within the prostatic urethra to measure prostatic IUP (via a strain amplifier).

The hypogastric nerves were sectioned bilaterally at approximately 1 cm distal to the inferior mesenteric ganglion. The distal end of the unilateral hypogastric nerve was attached to a stainless two-core sealed electrode (SS-3; Narishige, Tokyo, Japan). Simultaneously, a cannula was inserted into the femoral artery, and BP was measured using a strain amplifier (AP-601G; Nihon Kohden Co., Ltd., Tokyo, Japan) via a pressure transducer. The HR was obtained by leading the pulse waves to a tachometer (AT-601G; Nihon Kohden). Using an electrical stimulator (SEN-3301; Nihon Kohden), HNS was applied by passing a rectangular current at 10 V, 5 msec pulse width, and 10 Hz frequency through the electrode for 5 sec in every 10 min (Fig. 2). After the response had stabilized, a test drug was i.v. administered every 30 min in increasing doses. Between doses, HNS was performed every 10 min (three times). The maximal effects of a given test drug on the HNS-induced IUP response and on mean blood pressure (MBP) within 30 min after each dosing were used for the evaluation.

Data Analysis

Data are expressed as the mean ± standard error of the mean (SEM). In the in vitro study, the contractions induced

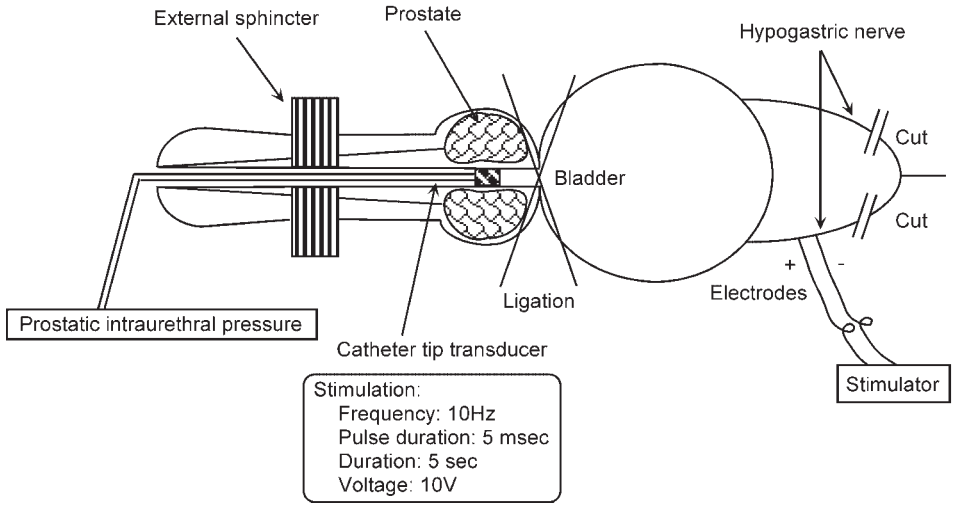

Fig. 2. Preparation used for the measurement of the intraurethral pressure (IUP) increase evoked by hypogastric nerve stimulation (HNS) in male dogs.

by NA were plotted as a percentage of the maximum increase for each concentration-response curve. Estimates of affinity are represented as the pK_B value, calculated using the following formula: $pK_B = \log (CR-1) - \log [\text{antagonist}]$, where CR is the ratio of NA concentrations that induced a similar response (i.e., half-maximal response) between the presence and absence of the test drug. The prostatic selectivity of each test drug was determined using the pK_B values obtained for prostate and carotid artery. In the in vivo experiments, ID_{50} values (the dose inhibiting the IUP increase by 50%) and ED_{15} values (dose at which MBP was decreased by 15%) were calculated by linear regression analysis. In addition, uroselectivity (ED_{15}/ID_{50}) was calculated for every animal. Statistical differences were analyzed using Aspin–Welch's *t*-test, differences being judged to be significant at the level of $P < 0.05$.

RESULTS

Effects on NA-Induced Contraction in Dog Prostate and Carotid Artery

Table I summarizes the inhibitory effects of silodosin and the other α_1-AR antagonists on NA-induced prostate and carotid artery contractions. NA induced concentration-dependent contractions in both tissues, its potency being higher for the carotid artery than for the prostate (pEC_{50} values 6.63 ± 0.12 and 5.77 ± 0.12, respectively). All the drugs tested concentration-dependently inhibited NA-induced contractions in both tissues, and each drug produced a rightward shift in the concentration-response curve for NA. In the case of the prostate, the pK_B value for the inhibitory effect of silodosin was similar to that of tamsulosin, and the rank order of potency was tamsulosin $\geqq$ silodosin > prazosin > naftopidil > BMY 7378. In the case of the carotid artery, however, prazosin was the most powerful antagonist of NA-induced contractions with a subnanomolar potency (pK_B value 9.74), although tamsulosin (pK_B value 9.29) was almost the equal of prazosin. In contrast, silodosin exhibited a very low potency in the carotid artery (pK_B value 7.54). The selectivity ratios for the above drugs (inhibition of NA-induced prostatic contractions vs. inhibition of NA-induced carotid artery contractions) are also given in Table I. The prostatic selectivity of silodosin was 79.4, and the rank order of selectivity was silodosin >> tamsulosin > naftopidil > BMY 7378 > prazosin.

TABLE I. Affinity Estimates for Various α_1-AR Antagonists in Dog Isolated Prostate and Carotid Artery

Drug	pK_B value		Prostatic selectivity[a]
	Prostate	Carotid artery	
Silodosin	9.44 ± 0.16	7.54 ± 0.12	79.4
Tamsulosin	9.54 ± 0.15	9.29 ± 0.08	1.78
Naftopidil	7.14 ± 0.12	7.40 ± 0.17	0.550
Prazosin	7.74 ± 0.03	9.74 ± 0.22	0.0100
BMY 7378	6.30 ± 0.06	7.24 ± 0.03	0.115

Each value represents the mean ± SEM from three to five experiments.
[a]"Prostatic selectivity" was obtained by calculating the values of 10 to the power M (10^M), where $M = pK_B$ [prostate] $- pK_B$ [carotid artery].

Effects on HNS-Induced IUP, and BP and HR

Figure 3 shows representative tracings of the effects induced by intravenous injections of silodosin (0.3–30 μg/kg), tamsulosin (0.3–30 μg/kg), and naftopidil (10–1,000 μg/kg) on BP, HR, and the HNS-induced increase in IUP. Silodosin reduced the HNS-induced increase in IUP in a dose-dependent manner, with no detectable effect on either BP or HR, whereas both tamsulosin and naftopidil lowered BP as well as reducing the HNS-induced increase in IUP. The basal tonic level of IUP was not influenced by the administration of any doses of the test drugs. Figure 4 shows, for all the test drugs, the dose-response relationships for their effects on the IUP responses and MBP (each measured at the point of maximal effect). The ID_{50} values for the IUP responses, the ED_{15} values for effects on MBP, and uroselectivity values (ED_{15}/ID_{50}) are given in Table II. The potency of silodosin against the HNS-induced IUP increase was similar to that of tamsulosin, the ID_{50} values being 1.86 ± 0.479 and 0.908 ± 0.300, respectively, while naftopidil displayed an approximately 30-fold lower potency than silodosin (ID_{50} value 50.3 ± 10.6) (Fig. 4 and Table II). Each of the drugs tested caused a dose-dependent decrease in MBP, although silodosin was weaker in this respect than tamsulosin and naftopidil. The highest doses of tamsulosin (300 μg/kg i.v.) and naftopidil (1,000 μg/kg i.v.) induced about a 50% reduction in MBP, but the highest dose of silodosin (1,000 μg/kg i.v.) induced only a 20% reduction (Fig. 4). As a result, the uroselectivity value for silodosin was significantly higher than those for tamsulosin and naftopidil (237 vs. 1.21 and 2.65, about 200- and 100-fold, respectively) (Table II).

DISCUSSION

Previous radio-ligand binding and functional studies of BPH have shown that a dynamic component, a factor in the voiding dysfunction that accompanies BPH, is caused by the α_1-AR found in human prostate smooth muscle [Lepor and Shapiro, 1984; Yamada et al., 1992], and the indication was that α_1-AR played an important role in the LUT. Currently, α_1-ARs are sub-classified into α_{1A}-, α_{1B}-, and α_{1D}-AR [Hieble et al., 1995], and each of these subtypes has a distinct expression pattern across various tissues. In the LUT, for example, α_{1A}-AR is predominant [Price et al., 1993; Walden et al., 1997; Nasu et al., 1998], while in the aorta α_{1B}- and α_{1D}-AR predominate [Hatano et al., 1994; Faure et al., 1995]. Dogs are fundamentally the same as humans in terms of α_1-AR subtype distribution in the LUT and aorta [Goetz et al., 1994; Hoo et al., 1994; Low et al., 1998], and BPH is an age-related disease in both humans and dogs [Brendler et al., 1983]. The incidence

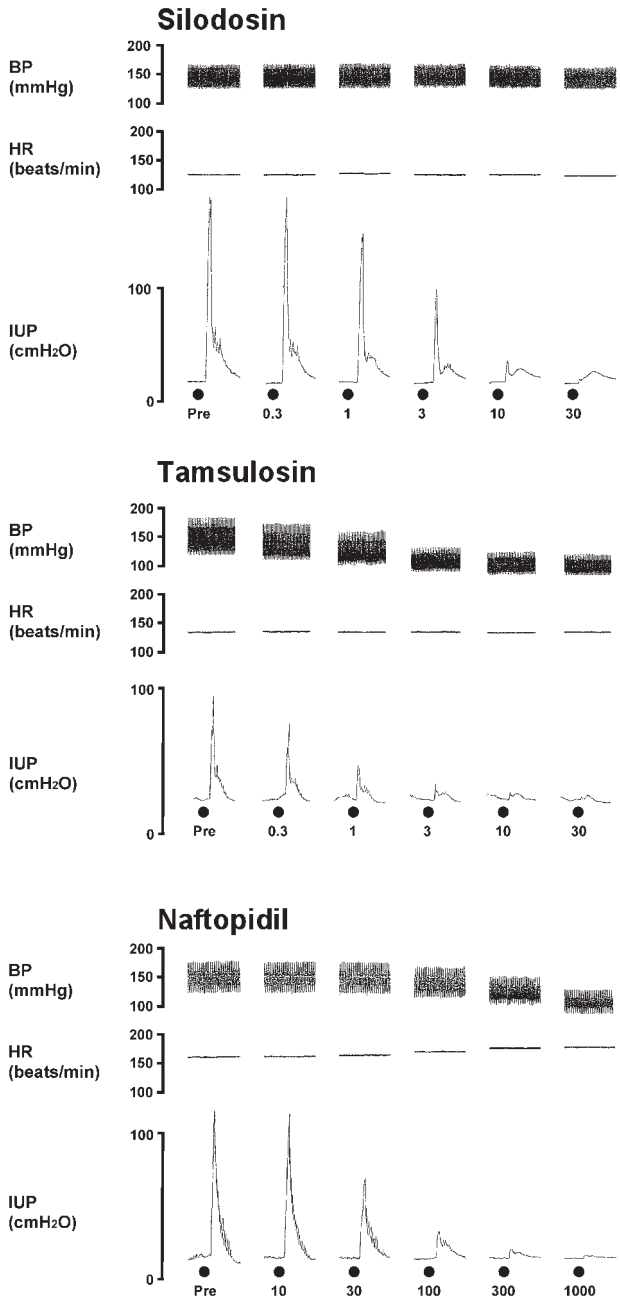

Fig. 3. Representative tracings of blood pressure (BP), heart rate (HR), and the hypogastric nerve stimulation (HNS)-induced increase in intraurethral pressure (IUP) before and after intravenous administration of various doses (shown in μg/kg) of silodosin, tamsulosin, or naftopidil in anesthetized male dogs. Electrical stimulation of the hypogastric nerve was applied at (●).

of BPH-related morphological changes reaches about 60% in men in their fifties and about 40% in male dogs at 2–3 years of age, with an associated diminution of prostatic secretory functions being observed in both species [Brendler et al., 1983]. On this basis, the morphological and etiological development of BPH in the dog should be considered when planning any approach to human BPH.

Hence, we examined the uroselectivity of silodosin and other α_1-AR antagonists in two sets of experiments: namely, in vitro and in vivo functional studies using male dogs. Our main aim was to compare the prostatic selectivity of silodosin with those of the other α_1-AR antagonists. In the first in vitro experiment, using prostate (α_{1A}-AR subtype) [Goetz et al., 1994] and carotid artery (α_{1B}-AR subtype) [Muramatsu et al., 1991] tissues isolated from male dogs, NA induced a concentration-dependent contraction in each tissue (pEC_{50} values, 5.77 and 6.63, respectively). These values are in good agreement with those reported for human prostate (pEC_{50}, 5.46) and mesenteric artery (pEC_{50}, 7.06) [Murata et al., 2000]. The physiology and pharmacology of the canine prostate have similar characteristics to those of the human prostate [Lepor et al., 1994]. Hence, it would seem that the responsiveness of the dog prostate to adrenergic agents might reflect that of the human prostate, and that dogs may represent a useful model for evaluating new α_1-AR antagonists. All the drugs tested produced a rightward shift in the NA-induced prostatic contractions in a concentration-dependent manner (α_{1A}-AR-mediated response), and silodosin's pK_B value was equal to that of tamsulosin and much higher than those of naftopidil, prazosin, and BMY 7378. In contrast, silodosin's pK_B value toward the carotid artery (α_{1B}-AR-mediated response) was quite low compared to that toward the prostate. As a result, silodosin displayed a 79.4-fold higher selectivity for the prostate than for the carotid artery, the highest prostatic selectivity (vs. blood vessels) among the α_1-AR antagonists we examined. This is one of the most important pharmacological characteristics of silodosin, and suggests that it has the potential to be a clinically beneficial drug with few side effects (such as orthostatic hypotension and dizziness). In fact, silodosin's high efficacy and prostatic selectivity toward the canine prostate reflects similar findings in humans [Murata et al., 2000], and our results should therefore be applicable to humans.

In our second in vivo experiment, we evaluated both the efficacy and uroselectivity (ED_{15}/ID_{50}) of silodosin toward the HNS-induced increase in IUP in anesthetized male dogs, in an attempt to confirm the results obtained in the in vitro experiment, and we also compared silodosin with tamsulosin and naftopidil. Electrical stimulation of the hypogastric nerve causes a release of endogenous neurotransmitters, which in turn contract the prostate and urethra without affecting cardiovascular parameters [Poirier et al., 1988; Imagawa et al., 1989]. We selected the HNS-induced increase in IUP as our test response, considering it to be closer to a physiological effect than the response induced by administration of an exogenous agonist like phenylephrine. Nasu et al. (1996) reported that in human prostatic tissue, α_{1A}-AR mRNA was almost nine times as abundant in BPH samples as in nonBPH samples, the ratio of the various subtype mRNAs being α_{1a}:α_{1b}:α_{1d} = 85:1:14 in BPH samples and 63:6:31 in nonBPH samples. They suggested that this increased expression of the α_{1A}-AR subtype may be primarily responsible for the enhanced contraction of the prostate in BPH. Although all the drugs we tested almost

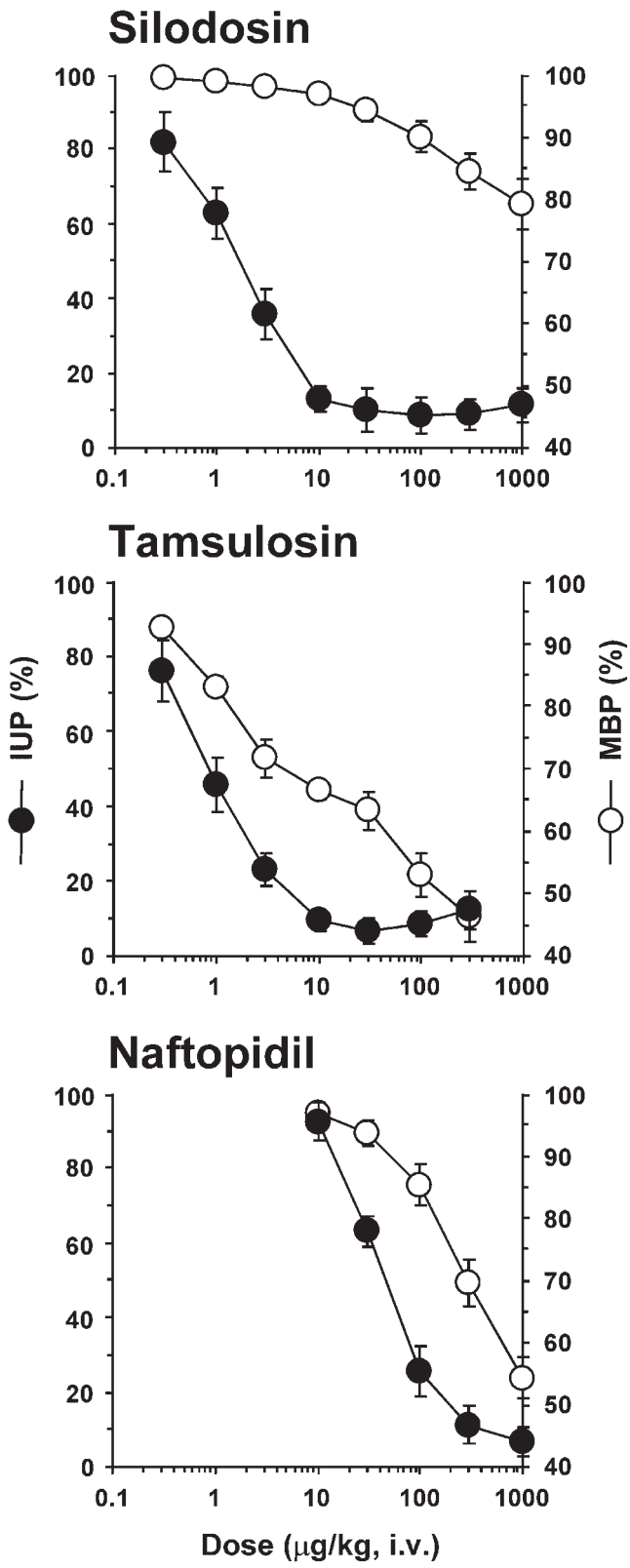

TABLE II. ID_{50}, ED_{15}, and uroselectivity values obtained for intravenously administered silodosin, tamsulosin, and naftopidil in anesthetized male dogs

	IUP	MBP	Uroselectivity
Drug	ID_{50} (μg/kg)[a]	ED_{15} (μg/kg)[b]	ED_{15}/ID_{50}
Silodosin	1.86 ± 0.479	440 ± 198	237 ± 76.6*,**
Tamsulosin	0.908 ± 0.300	0.837 ± 0.130	1.21 ± 0.296
Naftopidil	50.3 ± 10.6	108 ± 33.8	2.65 ± 1.10

Values represented the mean ± SEM from four to five experiments.
[a]ID_{50}: dose required to produce 50% inhibition of the pre-IUP response.
[b]ED_{15}: dose required to produce a 15% decrease in MBP (mean blood pressure).
*$P < 0.05$: versus tamsulosin, Aspin–Welch's t-test.
**$P < 0.05$: versus naftopidil, Aspin–Welch's t-test.

completely inhibited the HNS-induced increase in IUP, they differed in the maximum decrease in MBP they induced. Silodosin, a selective α_{1A}-AR antagonist, as summarized in Figure 1, lowered MBP at most by about 20% even at 1,000 μg/kg, a dose about 500-fold higher than its ID_{50} value toward the IUP response. On the other hand, tamsulosin and naftopidil lowered MBP by up to about 15 and 12% at a dose equivalent to their ID_{50} value, and by about 55% and 45%, respectively, at maximum. We hypothesize that the inhibitions of the IUP response induced by the various α_1-AR antagonists can be attributed mainly to α_{1A}-AR. Further, it is difficult to explain the differences in the hypotensive responses as resulting from their affinities only for α_{1B}-AR. Thus, these results indicate the possible participation of α_{1D}-AR as well as α_{1B}-AR in the cardiovascular response to these drugs. Indeed, an involvement of the α_{1D}-AR in the regulation of BP has been indicated by previous experimental findings [Villalobos-Molina et al., 1999; Tanoue et al., 2002; Hosoda et al., 2005]. It is suggested that a drug with low affinities for both α_{1B}- and α_{1D}-AR compared to α_{1A}-AR (like silodosin) should be suitable for clinical evaluation as a therapeutic drug with little or no hypotensive effect, even though the degree of similarity between dog and human in respect of the distribution of α_1-AR subtypes within the vasculature has yet to be fully elucidated. The in vivo results we obtained with silodosin and tamsulosin were almost completely in accord with those obtained in our in vitro experiments, thus confirming the uroselectivity of silodosin in the male dog in vivo. However, with regard to uroselectivity, our in vivo findings with naftopidil were not in

Fig. 4. Effects of i.v. administrations of silodosin, tamsulosin, and naftopidil on the hypogastric nerve stimulation (HNS)-induced increase in intraurethral pressure (IUP), and the mean blood pressure (MBP) level in anesthetized male dogs. Each data-point represents the mean ± SEM from four to five experiments. Values presented are the maximum responses observed during the 30-min period after administration at each dosage. ●IUP: The mean value obtained for the HNS-induced increase in IUP before administration of each drug was taken as 100%. ○MBP: The mean value of MBP obtained before administration of each drug was taken as 100%.

agreement with those we obtained in vitro. Naftopidil is metabolized into phenyl-OH-naftopidil in dogs, and the α_{1B}-AR potency of phenyl-OH-naftopidil is approximately 1/13th of that of naftopidil itself [Takei et al., 1999]. This may be why naftopidil displayed a higher uroselectivity than tamsulosin in the present in vivo experiment.

Recently, it was reported that silodosin improved irritative symptoms as well as obstructive symptoms in a phase III clinical trial, but an adverse event (namely, abnormal ejaculation) occurred simultaneously in this trial [Yoshida et al., 2005; Kawabe, 2006]. More detailed investigations will be necessary in the future to elucidate the mechanisms underlying these effects.

Thus, our study has demonstrated that silodosin has a higher uroselectivity in male dogs than the other α_1-AR antagonists we tested. The high uroselectivity of silodosin in this dog model seems to correlate well with its reported human α_{1A}-AR and prostatic selectivity.

CONCLUSION

In conclusion, we clearly demonstrated in the present experiments on dogs that silodosin, a selective α_{1A}-AR antagonist, has a potent and highly selective action on the LUT. On this basis, we suggest that a selective α_{1A}-AR antagonist such as silodosin may have good potential as a less-hypotensive drug for the treatment of BPH in humans.

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