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Effects of silodosin and tamsulosin on the urethra and cardiovascular system in young and old dogs with benign prostatic hyperplasia

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ABSTRACT

We examined whether the effects (efficacy on the urethra and hypotension) of silodosin (α_{1A}-adrenoceptor antagonist) and tamsulosin (α_{1A+1D}-adrenoceptor antagonist) in dogs with benign prostatic hyperplasia altered with age. We used young and old dogs, diagnosed as having benign prostatic hyperplasia by veterinarian's palpation. Under anesthesia, the increase in intraurethral pressure evoked by hypogastric nerve stimulation was measured, together with the level of systemic mean blood pressure. Each drug was administered intravenously in progressively increasing doses. At the end of the experiment, the prostate was isolated from each dog, then weighed and investigated pathologically to confirm benign prostatic hyperplasia. The wet weight of the prostate was greater in old dogs with benign prostatic hyperplasia than in young dogs with benign prostatic hyperplasia. By light microscopy, hyperplasia in the prostatic epithelium was confirmed in both groups. Silodosin (0.3–300 μg/kg) dose-dependently inhibited the hypogastric nerve stimulation-induced increase in intraurethral pressure (without significant hypotensive effects) in both young and old dogs with benign prostatic hyperplasia. Tamsulosin (0.3–300 μg/kg) also dose-dependently inhibited the intraurethral pressure increase in both groups, but it had a hypotensive effect that was significantly greater in old than in young dogs with benign prostatic hyperplasia. In conclusion, as regards the effect of silodosin on intraurethral pressure, potency was similar between young and old dogs with benign prostatic hyperplasia, and it was without significant hypotensive effects. We therefore suggest that silodosin might be a good medication for lower urinary tract symptoms in patients with benign prostatic hyperplasia in all age groups.

1. Introduction

Benign prostatic hyperplasia is one of the most commonly encountered diseases in middle-aged men (see Chapple, 2005). In the 1980s, nonselective α_1-adrenoceptor antagonists such as prazosin, which was originally developed as an antihypertensive drug, were used as first-generation therapeutic agents for the voiding dysfunction associated with benign prostatic hyperplasia. However, because of the existence of α_1-adrenoceptors in the vasculature (Lepor, 1993; Monda and Oesterling, 1993), the adverse effects of prazosin (such as orthostatic hypotension and dizziness) can limit its therapeutic applications for benign prostatic hyperplasia. Since some experiments had indicated the participation of the α_{1B}-adrenoceptor in the regulation of blood pressure (BP) (Cavalli et al., 1997; Hancock et al., 2002), tamsulosin was developed as an antagonist with a selectivity for the α_{1A}- versus α_{1B}-adrenoceptor and an affinity for the lower urinary tract. Tamsulosin has been used clinically as a second-generation therapeutic agent.

Recently, silodosin, a new highly selective α_{1A}-adrenoceptor antagonist, was developed. Its selectivity towards the α_{1A}- versus α_{1B}-adrenoceptor is much higher than that of second-generation drugs such as tamsulosin. In fact, Tatemichi et al. (2006a) reported that in radioligand-binding studies, silodosin displayed at least an approximately 160-fold higher affinity for the human α_{1A}-adrenoceptor than for the human α_{1B}-adrenoceptor. Further, Murata et al. (2000) found that silodosin was highly selective for the human prostate, in which the α_{1A}-adrenoceptor mediates contraction (pK_B value = 9.64). To judge from these publications, silodosin has potential as a third-generation α_{1A}-adrenoceptor antagonist that might strongly alleviate lower urinary tract symptoms without affecting BP.

Male dogs are reportedly the only animals other than humans in which benign prostatic hyperplasia develops spontaneously with aging (Evans and Christensen, 1979). In dogs as well as in humans, α_{1A}-adrenoceptors mediate prostatic contraction (Kenny et al. 1994; Marshall et al., 1995) and glandular hyperplasia and interstitial hyperplasia are observed (Wilson, 1980; Brendler et al., 1983). Thus, dogs are an important animal model emulating the benign prostatic

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hyperplasia symptoms of humans. Regarding the development of drugs for the treatment of voiding dysfunction in patients with benign prostatic hyperplasia, it is believed that the dog with benign prostatic hyperplasia is very useful for the evaluation of medications for human benign prostatic hyperplasia. However, reports in which dogs with benign prostatic hyperplasia have been used for the evaluation of α_1-adrenoceptor antagonists are very scarce.

In this study, we used young and old dogs with benign prostatic hyperplasia to investigate whether the effects of silodosin (selective α_{1A}-adrenoceptor antagonist) and tamsulosin (selective α_{1A+1D}-adrenoceptor antagonist) on intraurethral pressure and on the cardiovascular system alter during aging.

2. Materials and methods

2.1. Animals

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; Nihon SLG, Tokyo, Japan; Oriental Yeast, Tokyo, Japan) were maintained under a 12-hour light/12-hour dark cycle with free access to water and standard laboratory food until the day of the experiment. Before the start of experiments, dogs were initially diagnosed as having benign prostatic hyperplasia by veterinarian's palpation (on the basis of the magnitude and hardness of the prostate).

2.2. Hypogastric nerve stimulation-induced increase in intraurethral pressure, and blood pressure

Male beagle dogs weighing 9.4 to 17.3 kg were anesthetized by means of intravenously (i.v.) administered sodium pentobarbital (30 mg/kg), and anesthesia was maintained using a continuous i.v. infusion of the same drug (2 to 4 mg/kg/h). 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 preparation and protocol were described in detail in a previous paper (Tatemichi et al., 2006b). The penis was dissected free 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 the urine issuing from the kidneys was drained. The bladder neck (immediately above the prostate) was ligated to prevent any interaction between intraurethral pressure 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 allow measurement of prostatic intraurethral pressure (via a strain amplifier). A catheter (6 Fr) was inserted into the bladder body to measure intravesical pressure.

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

2.3. Pathological histology

At the end of the study, dogs were euthanized with an overdose of sodium pentobarbital. Immediately after removal of the prostate and measurement of its wet weight, each prostate was fixed in 10% phosphate-buffered paraformaldehyde, embedded in paraffin, mounted, sectioned at 4 μm, and stained with hemotoxylin and eosin.

2.4. 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) and tamsulosin hydrochloride were synthesized by Kissei Pharmaceutical Co. Ltd. (Matsumoto, Japan). Silodosin was dissolved in Hartmann's solution containing hydrobromide at a 2-fold equivalent to the silodosin. Tamsulosin hydrochloride was dissolved in physiological saline.

2.5. Data analysis

Data are expressed as the mean ± standard error of the mean (S.E.M.). The hypogastric nerve stimulation-induced increase in intraurethral pressure and the MBP level are expressed as a percentage (%) of the respective value measured before administration of a given test drug. ID_{50} values (the dose inhibiting the intraurethral pressure increase by 50%) and the percentage decrease in MBP were calculated. For statistical analysis, SAS system version 8.20 (SAS Institute, North Carolina, USA) was used, and data were analyzed using Aspin–Welch's *t*-test, univariate repeated-measures degrees of freedom-adjusted analysis as a split-plot design, and multiplicity adjustment of timewise comparisons for longitudinal measurement, with values of $P<0.05$ being considered statistically significant.

3. Results

3.1. Wet weight of prostate and histologic findings

Table 1 shows the wet weights of the prostate glands (which were isolated after the measurement of the other experimental parameters) and ages for the dogs used in this experiment. Prostatic wet weight was significantly greater in young dogs with benign prostatic hyperplasia than in young dogs without benign prostatic hyperplasia. Both age and prostatic wet weight were significantly greater in old dogs with benign prostatic hyperplasia than in young dogs with benign prostatic hyperplasia.

Histological images of the prostate in young dogs without benign prostatic hyperplasia, and in young and old dogs with benign prostatic

Table 1
Age, body weight, and prostatic wet weight in young dogs without benign prostatic hyperplasia, and in young and old dogs with benign prostatic hyperplasia.

Group	*N*	Age (months)	Body weight (kg)	Prostatic weight (g)
Young dog without benign prostatic hyperplasia	6	25.2 ± 1.7	12.2 ± 0.8	7.5 ± 1.0
Young dog with benign prostatic hyperplasia	12	24.7 ± 2.2	11.9 ± 0.5	12.0 ± 1.5[a]
Old dog with benign prostatic hyperplasia	12	84.2 ± 4.1[b]	14.5 ± 0.8[b]	24.9 ± 4.5[a,b]

[a] $P<0.05$: versus Young dog without benign prostatic hyperplasia.
[b] $P<0.05$: versus Young dog with benign prostatic hyperplasia.

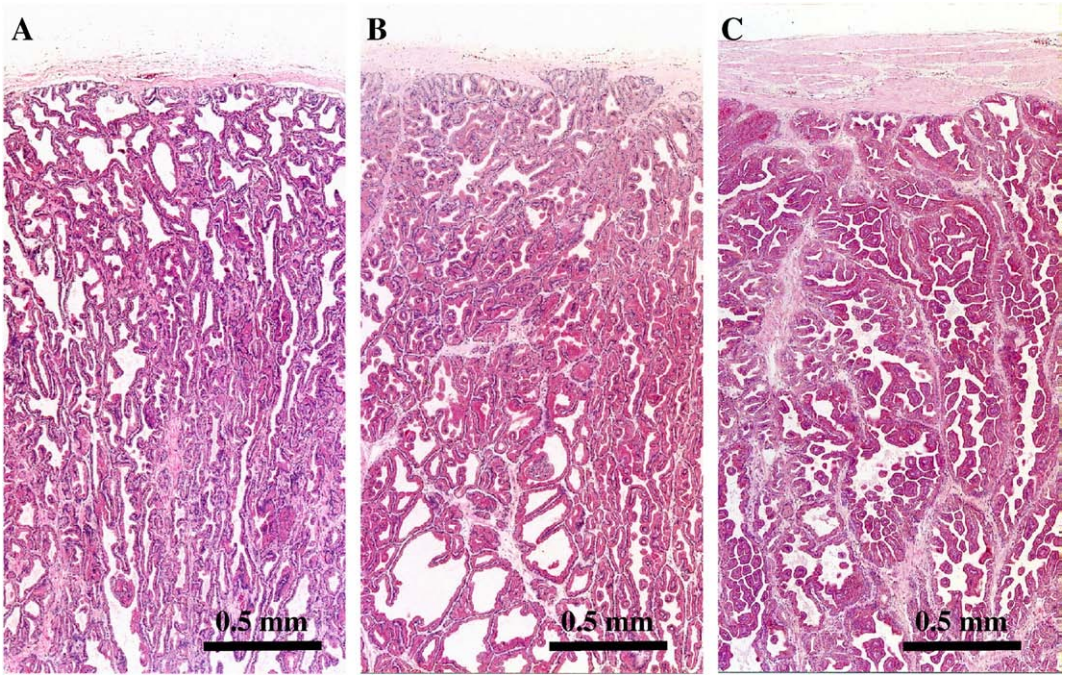

Fig. 1. Typical light microscope images of prostate. (A) young dog without benign prostatic hyperplasia, (B) young dog with benign prostatic hyperplasia, (C) old dog with benign prostatic hyperplasia.

hyperplasia are shown in Fig. 1. The glandular epithelial tissue was more markedly hyperplastic in old dogs with benign prostatic hyperplasia than in young dogs with benign prostatic hyperplasia. The number of stromal cells was more markedly increased in old dogs with benign prostatic hyperplasia than in young dogs with benign prostatic hyperplasia. On the other hand, neither glandular epithelial tissue hyperplasia nor an increase in the number of stromal cells was observed in young dogs without benign prostatic hyperplasia.

3.2. Drug effects on hypogastric nerve stimulation-induced intraurethral pressure, and on MBP and HR levels

The hypogastric nerve stimulation-induced increase in intraurethral pressure was significantly greater in both young and old dogs with benign prostatic hyperplasia than in young dogs without benign prostatic hyperplasia (Table 2). No significant difference in the hypogastric nerve stimulation-induced increase in intraurethral pressure ($P=0.85$) was observed between young and old benign prostatic hyperplasia dogs.

Fig. 2 shows typical tracings of the effects induced by i.v. injection of silodosin and tamsulosin (0.3–10 μg/kg), respectively, on BP, HR and the hypogastric nerve stimulation-induced increases in intraurethral and

Table 2
Hypogastric nerve stimulation-induced increases in intraurethral pressure, and levels of MBP and HR, before drug administration in young dogs without benign prostatic hyperplasia, and in young and old dogs with benign prostatic hyperplasia.

Group	*N*	Increase in intraurethral pressure	MBP	HR
		(cm H_2O)	(mm Hg)	(bpm)
Young dog without benign prostatic hyperplasia	6	28.1 ± 1.7	147.8 ± 4.3	182.3 ± 6.9
Young dog with benign prostatic hyperplasia	12	101.2 ± 20.0[a]	147.4 ± 3.9	171.0 ± 4.2
Old dog with benign prostatic hyperplasia	12	105.7 ± 11.7[a]	132.9 ± 6.4[b]	173.2 ± 8.3[a]

[a] $P<0.05$: versus Young dog without benign prostatic hyperplasia.
[b] $P<0.05$: versus Young dog with benign prostatic hyperplasia.

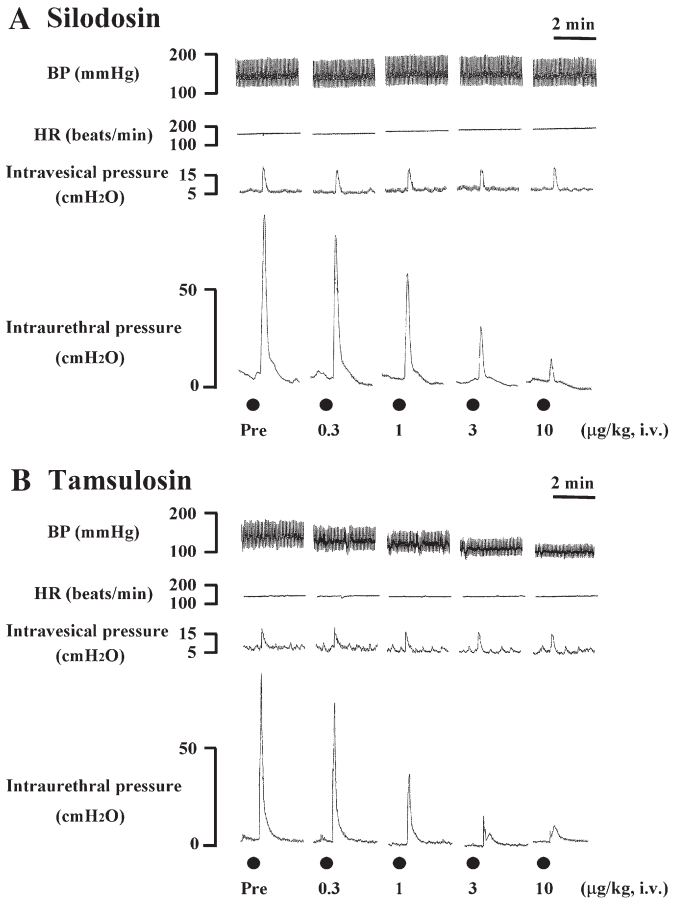

Fig. 2. Typical tracings of BP, HR, and hypogastric nerve stimulation-induced increases in intraurethral and intravesical pressures before and after intravenous administration of various doses (shown in μg/kg) of silodosin (A) and tamsulosin (B) in anesthetized old dogs with benign prostatic hyperplasia. Electrical stimulation of hypogastric nerve was applied at ●.

intravesical pressures in old dogs with benign prostatic hyperplasia. Neither of the two drugs affected the induced increase in intravesical pressure. The effects of the two drugs on the induced increase in intraurethral pressure persisted for at least 30 min after administration of each dose. Silodosin decreased MBP in a dose-dependent manner in both young and old dogs with benign prostatic hyperplasia (Fig. 3A). The values obtained for the maximum reduction in MBP induced by silodosin at the dose of 300 μg/kg in young and old dogs with benign prostatic hyperplasia were 78.3 ± 2.9% and 72.3 ± 3.6%, respectively. There was no significant difference between these values ($P = 0.15$). Tamsulosin lowered MBP in a dose-dependent manner in both young and old dogs with benign prostatic hyperplasia (Fig. 3A). At doses of 3 μg/kg or more tamsulosin induced a significantly greater decrease in MBP in old dogs with benign prostatic hyperplasia than in young dogs with benign prostatic hyperplasia. The reduction in MBP induced by tamsulosin was significantly greater than that induced by silodosin in both young and old dogs with benign prostatic hyperplasia.

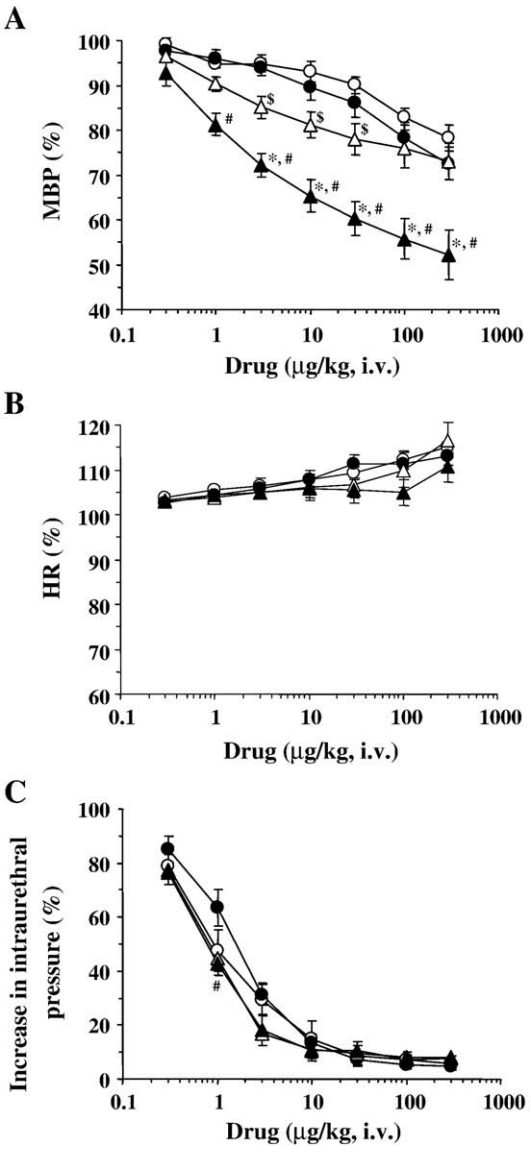

Fig. 3. Effects of intravenous administrations of silodosin and tamsulosin on MBP (A), HR (B), and the hypogastric nerve stimulation-induced increase in intraurethral pressure (C) in anesthetized dogs with benign prostatic hyperplasia. Each data-point represents the mean ± S.E.M. from six experiments. Values presented are the maximum responses observed during the 30-min period after administration at each dosage. The mean values obtained before administration of drugs for MBP, HR, and for the hypogastric nerve stimulation-induced increase in intraurethral pressure were each taken as 100%. Young dog with benign prostatic hyperplasia, silodosin (open circle); old dog with benign prostatic hyperplasia, silodosin (closed circle); young dog with benign prostatic hyperplasia, tamsulosin (open triangle); old dog with benign prostatic hyperplasia, tamsulosin (closed triangle). *$P<0.05$: versus young dog with benign prostatic hyperplasia treated with tamsulosin. # $P<0.05$: versus old dog with benign prostatic hyperplasia treated with silodosin. $ $P<0.05$: versus young dog with benign prostatic hyperplasia treated with silodosin.

Silodosin increased HR in a dose-dependent manner in both young and old dogs with benign prostatic hyperplasia (Fig. 3B). No statistically significant difference was observed in the silodosin-induced increase in HR between these two groups of dogs ($P = 0.80$). Tamsulosin also increased HR in a dose-dependent manner in both young and old dogs with benign prostatic hyperplasia (Fig. 3B), and there was no significant difference in this effect between the two groups of dogs ($P = 0.29$). Concerning the effects on HR, no significant difference was observed among silodosin- and tamsulosin-treated young or old dogs with benign prostatic hyperplasia.

Silodosin suppressed the hypogastric nerve stimulation-induced increase in intraurethral pressure in a dose-dependent manner in both young and old dogs with benign prostatic hyperplasia (Fig. 3C). The ID_{50} values for the effect of silodosin on the hypogastric nerve stimulation-induced increase in intraurethral pressure showed no significant difference ($P = 0.75$) between young (1.5 ± 0.5 μg/kg) and old dogs with benign prostatic hyperplasia (1.7 ± 0.3 μg/kg). Likewise, tamsulosin reduced the hypogastric nerve stimulation-induced increase in intraurethral pressure in a dose-dependent manner in both young and old dogs with benign prostatic hyperplasia (Fig. 3C), and the ID_{50} values for its effects were not significantly different between young (0.9 ± 0.1 μg/kg) and old dogs with benign prostatic hyperplasia (0.9 ± 0.2 μg/kg). In old dogs with benign prostatic hyperplasia, intravenous administration of 1 μg/kg tamsulosin caused a significantly greater reduction in the increase in intraurethral pressure than did 1 μg/kg silodosin (57.0% verses 36.4%). However, in young dogs with benign prostatic hyperplasia, no significant difference in the increase in intraurethral pressure was observed between the silodosin- and tamsulosin-treated groups at any dose.

4. Discussion

Apart from humans, dogs are the only species in which males are known to develop benign prostatic hyperplasia with aging. Signs of benign prostatic hyperplasia can reportedly be observed in dogs from about 24 months old, and the prostate appears to continue to mature until 72 months old (Brendler et al., 1983). In the present study, we used dogs diagnosed as having benign prostatic hyperplasia by veterinarian's palpation, and they were classified as either young (about 24 months old) or old (about 84 months old) dogs with benign prostatic hyperplasia. First, we observed the morphological changes in the prostate and the hypogastric nerve stimulation-induced increases in intraurethral pressure in young and old dogs with benign prostatic hyperplasia. Then, we investigated whether the effects of silodosin and tamsulosin on these stimulation-induced responses in the lower urinary tract might differ between the age groups.

Glandular epithelial tissue exhibiting hyperplasia, one of the typical pathological features of benign prostatic hyperplasia (Murakoshi et al., 2001), was observed in the prostates isolated from both our young and old dogs with benign prostatic hyperplasia. A more obvious increase in the number of stromal cells was observed in old dogs with benign prostatic hyperplasia than in young dogs with benign prostatic hyperplasia. The wet weight of the prostate, which was isolated after the measurement of the other experimental parameters, was significantly greater in both young and old dogs with benign prostatic hyperplasia than in young dogs without benign prostatic hyperplasia, in agreement with the veterinarian's diagnosis before the drug evaluation. Lowseth et al. (1990) reported that an increase in the weight of the prostate is associated with an increase in its absolute volume, and suggested that mechanical obstruction of the

urethra, which is the cause of the lower urinary tract obstruction associated with human benign prostatic hyperplasia, occurs in dogs with benign prostatic hyperplasia. In our experiments, the hypogastric nerve stimulation-induced increase in intraurethral pressure was significantly greater in both young and old dogs with benign prostatic hyperplasia than in young dogs without benign prostatic hyperplasia. It would appear that functional obstruction, which increases the contractile force of the prostatic and urethral smooth muscle, occurred in our dogs with benign prostatic hyperplasia. Hence, we presumed that mechanical and functional obstructions in the lower urinary tract had developed in both young and old dogs with benign prostatic hyperplasia. As described above, the signs of lower urinary tract obstruction we detected in both benign prostatic hyperplasia groups were very similar to those seen in humans, and so it seemed appropriate to use such dogs with benign prostatic hyperplasia to evaluate drug efficacies against the voiding dysfunction accompanying benign prostatic hyperplasia.

Concerning the increase in intraurethral pressure induced by hypogastric nerve stimulation before drug administration, the values were significantly greater in young dogs with benign prostatic hyperplasia than in young dogs without benign prostatic hyperplasia, which may be related to the difference between these groups in the wet weight of the prostate (see Table 1). This is consistent with the observation that intraurethral pressure is more strongly affected by prostatic than urethral α_{1A}-adrenoceptors (Michel and Vrydag, 2006). On the other hand, although the wet weight of the prostate was significantly greater in old than in young dogs with benign prostatic hyperplasia, there was no significant difference between these two groups in the increase in intraurethral pressure induced by hypogastric nerve stimulation before drug administration. In anesthetized rats, the maximal intraurethral pressure measured by cystomanometry was not different between 6- and 24-month-old animals (Lluel et al., 2003). In dogs with benign prostatic hyperplasia, our data suggest that the increase in intraurethral pressure induced by hypogastric nerve stimulation is hardly elevated during aging.

In our experiment, silodosin dose-dependently inhibited the hypogastric nerve stimulation-induced increase in intraurethral pressure, with the ID_{50} values in young and old dogs with benign prostatic hyperplasia being 1.5 and 1.7 μg/kg, respectively. Tamsulosin also dose-dependently inhibited the hypogastric nerve stimulation-induced increase in intraurethral pressure, with its ID_{50} value being 0.9 μg/kg in each benign prostatic hyperplasia group. These values for young and old dogs with benign prostatic hyperplasia are in good agreement with those previously reported for dogs without benign prostatic hyperplasia (silodosin; 1.9 μg/kg, tamsulosin; 0.9 μg/kg) (Tatemichi et al., 2006b). The potencies obtained for silodosin and tamsulosin in the present study were about two- to five-times greater than those reported for their effects on the phenylephrine-induced increase in intraurethral pressure in anesthetized dogs (Noguchi et al., 2008). It seems likely that the phenylephrine had a more powerful effect on α_1-adrenoceptors in the prostatic urethra than hypogastric nerve stimulation. Tamsulosin was thus about twice as potent as silodosin in its inhibitory effect on the hypogastric nerve stimulation-induced increases in intraurethral pressure, which is in accordance with two recent reports (Tatemichi et al., 2006b; Noguchi et al., 2008). This result is roughly in line with the ratio of their affinities (about three) for the human α_{1A}-adrenoceptor (Tatemichi et al., 2006a).

Although both silodosin and tamsulosin decreased MBP in a dose-dependent manner, silodosin was significantly less potent than tamsulosin in both young and old dogs with benign prostatic hyperplasia. With each drug, however, the effect on HR did not differ significantly between young and old dogs with benign prostatic hyperplasia. Therefore, tamsulosin probably had a greater inhibitory influence over the baroreceptor reflex effect on HR. It has been reported that α_{1B}-adrenoceptors mediate both blood vessel contraction (Hatano et al., 1994; Take et al., 1998) and baroreceptor-induced inotropic effects (Townsend et al., 2004). Further, doxazosin and terazosin reportedly reduce blood pressure by blockade of central α_1-adrenoceptors (Ramage and Wyllie, 1995), although the subtypes have not been identified. Tamsulosin has a higher affinity for the α_{1B}-adrenoceptor than silodosin (Tatemichi et al., 2006a), so the decrease in MBP induced by tamsulosin may be mediated via its blocking action on the α_{1B}-adrenoceptors participating in blood vessel contraction and baroreceptor-induced inotropic effects. On this basis, a selective α_{1A}-adrenoceptor antagonist might be expected to have minimal effects on the cardiovascular system (Michel and Vrydag, 2006).

In this study, we examined whether changes might occur with aging in the hypotensive effects of the two drugs and/or in their suppressive effects on intraurethral pressure responses. The inhibitory effect of silodosin on the hypogastric nerve stimulation-induced increase in intraurethral pressure (as indicated by the ID_{50} value) was not different between young and old dogs with benign prostatic hyperplasia. Likewise, quantitatively similar effects were observed between the two tamsulosin-treated groups. Although the effect of silodosin on MBP hardly altered with aging, the effect of tamsulosin on MBP was significantly augmented by aging at doses of 3 μg/kg or more. It has been reported that total α_{1B}-adrenoceptor protein expression increases with aging in humans (Rudner et al., 1999). Moreover, in a clinical study (Andros et al., 1996) the hypotensive effect of prazosin (nonselective α_1-adrenoceptor antagonist), which has a high affinity for the α_{1B}-adrenoceptor, was found to be augmented by aging. It is therefore likely that an elevation of α_{1B}-adrenoceptor expression during aging was responsible for potentiating the hypotensive effect of tamsulosin, which has a high affinity for the α_{1B}-adrenoceptor as well as for the α_{1A}-adrenoceptor in dogs. However, Conley et al. (2001) reported that the α_{1B}-adrenoceptor antagonist RS-513815 did not reduce systemic mean blood pressure in rats anesthetized with urethane. It therefore may be that the effects of α_{1B}-adrenoceptor antagonists on blood pressure depend on species, anesthesia, and/or aging. Although we speculate that any antagonist with a high affinity for the α_{1B}-adrenoceptor will show an augmented hypotensive effect with aging in humans (and dogs), further investigation will be needed to clarify the α_1-adrenoceptor subtype (s) related to hypotension.

If, in humans, aging augments the hypotensive effects only of drugs with an α_{1B}-adrenoceptor blocking action, then a highly selective α_{1A}-adrenoceptor antagonist such as silodosin would be expected to improve lower urinary tract symptoms without seriously affecting the cardiovascular system in patients with benign prostatic hyperplasia.

In the bladder, the sympathetic nerve supply causes relaxation and relatively weak contraction via β_3- and α_1-adrenoceptors, respectively (Michel and Vrydag, 2006). The α_1-adrenoceptors distributed in the bladder trigone play an important role in contraction (Tatemichi et al., 2006a). Indeed, the α_1-adrenoceptor agonist midodrine reduced bladder capacity in anesthetized aged dogs (Takahashi et al., 1996). Thus, activation of the α_1-adrenoceptors present in the trigonal area may be causally related to the storage symptoms (such as frequency and urgency) experienced by patients with an overactive bladder. Collectively, the above data suggest that α_1-adrenoceptor antagonists might increase bladder capacity via inhibitory effects on the contraction of the bladder trigone. However, in the present study neither silodosin nor tamsulosin had any effects on the increases in intravesical pressure induced by hypogastric nerve stimulation (Fig. 2). Incidentally, since in our dogs the hypogastric nerves were cut bilaterally, the two drugs could not have affected the bladder via central alterations in the sympathetic outflow through these nerves.

In conclusion, this study showed that silodosin strongly suppresses the hypogastric nerve stimulation-induced increase in intraurethral pressure without seriously altering MBP in both young and old dogs with benign prostatic hyperplasia, and revealed that neither of these effects was altered by aging. In contrast, in the case of tamsulosin, which exhibits only a small difference in affinity between the α_{1A}-

adrenoceptor and α_{1B}-adrenoceptor (compared to silodosin), the hypotensive effect was significantly potentiated by aging. On the basis of these results, we suggest that a highly selective α_{1A}-adrenoceptor antagonist such as silodosin may prove useful for the improvement of lower urinary tract symptoms in patients with benign prostatic hyperplasia across a wide range of ages.

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