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Effect of JTH-601, a novel α_1-adrenoceptor antagonist, on prostate function in dogs

Yasunori Suzuki [1], Atsunori Kanada [1], Yuki Okaya [1], Kazuo Aisaka *

Central Pharmaceutical Research Institute, Japan Tobacco Inc., 1-1, Murasaki-cho Takatsuki, Osaka 569-1125, Japan

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Abstract

We examined the effect of JTH-601 (3-{*N*-[2-(4-hydroxy-2-isopropyl-5-methylphenoxy)ethyl]-*N*-methylaminomethyl}-4-methoxy-2,5,6-trimethylphenol hemifumarate), a new α_{1L}-adrenoceptor antagonist, on prostatic function in isolated canine prostate and in anesthetized dogs. In the contraction study, phenylephrine and noradrenaline produced concentration-dependent contractions in canine prostate and carotid artery, respectively. In these tissues, JTH-601, prazosin (a non-selective α_1-adrenoceptor antagonist), and tamsulosin (an α_{1A}-adrenoceptor antagonist) competitively antagonized contraction in a concentration-dependent manner. The pA_2 (pK_B) values with prostate were 8.49 ± 0.07 for JTH-601, 7.94 ± 0.04 for prazosin and 9.42 ± 0.22 for tamsulosin. The ratio of pA_2 (carotid artery/prostate), i.e. prostatic selectivity, was 10.471 for JTH-601, 0.008 for prazosin and 0.371 for tamsulosin, respectively. In anesthetized dogs, JTH-601 (1 mg/kg, i.d.) significantly decreased urethral pressure by 15% without affecting blood pressure or heart rate. Tamsulosin (0.1 mg/kg, i.d.) decreased urethral pressure to the same extent as did JTH-601, but with a significant effect on blood pressure and heart rate. JTH-601 showed higher selectivity for canine prostate both in vitro and in vivo. In prostate, an important role of the α_{1L}-adrenoceptor is suggested in the smooth muscle contraction mediated by α_1-adrenoceptors. JTH-601 is expected to be an effective α_1-adrenoceptor antagonist for the treatment of urinary outlet obstruction by benign prostatic hypertrophy with a minimum effect on the cardiovascular system.

Keywords: α_1-Adrenoceptor; α_{1L}-Adrenoceptor; JTH-601; Prostate; (Dog)

1. Introduction

Benign prostatic hypertrophy, a progressive enlargement of the prostate, is an age-related disorder characterized by urinary outlet obstruction. Many studies have revealed that this obstruction is due to both mechanical compression of the urethra by the hypertrophied prostate and to functional contraction of the prostate and urethra by sympathetic stimulation (Shapiro et al., 1981; Furuya et al., 1982; Hedlund et al., 1983; Hieble et al., 1985; Caine, 1986; Caine et al., 1975, 1978; Yamada et al., 1987). The functional importance of α_1-adrenoceptors in the prostate has been demonstrated by many researchers (Hedlund et al., 1985; Kunisawa et al., 1985; Kitada and Kumazawa, 1987). In addition, radioligand binding studies with α_1-adrenoceptor antagonists also showed the existence of α_1-adrenoceptors in human prostate (Lepor and Shapiro, 1984; Hedlund et al., 1985; Yamada et al., 1987, 1991; Kawabe et al., 1990). Since it was reported that phenoxybenzamine is effective in the treatment of urinary outlet obstruction by benign prostatic hypertrophy (Caine et al., 1976, 1978), α_1-adrenoceptor antagonists have been used as therapy for this symptom. Most α_1-adrenoceptor antagonists have been developed as antihypertensive drugs, and thus, adverse effects associated with blood vessel dilation have been reported for the treatment of urinary outlet obstruction by benign prostatic hypertrophy (Scott et al., 1989; Wilde et al., 1993).

At present, α_1-adrenoceptors are generally subclassified into α_{1A}, α_{1B} and α_{1D} (Bylund et al., 1994; Ford et al., 1994; Hieble et al., 1995). Each of these subtypes has been

* Corresponding author. Tel.: +81-726-81-9700; fax: +81-726-81-9722.

E-mail address: kazuo.aisaka@ims.jti.co.jp (K. Aisaka).

[1] Tel.: +81-726-81-9700; fax: +81-726-81-9722.

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observed to have a distinct expression pattern in various tissues: in the prostate, the α_{1A}-adrenoceptor is preferentially expressed (Hirasawa et al., 1993; Price et al., 1993; Weinberg et al., 1994), while in the aorta, α_{1B} and α_{1D} predominate (Price et al., 1994; Faure et al., 1995). These findings, which suggest that the α_{1A}-adrenoceptor plays a role in mediating the prostatic contractile response to α_1-adrenoceptor activation, are consistent with the ability of potent and selective α_{1A}-adrenoceptor antagonists to produce functional blockade of noradrenaline-induced contraction of human prostate, and the functional antagonist potency in human prostate correlates well with affinity for the recombinant human α_{1A}-adrenoceptor (Forray et al., 1994a,b). However, compounds have been identified, such as *RS*-17053 (*N*-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro-α,α-dimethyl-1*H*-indol-3-ethanamine hydrochloride) and abanoquil, that have high affinity for the α_{1A}-adrenoceptor and yet are very weak functional antagonists of noradrenaline-induced contraction of human prostate (Marshall et al., 1992; Ford et al., 1996).

In addition, α_1-adrenoceptors can also be divided into the α_{1H} (α_{1A}, α_{1B} and α_{1D}-adrenoceptors) and α_{1L} classes, which display high and low affinity for prazosin, respectively (Flavahan and Vanhoutte, 1986; Muramatsu et al., 1990; Oshita et al., 1991; Ohmura et al., 1992). For human prostate, there is evidence, based on both radioligand binding and functional experiments, for another additional α_1-adrenoceptor population, distinct from the α_{1A}, α_{1B} and α_{1D}-adrenoceptors (Muramatsu et al., 1994). Furthermore, this α_1-adrenoceptor, designated as α_{1L}-adrenoceptor on the basis of its relatively low sensitivity to blockade by prazosin, has been characterized functionally in several tissues by Muramatsu et al. (1995).

Recently, we found a novel α_1-adrenoceptor antagonist, JTH-601, (3-{*N*-[2-(4-hydroxy-2-isopropyl-5-methylphenoxy)ethyl]-*N*-methylaminomethyl}-4-methoxy-2,5,6-trimethylphenol hemifumarate, Fig. 1). Muramatsu et al., (1996) demonstrated that JTH-601 has a higher affinity for the α_{1L}-adrenoceptor group and a lower affinity for the α_{1H}-adrenoceptor group, except the α_{1A} subtype. This finding prompted us to evaluate the effect of JTH-601 on prostatic function. As α_1-adrenoceptor antagonists are used for the treatment of both benign prostatic hypertrophy and hypertension, we now aimed to evaluate the dilating effect of JTH-601 on prostatic smooth muscle and its hypotensive effect in dogs.

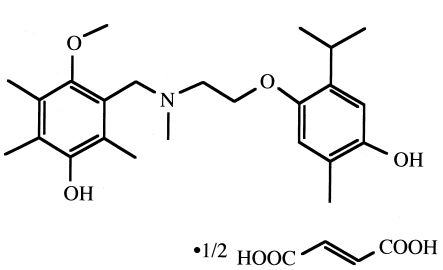

Fig. 1. Chemical structure of JTH-601.

2. Materials and methods

2.1. Effects on isolated canine prostate and carotid artery

Male beagle dogs (Keari, Osaka, Japan) weighing 9.4–12.8 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and killed by bleeding. The prostate and right common carotid artery were isolated and quickly immersed in ice-cold Krebs–Henseleit solution (composition in mM: NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; and glucose, 10.0). After visible connective tissue and fat had been removed, endothelial cells were removed from the carotid artery by rubbing them with cotton swabs. Smooth muscle strips (width, 3 mm × length, 10 mm) from the prostate and open-ring strips from the carotid artery (width, 3 mm) were then prepared. The preparations were mounted vertically under basal tensions of 0.5 g for the prostate and 1.0 g for the carotid artery, respectively, in an organ bath filled with 10 ml of Krebs–Henseleit solution, maintained at 37°C and continuously bubbled with a gas mixture consisting of 95% O_2 and 5% CO_2. Changes in the tension of the preparations were measured isometrically with force transducers (T7-8-240 or T7-30-240, Orientec, Tokyo, Japan) and recorded with a pen recorder (R-304V, Rikadenki, Tokyo, Japan).

Each preparation was allowed to equilibrate for at least 1 h prior to initiation of experimental procedures, and during this period, the Krebs–Henseleit solution was changed every 15 min before addition of drugs. After equilibration, submaximal contractions of the prostate and carotid artery were first elicited by repeated additions of 30 μM of phenylephrine and 3 μM of noradrenaline, respectively, until constant responses had been obtained. Then, the maximum contraction obtained with the last addition was taken as 100%. Thirty minutes before noradrenaline addition, desmethylimipramine (1 μM), pargyline (10 μM) and propranolol (1 μM) were added to the bath solution to block neuronal and extraneuronal uptake of noradrenaline and to block β-adrenoceptors, respectively. Cumulative concentrations of phenylephrine (10^{-7}–10^{-3} M) or noradrenaline (10^{-9}–10^{-4} M) were then added to the organ bath as α_1-adrenoceptor agonist, and concentration–response curves were obtained to determine the relationship between agonist concentrations and contractile responses. After a cumulative concentration–response curve for the agonist had been obtained, JTH-601 (3×10^{-9}–10^{-6} M), prazosin (10^{-9}–3×10^{-7} M) or tamsulosin (3×10^{-10}–3×10^{-8} M) were added to the bath. Responses to the agonist in the presence of the

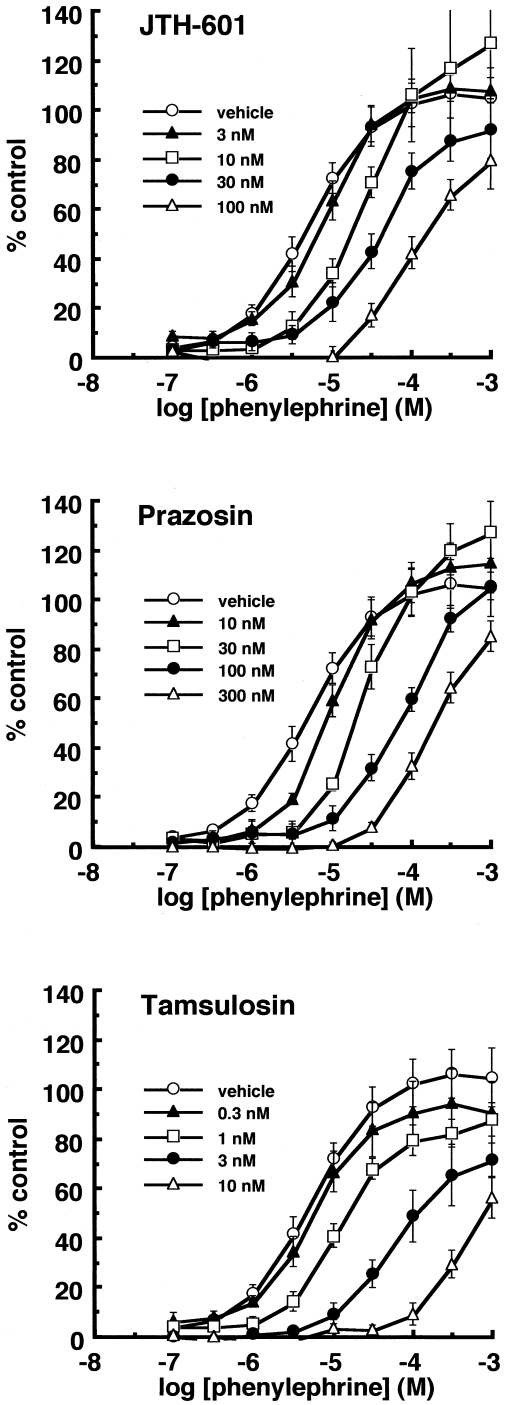

Fig. 2. Effect of JTH-601, prazosin and tamsulosin on phenylephrine-induced contraction in isolated canine prostate. Ordinate scale: phenylephrine (30 μM)-induced precontraction as 100%. JTH-601, prazosin, tamsulosin or vehicle (0.1% dimethyl sulfoxide) was added to the bath 30 min before the addition of phenylephrine. Each point represents the mean ± S.E.M. from five experiments. The ability of phenylephrine to induce contraction was determined using a cumulative protocol.

antagonists were calculated as percentages of the maximal response. Schild plots were constructed and pA_2 values were determined from the intercept on the abscissa scale (Arunlakshana and Schild, 1959).

2.2. Effect on urethral pressure in anesthetized dogs

Male beagle dogs (Keari, Nosan Animal Research Center, Chiba and Kasho, Tokyo, Japan) weighing 9.0– 13.0

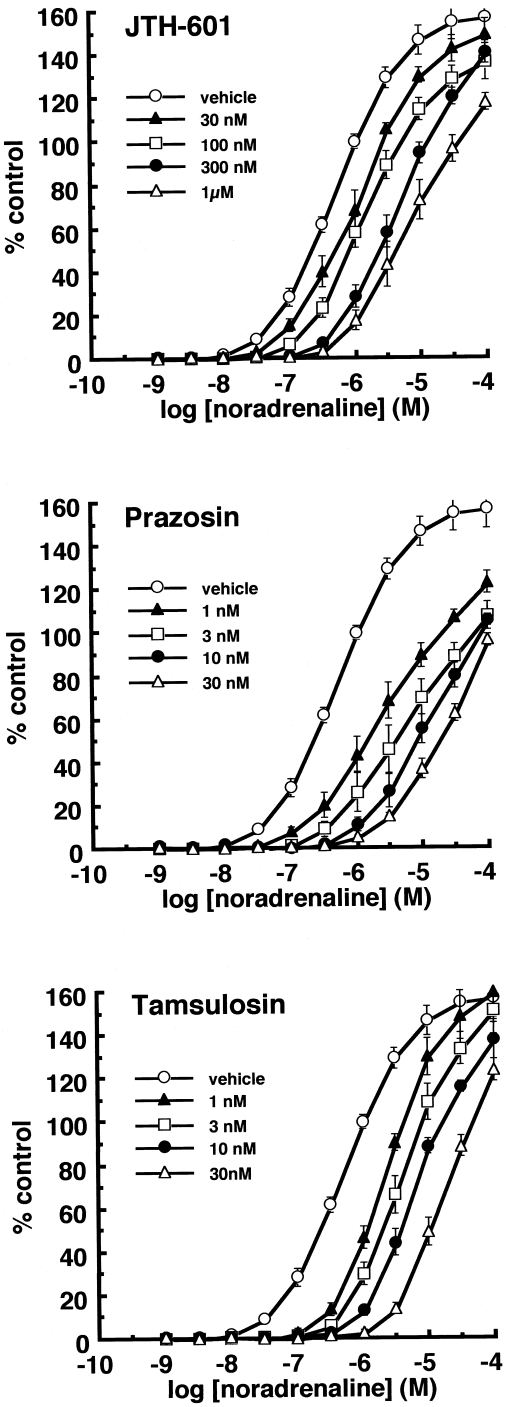

Fig. 3. Effect of JTH-601, prazosin and tamsulosin on noradrenaline-induced contraction in isolated canine carotid artery. Ordinate scale: noradrenaline (3 μM)-induced precontraction as 100%. JTH-601, prazosin, tamsulosin or vehicle (0.1% dimethyl sulfoxide) was added to the bath 30 min before the addition of noradrenaline. Each point represents the mean ± S.E.M. from five experiments. The ability of noradrenaline to induce contraction was determined using a cumulative protocol.

Table 1
The pA_2 values for JTH-601, prazosin and tamsulosin in isolated canine prostate and carotid artery
The effects of the drugs on phenylephrine-induced contraction of prostate and noradrenaline-induced contraction of carotid artery were examined, and pA_2 values and slopes were determined by Schild analysis. Data represent the means ± S.E.M. (pA_2) or the mean with 95% confidence limits (slope) from five experiments.

	Prostate		Carotid artery		Ratio[a] (carotid artery/prostate)
	pA_2	Slope	pA_2	Slope	
JTH-601	8.49 ± 0.07[b]	–	7.47 ± 0.12	0.91 (0.49–1.33)	10.471
Prazosin	7.94 ± 0.04	1.16 (0.97–1.35)	10.02 ± 0.10	0.77 (0.47–1.06)	0.008
Tamsulosin	9.42 ± 0.22[b]	–	9.85 ± 0.12[b]	0.71 (0.55–0.86)[c]	0.371

[a]Ratio of each value of 10^{-pA_2}.
[b]Apparent pK_B value.
[c]Significantly different from unity ($P < 0.05$).

kg were fasted overnight and anesthetized with sodium thiopental (20 mg/kg, i.v.), then a tracheal cannula was inserted for artificial ventilation (respirator: MODEL 613, Harvard Apparatus, Boston MA, USA). Subsequent anesthesia was maintained with 0.5% halothane and a gas mixture ($N_2O:O_2 = 2:1$) with a respirator. A polyethylene catheter connected to a pressure transducer (DX-360, Nihon Kohden, Tokyo, Japan) was inserted into the femoral artery and blood pressure was measured via a pressure amplifier (AP-641G, Nihon Kohden). Heart rate was measured with a cardiotachometer (AT-601G, Nihon Kohden) triggered by the blood pressure pulse wave. The urinary bladder was exposed by an abdominal median incision and emptied by vesicle puncture. Urine was drained by polyethylene catheters inserted into bilateral ureters. A catheter (UPP catheter, 10 Fr., Create Medic, Yokohama, Japan) for measurement of urethral pressure was then inserted into the urinary bladder through the external urethral meatus. The urethral catheter was connected with a syringe infusion pump (STC-521, Terumo, Tokyo, Japan) and a pressure transducer. After blood pressure had been stabilized following the operation, physiological saline was infused into the urinary bladder via the urethral catheter at 2 ml/min using the syringe infusion pump, and simultaneously, the urethral catheter was withdrawn at 25 mm/min using an automatic pulling unit (AU-601G, Nihon Kohden). The change in urethral pressure between urinary bladder neck and external urethral meatus (urethral pressure profile), blood pressure and heart rate was continuously recorded on a pen recorder (WI-641G, Nihon Kohden). Effects of drugs on urethral pressure profile were evaluated on the maximum urethral pressure at the prostatic section. The urethral pressure measurement was repeated at intervals of 20–30 min until constant responses had been obtained. Test drugs were then administered via a cannula inserted into the duodenum. Urethral pressure was measured 30, 60, 90, 120 and 180 min after administration (JTH-601, 1 and 3 mg/kg and tamsulosin, 0.1 mg/kg).

2.3. Chemicals

JTH-601 and tamsulosin hydrochloride were synthesized at Toyobo (Osaka, Japan). Other chemicals were purchased from the following sources: prazosin hydrochloride, L-phenylephrine hydrochloride, noradrenaline, D,L-propranolol, deoxycorticosterone acetate and desmethylimipramine (Sigma, St. Louis MO, USA), dimethyl sulfoxide (Nacalai Tesque, Kyoto, Japan), distilled water (Otsuka, Tokyo, Japan), sodium pentobarbital (Nembutal®, Dainabot, Osaka, Japan), sodium thiopental (Ravonal®, Tanabe, Osaka, Japan) and halothane (Flouthane®, Takeda, Osaka, Japan). For the in vitro contraction study, drug solutions were made up in dimethyl sulfoxide, distilled water or 0.1 N HCl. For the in vivo study, drugs were suspended in 0.5% methyl cellulose.

2.4. Data and statistical analysis

Data are presented as the means ± S.E.M. In the contraction study with isolated tissues, pA_2 values were estimated from Schild plots by plotting the $-\log$(antagonist concentration) and the $\log(CR - 1)$, where CR is the concentration ratio which was obtained from the ratio of EC_{50} (concentration of agonist that produces half-maximal response) for each agonist in the presence or absence of an antagonist (Arunlakshana and Schild, 1959). The statistical significance of differences between the calculated slopes and unity was tested by Student's *t*-test under the null hypothesis. When the maximum contraction was reduced at a high concentration of an antagonist or when the slope was significantly different from unity, the potencies of drugs were expressed as apparent pK_B values obtained at

Table 2
Basal values for urethral pressure, mean blood pressure and heart rate in anesthetized dogs
Each value represents the mean ± S.E.M. ($n = 4$).

Group	Dose (mg/kg)	Urethral pressure[a] (mm Hg)	Mean blood pressure (mm Hg)	Heart rate (beats/min)
Vehicle	0.5	26.5 ± 4.0	114 ± 3	111 ± 9
JTH-601	1	30.3 ± 3.9	116 ± 3	116 ± 7
	3	22.5 ± 3.1	110 ± 5	122 ± 9
Tamsulosin	0.1	29.4 ± 3.9	103 ± 6	113 ± 14

[a]Maximum intra-urethral pressure at prostatic region.

concentrations of the agonist according to the methods described by Takayanagi et al. (1986). In the in vivo experiment, the significance of differences between vehicle and drug groups was determined by two-factor analysis of variance followed by Tukey–Kramer's test. Differences were considered significant at $P < 0.05$.

3. Results

3.1. Effects on isolated canine prostate and carotid artery

JTH-601, prazosin and tamsulosin had no influence on the resting tension of the preparations (data not shown). Phenylephrine and noradrenaline produced concentration-dependent contractions in canine prostate and common carotid artery, respectively. Figs. 2 and 3 show the effects of JTH-601, prazosin and tamsulosin on the α_1-adrenoceptor agonist-induced contraction in isolated canine prostate and common carotid artery, respectively. With these tissues, all drugs shifted the phenylephrine- or noradrenaline-induced response curves to the right in a concentration-dependent manner. However, in prostate, JTH-601 and tamsulosin at high concentrations reduced the maximum response. In addition, the Schild slope for tamsulosin in carotid artery was significantly different from unity. In these cases, apparent pK_B values were obtained at the antagonist concentrations used (Takayanagi et al., 1986). Table 1 summarizes the mean pA_2 (pK_B) values and slopes determined from Schild plots for these antagonists. The corresponding ratios for prostate and carotid artery for each antagonist are also indicated in Table 1. JTH-601 showed an approximately 10 times greater selectivity for prostate than for carotid artery. On the contrary, prazosin showed an approximately 125 times greater selectivity for carotid artery than for prostate. Tamsulosin was shown to affect prostate and carotid artery equipotently.

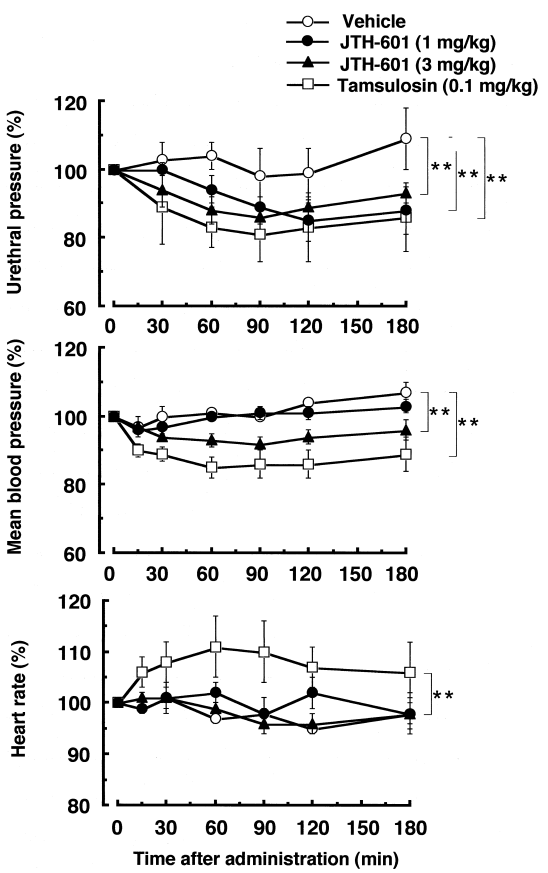

Fig. 4. Effects of JTH-601 and tamsulosin on urethral pressure, mean blood pressure and heart rate in anesthetized dogs. Each point represents the mean ± S.E.M. ($n = 4$). $^{**}P < 0.01$ vs. vehicle (two-factor analysis of variance followed by Tukey–Kramer's test). Urethral pressure represents the maximum intra-urethral pressure at prostatic section.

3.2. Effect on urethral pressure in anesthetized dogs

Basal values for urethral pressure at the prostatic section, mean blood pressure and heart rate before drug administration are summarized in Table 2. There were no significant differences between test groups for any parameter. Fig. 4 shows that JTH-601 (1 and 3 mg/kg) and tamsulosin (0.1 mg/kg) significantly decreased urethral pressure at the prostatic section to the same extent. The lowering effects of JTH-601 and tamsulosin on urethral pressure were maximal at 2–3 h after administration (−7% to −17% before administration, respectively). The lower dose of JTH-601 did not affect mean blood pressure but the higher dose of this drug caused a significant decrease (maximum; −8%). JTH-601 did not affect heart rate at either dose. On the other hand, tamsulosin diminished mean blood pressure by 11–15% and increased heart rate by 6–11%.

4. Discussion

Recently, the α_{1L}-adrenoceptor has been identified as a fourth subtype of α_1-adrenoceptor. The three subtypes (α_{1A}, α_{1B} and α_{1D}) now classified (Bylund et al., 1994; Ford et al., 1994; Hieble et al., 1995) have a high affinity for prazosin ($pA_2 > 9$) and hence, are classified as α_{1H}-adrenoceptors. On the other hand, the α_{1L}-adrenoceptor shows a low affinity for prazosin ($pA_2 < 9$) (Flavahan and Vanhoutte, 1986; Muramatsu et al., 1990; Oshita et al., 1991; Marshall et al., 1992; Ohmura et al., 1992; Ford et al., 1994; Forray et al., 1994a,b; Price et al., 1994; Faure et al., 1995). According to this classification, the α_1-adrenoceptor subtypes in canine prostate and carotid artery should belong to the α_{1L}-group and the α_{1H}-group, respectively, based on the pA_2 values for prazosin in the contraction study with isolated tissues.

Although it was suggested that both the α_{1H} (mainly α_{1A})- and α_{1L}-adrenoceptors are present in human prostate (Hirasawa et al., 1993; Price et al., 1993; Weinberg et al., 1994), the α_{1L}-adrenoceptor is thought to be functionally important in the α_1-adrenoceptor agonist-induced contrac-

tion of smooth muscle of this tissue (Ford et al., 1994, 1996; Muramatsu et al., 1994). On the other hand, it has been demonstrated in blood vessels that the contraction response to noradrenaline is mediated by the α_{1B}- and/or α_{1D}-subtype (Bylund et al., 1994; Price et al., 1994; Faure et al., 1995; Muramatsu et al., 1995). It has been reported that the α_{1B}-subtype dominates in the canine carotid artery (Muramatsu et al., 1995).

We now found that JTH-601 was more selective for prostate than were prazosin and tamsulosin in the α_1-adrenoceptor agonist-induced contraction study with isolated canine prostate and carotid artery. Although we also evaluated the effects of the drugs on phenylephrine-induced contraction in carotid artery, the slopes of Schild plots were significantly different from unity. In the noradrenaline-induced contraction study, blockers for neuronal and extraneuronal uptake of noradrenaline and for β-adrenoceptors were added to the organ bath. We previously confirmed that JTH-601 antagonizes α_2-adrenoceptors about 200 times less potently than α_1-adrenoceptors (Suzuki et al., 1999). Therefore, we used the data for noradrenaline-induced contraction to evaluate the α_1-adrenoceptor antagonistic effects of the drugs in carotid artery. Takahashi et al. (1999) have also reported that JTH-601 showed prostatic selectivity as compared with arteries (mesenteric artery and aorta) in isolated human tissues. In our experiments, it was also revealed that prazosin has arterial selectivity. Because prazosin is a non-selective α_1-adrenoceptor antagonist but has a low affinity for prostate (Muramatsu et al., 1995), it may antagonize α_1-adrenoceptor agonist-induced contraction more potently in carotid artery than in prostate. Although it has been reported that tamsulosin is a selective α_{1A}-adrenoceptor antagonist and has prostatic selectivity (Hanft et al., 1989; Michel and Insel, 1994), tamsulosin was shown to affect prostate and artery equipotently in the present study. Because some compounds with high affinity for the α_{1A}-adrenoceptor have been reported to be very weak functional antagonists of noradrenaline-induced contraction of human prostate (Marshall et al., 1992; Ford et al., 1996), an explanation of the prostate selectivity of the α_1-adrenoceptor antagonist based only on α_{1A}-adrenoceptor selectivity does not appear to be sufficient. Regarding these points, α_{1L}-adrenoceptors also may play an important role in α_1-adrenoceptor-mediated smooth muscle contraction of canine prostate.

In the contraction study using isolated prostate and artery, JTH-601 showed prostatic selectivity, suggesting it has a minimal effect on blood pressure compared with urethral pressure. In the treatment of urinary outlet obstruction by benign prostatic hypertrophy, the use of α_1-adrenoceptor antagonists often results in orthostatic hypotension, due to the reduction in vascular resistance mediated by the blockade of the α_1-adrenoceptor in the blood vessel (Scott et al., 1989; Wilde et al., 1993). Therefore, α_1-adrenoceptor antagonists must have a minimal effect on blood pressure during treatment of the symptom.

We evaluated the effect of JTH-601 on urethral pressure (spontaneous tone), blood pressure and heart rate in anesthetized dogs. In this experiment, JTH-601 decreased urethral pressure without affecting blood pressure or heart rate, while tamsulosin not only reduced urethral pressure but also changed blood pressure and heart rate significantly. These data indicated that in vivo JTH-601 is also more selective for prostate than is tamsulosin. These findings suggest that an α_1-adrenoceptor antagonist, which has a high affinity for the α_{1L}-adrenoceptor, may be a therapeutic agent for urinary outlet obstruction by benign prostatic hypertrophy with minimum effects on the cardiovascular system.

The existence of a distinct α_1-adrenoceptor with low affinity for prazosin has been well demonstrated especially in functional experiments. However, because the α_{1L}-adrenoceptor has not been cloned yet, its identity has not been fully established. Ford et al. (1996, 1997) and Williams et al. (1996) proposed that the receptor may represent a particular conformational state of the α_{1A}-adrenoceptor. They suggested that the environmental factors around cells (whole cell or homogenate and temperature) influence the state of the receptor and that both the α_{1L}-adrenoceptor and the α_{1A}-adrenoceptor may be based on the same gene (α_{1a}). They reported that the several α_1-adrenoceptor antagonists may be divided into two groups: those which gave affinity estimates for the α_{1A}-adrenoceptor in the assay of noradrenaline-induced accumulation of inositol phosphates using whole cells which were not different from those found in membrane homogenate binding assays; and those which show a clear separation in affinity estimates between the two assays (Ford et al., 1997). It has been reported that JTH-601 has a higher affinity for both the α_{1L}-adrenoceptor and the α_{1A}-adrenoceptor ($pK_B = 9.1–9.8$) and a lower affinity for the α_{1H}-adrenoceptor group ($pK_B = 7.6–8.8$), except the α_{1A}-subtype (Muramatsu et al., 1996). Therefore, JTH-601 may affect the α_{1L}-adrenoceptor, which is the pharmacological phenotype of the α_{1A}-adrenoceptor and is located in the lower urinary tract. Because we did not have details of the several experimental conditions used by Ford et al. (1997) and Williams et al. (1996) in their examination of the affinity of JTH-601 for the α_1-adrenoceptor, it is unknown which group JTH-601 belongs to. To clarify this property of JTH-601, it will be necessary to do further investigations.

5. Conclusion

JTH-601 showed a higher selectivity for canine prostate both in vitro and in vivo. In prostate, an important role of the α_{1L}-adrenoceptor is suggested in the smooth muscle contraction mediated by α_1-adrenoceptors. JTH-601 is expected to be an effective α_1-adrenoceptor antagonist for

the treatment of urinary outlet obstruction by benign prostatic hypertrophy with a minimum effect on the cardiovascular system.

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