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European Journal of Pharmacology 374 (1999) 495–502

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Effect of JTH-601, a novel α_1-adrenoceptor antagonist, on the function of lower urinary tract and blood pressure

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Received 21 December 1998; received in revised form 3 May 1999; accepted 5 May 1999

Abstract

In the present study, we investigated 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 novel α_1-adrenoceptor antagonist, in vitro and in vivo. JTH-601 (10^{-9}–3×10^{-8} M) competitively antagonized phenylephrine-induced contraction in lower urinary tract tissues (prostate, urethra and bladder trigon) in a concentration-dependent manner. The mean pA_2 values for JTH-601 were 8.59 ± 0.14, 8.74 ± 0.09 and 8.77 ± 0.11 for prostate, urethra and bladder trigon, respectively. In anesthetized rabbits, intraduodenal administration of JTH-601 (0.3–3 mg/kg), prazosin (0.03–0.3 mg/kg) and tamsulosin (0.03–0.3 mg/kg) dose dependently inhibited the phenylephrine-induced increase in urethral pressure for 3 h. Although these drugs also decreased mean blood pressure, JTH-601 was less potent than prazosin or tamsulosin. In conscious rabbits, administered JTH-601 (0.01–1 mg/kg, i.v.) had a tendency to augment orthostatic hypotension, but dose dependency was not evident. Prazosin (0.01–1 mg/kg) and tamsulosin (0.001–1 mg/kg) dose dependently augmented orthostatic hypotension. These results indicate that JTH-601 antagonized α_1-adrenoceptor-mediated contractile responses more potently than prazosin or tamsulosin in rabbit lower urinary tract both in vitro and in vivo. JTH-601 is therefore expected to be effective in the treatment of urinary outlet obstruction in benign prostatic hypertrophy.

Keywords: Benign prostatic hypertrophy; Urinary outlet obstruction; α_{1L}-Adrenoceptor; JTH-601

1. Introduction

Benign prostatic hypertrophy is a common disease in old men that causes urinary outlet obstruction. This symptom results from compression of the urethra by the enlarging prostate which surrounds it. Urinary outlet obstruction by benign prostatic hypertrophy is attributed to both a mechanical and a dynamic component. The mechanical component is related to the anatomical obstruction caused by the enlarged gland, while the dynamic component is related to the contraction of smooth muscle in the prostate.

Although the prostate is innervated by adrenergic, cholinergic and nonadrenergic noncholinergic nerves (Dail, 1993), α_1-adrenoceptors are considered to be of primary functional importance in the prostate (Hedlund et al., 1985; Shapiro and Lepor, 1986). The administration of α-adrenoceptor antagonists such as phenoxybenzamine (Caine et al., 1976) and prazosin (Hedlund and Andersson, 1983) to men with benign prostatic hypertrophy has been shown to decrease intraurethral pressure and to increase urinary flow rate.

Multiple α_1-adrenoceptor subtypes have been identified by both pharmacological and molecular biological techniques (Morrow and Creese, 1986; Cotecchia et al., 1988; Schwinn et al., 1990; Lomasney et al., 1991). Currently, the α_1-adrenoceptor is classified into three native subtypes, termed α_{1A}, α_{1B} and α_{1D}, and their cloned counterparts designated α_{1a}, α_{1b} and α_{1d} (Bylund et al., 1994; Ford et al., 1994; Hieble et al., 1995). These three subtypes have distinct expression patterns in various tissues. In human prostate, although all three currently cloned α_1-adrenoceptors have been detected, the α_{1A} subtype appears to play the primary role in smooth muscle contrac-

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0014-2999/99/$ - see front matter
PII: S0014-2999(99)00344-1

tion (Price et al., 1993; Marshall et al., 1995). Accordingly, a selective α_{1A}-adrenoceptor antagonist may be therapeutically advantageous in the treatment of urinary outlet obstruction due to benign prostatic hypertrophy; however, an α_{1A}-adrenoceptor selective agent is not likely to be devoid of vascular activity (Han and Minneman, 1990; Piascik et al., 1994; Muramatsu et al., 1995). Muramatsu et al. (1990, 1995) found that α_1-adrenoceptors can be pharmacologically divided into α_{1H} (α_{1A}, α_{1B} and α_{1D}) and α_{1L} subtypes which possess high and low affinity for prazosin, respectively. In human prostate, evidence from both radioligand binding and functional studies has also indicated the presence of putative $\alpha_{1H/L}$-adrenoceptors, and that these α_{1L}-adrenoceptors may be predominantly involved in the contraction of prostatic smooth muscle (Takeda et al., 1993; Muramatsu et al., 1994).

Recently, we reported that JTH-601 (3-{*N*-[2-(4-hydroxy-2-isopropyl-5-methylphenoxy)ethyl]-*N*-methylaminomethyl}-4-methoxy-2,5,6-trimethylphenol hemifumarate), a novel α_1-adrenoceptor antagonist, has a higher affinity for the α_{1L} subtype and lower affinity for the α_{1H} subtype (except the α_{1A} subtype) than prazosin (Muramatsu et al., 1996). In the present study, therefore, we evaluated the effect of JTH-601 on prostatic function in vitro and in vivo.

2. Materials and methods

2.1. α_1-Adrenoceptor blocking effects in isolated rabbit lower urinary tract

The prostate, urethra (proximal section) and bladder trigon were isolated from male Japanese White rabbits (2.0–3.0 kg) after cervical dislocation under sodium pentobarbital (50 mg/kg, i.v.) anesthesia. Isolated organs were immediately rinsed with 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) and connective tissue was removed.

Tissue preparations were suspended in a 20-ml organ bath filled with Krebs–Henseleit solution. Each bath was maintained at 37°C and continuously aerated with a gas mixture consisting of 95% O_2 and 5% CO_2. The responses of the preparation were isometrically recorded with an automatic magnus system (IM-400C, Japan Tobacco, Tokyo, Japan) under a resting tension of 1.0 g. The preparations were equilibrated for about 1 h and contracted twice by 3×10^{-5} M of phenylephrine; the maximum contraction of the second time was taken as 100%. Cumulative concentrations of phenylephrine (10^{-7}–10^{-4} M) were then added to the organ bath as an α_1-adrenoceptor agonist, and concentration–response curves were obtained to determine the relationship between agonist concentration and contractile response. After a successive concentration–response curve for the agonist had been obtained, JTH-601 (10^{-9}–3×10^{-8} M), prazosin (10^{-8}–10^{-7} M) or tamsulosin (3×10^{-10}–10^{-8} M) was added to the bath. Responses for the agonist in the presence of the antagonists were calculated as a percentage of the maximal response. Schild plots were constructed and pA_2 values were determined from the intercept on the abscissa (Arunlakshana and Schild, 1959).

2.2. α_2-Adrenoceptor blocking effects in isolated rat vas deferens

The α_2-adrenoceptor blocking effects of JTH-601 and other α-adrenoceptor antagonists were examined against the inhibitory effect of clonidine, a selective prejunctional α_2-adrenoceptor agonist, on electrical transmural stimulation-induced contraction in rat vas deferens. The vas deferens was isolated from male Wistar rats (220–300 g) after cervical dislocation under sodium pentobarbital (50 mg/kg, i.p.) anesthesia. The isolated vas deferens was immediately rinsed with ice-cold Krebs–Henseleit solution and connective tissue was removed. The preparation was suspended in an organ bath filled with 20 ml of Krebs–Henseleit solution maintained at 30°C and continuously aerated with a gas mixture (95% O_2 and 5% CO_2). After an equilibration period of about 1 h, electrical transmural stimulation (duration, 0.3 ms; frequency, 1/60 Hz; supramaximal voltage, 10 V) was applied via a pair of platinum-wire electrodes. The contractile responses of the preparation were isometrically recorded with a transducer (TB611T, Nihon Kohden, Tokyo, Japan) under a resting tension of 0.5 g. Thirty minutes after treatment with vehicle, yohimbine (3×10^{-8}–10^{-6} M), JTH-601 (10^{-7}–10^{-5} M), prazosin (3×10^{-6}–10^{-4} M) or tamsulosin (10^{-6}–10^{-5} M), cumulative concentrations of clonidine (3×10^{-10}–10^{-7} M) were added to the organ bath and concentration–response curves were then obtained to determine the relationship between concentrations of clonidine and the electrical transmural stimulation-induced contractile responses. Schild plots were constructed and pA_2 values determined.

2.3. Effect on internal urethral pressure in anesthetized rabbits (i.d. and i.v.)

Male Japanese White rabbits weighing 2.1–2.7 kg were anesthetized with urethane (0.2 g/kg, i.v. + 0.4 g/kg, s.c.) and α-chloralose (20 mg/kg i.v. + 40 mg/kg, s.c.), and a polyethylene cannula (4 Fr.) was inserted into the left carotid artery for blood pressure measurement. Blood pressure was measured with a pressure amplifier (AP-621G, Nihon Kohden) via a pressure transducer (SCK-721, Spectramed, Tokyo, Japan) connected to the cannula. The urinary bladder was emptied by vesical puncture and the urine was drained. A Neraton catheter (CLINY urodynamic catheter 10 Fr., Createmedic, Yokohama, Japan) was inserted into the urinary bladder through the penis. The catheter was connected to a pressure transducer (SCK-

721, Spectramed) for internal urethral pressure measurement and a syringe pump (RAZEL Model A-99, Muromachi, Kyoto, Japan) for physiological saline infusion. The urethral catheter was withdrawn with an automatic pulling unit (AU-601G, Nihon Kohden) at a rate of 25 mm/min while infusing saline (0.5 ml/min). When the top of the catheter had reached the urethra (about 30 s after), phenylephrine (30 μg/kg) was intravenously injected via a cannula inserted into the left jugular vein. Urethral pressure was continuously measured with a pressure amplifier (AP-621G, Nihon Kohden) at the point between the bladder neck and external urethral meatus. Blood pressure and urethral pressure were recorded on a thermal recorder (RTM-1200 M, Nihon Kohden). After stable basal urethral pressure was obtained, vehicle or drugs were administered via a canula inserted into the duodenum or left jugular vein. In the i.d. administration experiment, JTH-601 was administered at doses of 0.3–3 mg/kg, while prazosin and tamsulosin were administered at doses of 0.03–0.3 mg/kg;

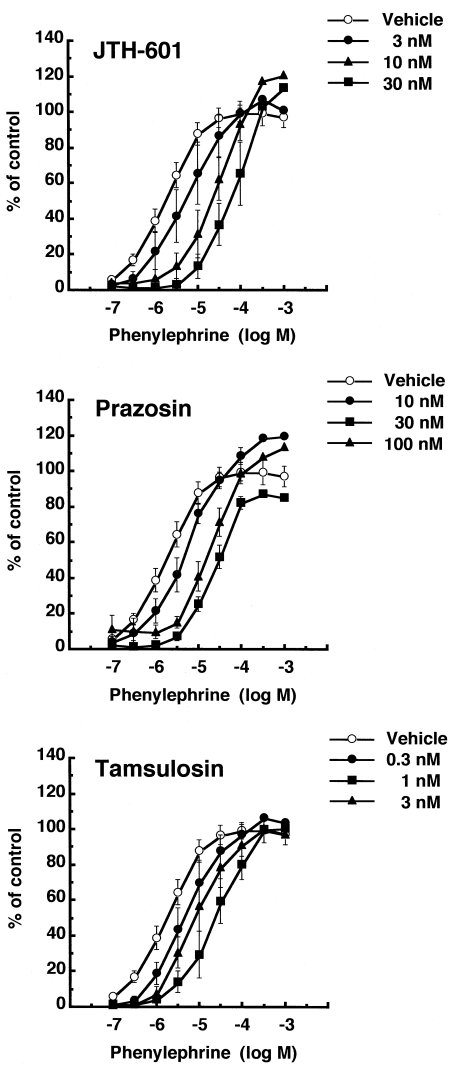

Fig. 1. Effect of JTH-601 prazosin and tamsulosin on phenylephrine-induced contraction in isolated rabbit bladder trigon. Each point represents the mean ± S.E. of five or six experiments.

Table 1
The pA_2 values and slopes for JTH-601, prazosin and tamsulosin obtained with isolated rabbit prostate, urethra and bladder trigon. Data represent the means ± S.E. of five or six experiments

Drug	Prostate		Urethra		Bladder trigon	
	pA_2	Slope	pA_2	Slope	pA_2	Slope
JTH-601	8.59 ± 0.14	1.28	8.74 ± 0.09	0.88	8.77 ± 0.11	1.23
Prazosin	7.62 ± 0.24	1.25	8.51 ± 0.09	0.80	8.02 ± 0.18	1.03
Tamsulosin	9.77 ± 0.25	1.22	9.54 ± 0.08	0.97	9.54 ± 0.17	0.90

the urethral pressure measurement was repeated at 15-min intervals for 180 min post-administration. In the i.v. administration experiment, JTH-601 (0.0003–0.1 mg/kg), prazosin (0.0003–0.1 mg/kg) and tamsulosin (0.0001–0.1 mg/kg) were administered in increasing doses, and urethral pressure was measured 5 min after each administration.

2.4. Effect on orthostatic hypotension in conscious rabbits (i.v.)

Male Japanese White rabbits weighing 2.3–2.7 kg were anesthetized with sodium pentobarbital (25 mg/kg, i.v.). Polyethylene cannulas were inserted into the femoral artery and vein for blood pressure measurement and drug administration, respectively. Blood pressure was measured by the method described above. After dehypnotization from anesthesia, blood pressure responses were measured under baseline conditions and during 1-min head-up tilts (90°). Several control tilts were performed at 15-min intervals prior to dosing with vehicle or drugs. Five minutes after administration, a tilt was performed. JTH-601 and prazosin were administered at increasing doses of 0.01–1 mg/kg, while tamsulosin was administered at increasing doses of 0.001–0.1 mg/kg.

2.5. Drugs

JTH-601 and tamsulosin were synthesized at Toyobo (Osaka, Japan). Other chemicals were purchased from the following sources: prazosin hydrochloride, L-hydrochloride, noradrenaline, D,L-propranolol, deoxycorticosterone, desmethylimipramine and clonidine hydrochloride (Sigma, St. Louis MO, USA), yohimbine hydrochloride and dimethyl sulfoxide (Nacalai Tesque Kyoto, Japan), distilled water (Otsuka Pharma, Tokyo, Japan), sodium pentobarbital (Dainabot, Osaka, Japan), urethane and α-chloralose (Tokyokasei, Tokyo, Japan).

3. Results

3.1. α_1-Adrenoceptor blocking effects in isolated rabbit lower urinary tract

JTH-601, prazosin and tamsulosin had no influence on the resting tension of the preparations (data not shown).

Table 2
The α_2-Adrenoceptor blocking effect (pA_2) of JTH-601, prazosin, tamsulosin and yohimbine in isolated rat vas deferens. Data represent the means ± S.E. of 4–23 experiments

Drug	pA_2[a]
JTH-601	6.31 ± 0.15
Prazosin	< 6.5
Tamsulosin	6.28 ± 0.11
Yohimbine	7.81 ± 0.13

[a] pA_2 values were determined by the antagonistic effect of these drugs against the inhibitory effect of clonidine on electrical transmural stimulation-induced contractile responses.

Phenylephrine-stimulated contractions in isolated rabbit prostate, urethra and bladder trigon were concentration dependent. JTH-601, prazosin and tamsulosin shifted the phenylephrine-induced contraction response curves of the lower urinary tract tissues to the right and competitively antagonized the contraction in a concentration-dependent manner. Fig. 1 shows the effects of these drugs on phenylephrine-induced contractions in the bladder trigon; Table 1 summarizes the mean pA_2 values and slopes determined from Schild plots for these drugs in the lower urinary tract tissues. JTH-601 potently inhibited phenylephrine-induced contractions in the isolated rabbit prostate ($pA_2 = 8.59 \pm 0.14$), urethra ($pA_2 = 8.74 \pm 0.09$) and bladder trigon ($pA_2 = 8.77 \pm 0.11$). Tamsulosin was the most potent agent in inhibiting phenylephrine-induced contractions in each tissue followed by JTH-601 and prazosin.

3.2. α_2-Adrenoceptor blocking effects in isolated rat vas deferens

Clonidine (3×10^{-10}–10^{-7} M) inhibited the electrical transmural stimulation-induced contraction of rat vas deferens in a concentration-dependent manner by the stimulation of prejunctional α_2-adrenoceptors situated on the sympathetic nerve terminals. JTH-601, tamsulosin and yohimbine, but not prazosin, antagonized the inhibitory effect of clonidine on the electrical transmural stimulation-induced contractile response. Table 2 summarizes the α_2-adrenoceptor blocking effect (pA_2) of these antagonists determined from Schild plots. Yohimbine inhibited the effect of clonidine about 32 times more potently than JTH-601. The α_2-adrenoceptor blocking effect of JTH-601 was about 200 times less potent than its α_1-adrenoceptor blocking effect in rabbit prostate.

3.3. Effect on internal urethral pressure in anesthetized rabbits (i.d. and i.v.)

Urethral pressure at the prostatic site and mean blood pressure values before i.d. administration of drugs are summarized in Table 3. There were no significant differences in urethral pressure and mean blood pressure values before drug administration. Urethral pressure was increased approximately 2- to 3-fold by phenylephrine (30 μg/kg, i.v.). In a preliminary study, we confirmed the stability of urethral pressure and mean blood pressure in this protocol (data not shown).

The time course of changes in mean blood pressure and phenylephrine-induced urethral pressure elevation after i.d. administration of JTH-601 (0.3–3 mg/kg), tamsulosin (0.03–0.3 mg/kg) and prazosin (0.03–0.3 mg/kg) are shown in Fig. 2. These drugs antagonized the phenylephrine-induced increase in urethral pressure in a dose-dependent manner, the effect lasted 3 h. Mean blood pressure was decreased by these three drugs but the lowering effect of JTH-601 was less potent than that of prazosin or tamsulosin. Vehicle did not affect mean blood pressure or phenylephrine-induced urethral pressure elevation.

Table 3
Initial values of urethral pressure and mean blood pressure before intraduodenal administration of drugs. Each value represents the mean ± S.E.

Drug	Dose (mg/kg)	n	Urethral pressure (mm Hg)		Mean blood pressure[a] (mm Hg)
			Phenylephrine administration		
			Before[a]	After[b]	
Vehicle (0.5% methyl cellulose)		5	6.4 ± 0.9	11.9 ± 1.1	93 ± 3
	0.3	7	4.6 ± 0.7	10.6 ± 1.0	94 ± 2
JTH-601	1	7	4.9 ± 0.7	10.6 ± 0.6	90 ± 4
	3	5	6.8 ± 0.8	14.3 ± 1.6	97 ± 3
	0.03	7	5.2 ± 0.7	12.5 ± 1.0	89 ± 5
Prazosin	0.1	7	4.7 ± 0.6	12.2 ± 0.7	88 ± 1
	0.3	3	5.0 ± 0.7	12.3 ± 2.0	98 ± 3
	0.03	4	8.6 ± 2.1	13.3 ± 2.9	95 ± 2
Tamsulosin	0.1	5	4.9 ± 1.0	10.1 ± 1.2	92 ± 3
	0.3	3	4.9 ± 0.5	11.4 ± 0.8	98 ± 3

[a] Values before phenylephrine administration.
[b] Peak values after phenylephrine administration.

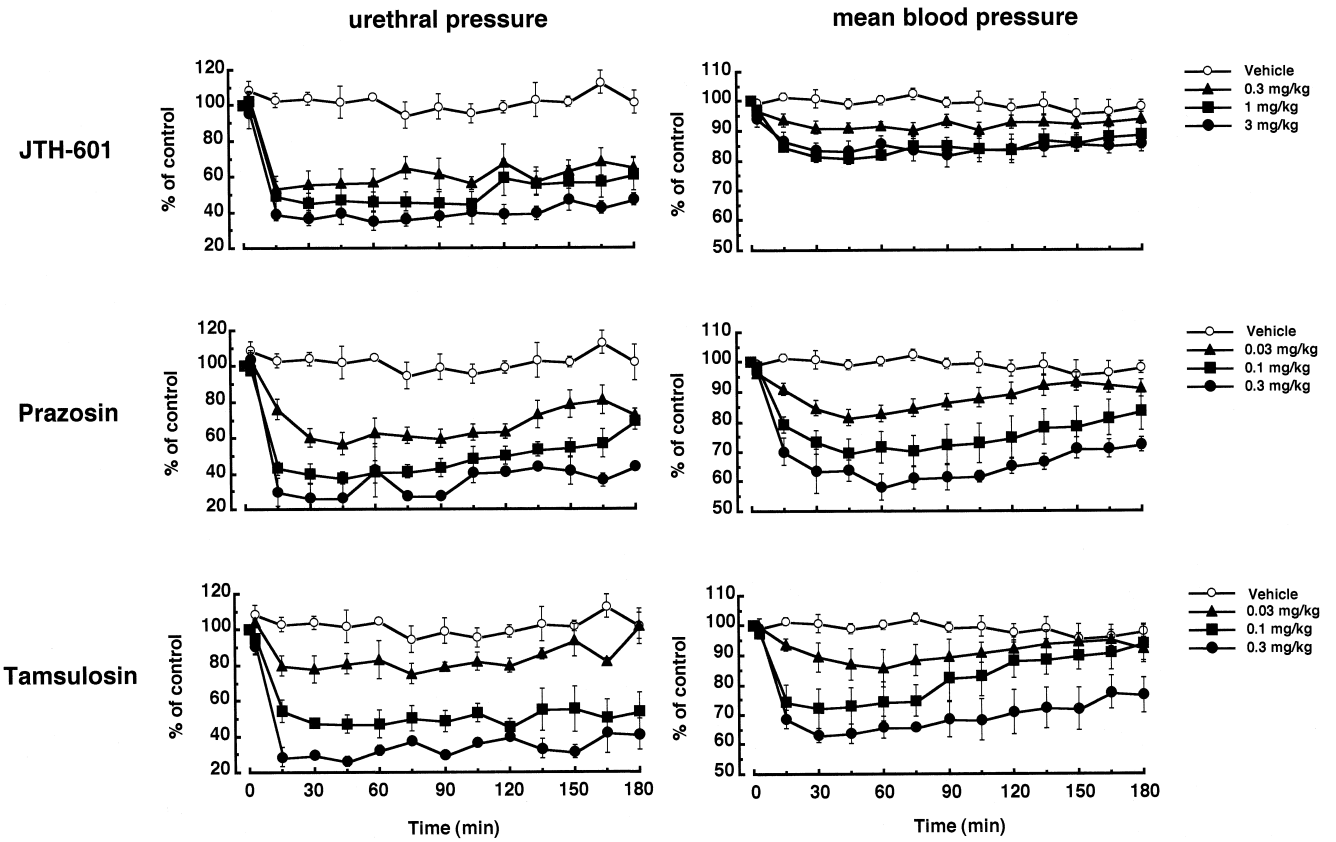

Fig. 2. Effects of JTH-601, prazosin and tamsulosin on phenylephrine-induced increase in urethral pressure and mean blood pressure in anesthetized rabbits (time course). Each drug was intraduodenally administered. Each point represents the mean ± S.E. ($n = 3–7$). Control responses are shown in Table 3.

Fig. 3 shows the dose–response curve for inhibition of phenylephrine-induced increases in urethral pressure and the decrease of mean blood pressure by JTH-601, prazosin and tamsulosin. The changes in the inhibition of phenylephrine-induced urethral pressure elevation and mean blood pressure were taken as the average of values recorded at 30–180 min post-administration since urethral pressure and mean blood pressure were almost constant at these time points for each dose (Fig. 2). JTH-601, prazosin and tamsulosin dose dependently suppressed the phenylephrine-induced urethral pressure elevation by 39–60, 34–64 and 17–66%, respectively. Prazosin and tamsulosin reduced mean blood pressure by 12–35 and 9–30%, respectively, in a dose-dependent manner. The reduction in mean blood pressure by JTH-601 was 4, 15 and 16% at 0.3, 1 and 3 mg/kg, respectively.

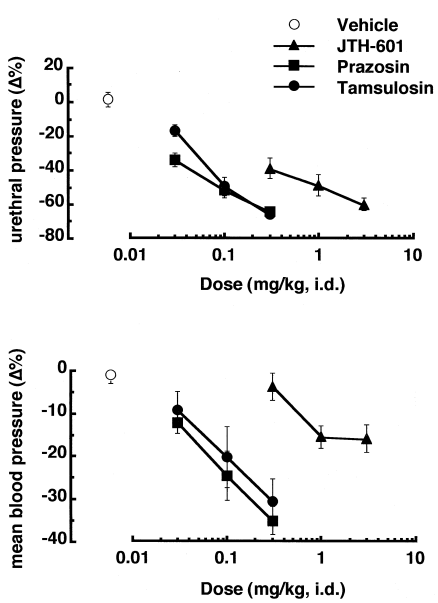

Fig. 3. Effects of JTH-601, prazosin and tamsulosin on phenylephrine-induced increase in urethral pressure and mean blood pressure in anesthetized rabbits (dose response). The values of changes in urethral pressure and mean blood pressure are the average recorded between 30 and 180 min post-administration in Fig. 2 (i.d.). Each point represents the mean ± S.E. ($n = 3–7$).

The effects of i.v. administration of JTH-601 (0.0003–0.1 mg/kg), prazosin (0.0003–0.1 mg/kg) and tamsulosin (0.0001–0.1 mg/kg) on urethral pressure and mean blood pressure are shown in Fig. 4. Urethral pressure and mean blood pressure values before each of the drug administrations are summarized in Table 4. In this study, urethral pressure and mean blood pressure were evaluated at 5 min after administration of the α_1-adrenoceptor antagonists because the maximal change in blood pressure produced by these antagonists was observed at approximately this time. JTH-601, prazosin and tamsulosin inhibited the phenylephrine-induced urethral pressure elevation and decreased mean blood pressure in a dose-dependent manner.

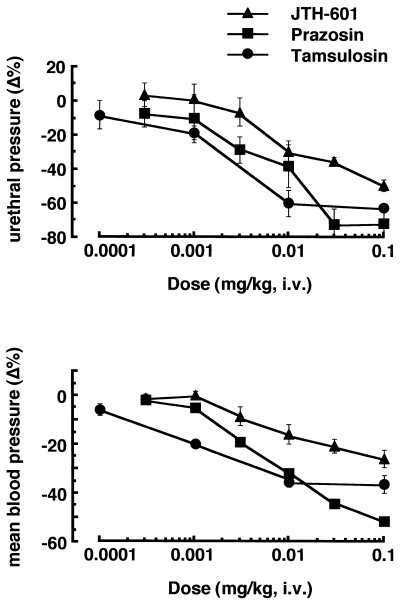

Fig. 4. Effects of JTH-601, prazosin and tamsulosin on phenylephrine-induced increase in urethral pressure and mean blood pressure in anesthetized rabbits (dose response). Each drug was intravenously administered at increasing doses. Each point represents the mean ± S.E. ($n = 3–4$).

There were no significant differences in either the potency of inhibition of the phenylephrine-induced urethral pressure elevation or the decrease of mean blood pressure between these drugs.

3.4. Effect on orthostatic hypotension in conscious rabbits (i.v.)

The effects of i.v. administration of JTH-601 (0.01–1 mg/kg), prazosin (0.01–1 mg/kg) and tamsulosin (0.001–1 mg/kg) on orthostatic hypotension in conscious rabbits are shown in Fig. 5. The initial values of mean blood pressure before intravenous administration of vehicle, JTH-601, prazosin and tamsulosin in this model were 95 ± 2, 95 ± 2, 89 ± 3 and 105 ± 3 mm Hg, respectively. To compare the effects of these α_1-antagonists on orthostatic hypotension and urethral pressure, the effects of i.v. administration of these drugs on the phenylephrine-induced urethral pressure elevation in anesthetized animals are included in this figure. In the vehicle control, mean blood pressure decreased by 2–4 mm Hg by head-up tilting. Although JTH-601 had a tendency to augment orthostatic hypotension (−10 mm Hg), dose dependency was not evident. Prazosin and tamsulosin dose dependently augmented orthostatic hypotension (−15 to −30 and −7 to −25 mm Hg, respectively).

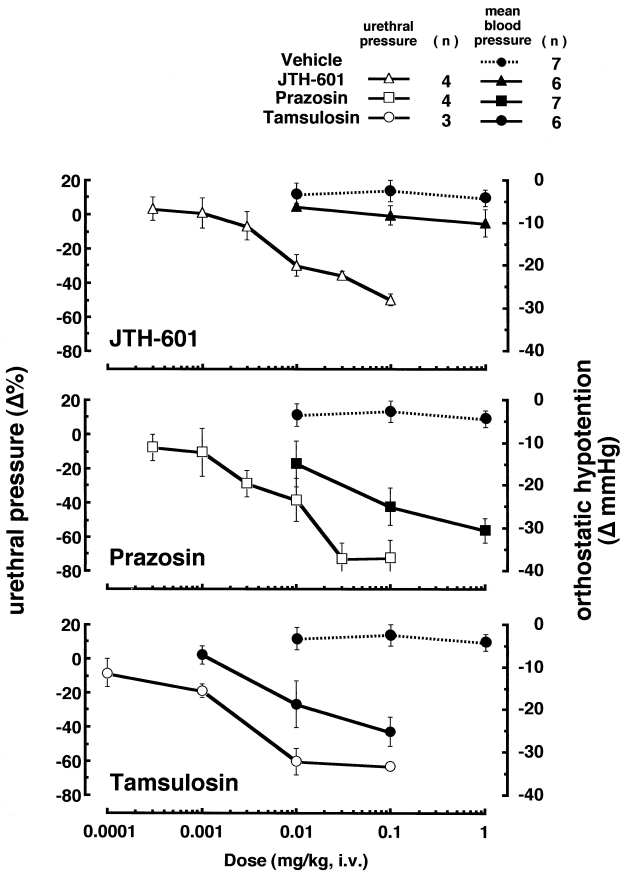

Fig. 5. Effects of JTH-601, prazosin and tamsulosin on orthostatic hypotension and phenylephrine-induced increase in urethral pressure (dose response). Each drug was intravenously administered at increasing doses. Each point represents the mean ± S.E.

Table 4
Initial values of UP and MAP before intravenous administration of drugs. Each value represents the mean ± S.E.

Drug	*n*	Urethral pressure (mm Hg)		Mean blood pressure[a] (mm Hg)
		Phenylephrine administration		
		Before[a]	After[b]	
JTH-601	4	3.6 ± 0.4	10.7 ± 1.5	93 ± 5
Prazosin	4	5.4 ± 1.2	10.8 ± 1.4	91 ± 3
Tamsulosin	3	6.7 ± 1.8	11.3 ± 0.7	94 ± 3

[a] Values before phenylephrine administration.
[b] Peak values after phenylephrine administration.

4. Discussion

Currently, the α_1-adrenoceptor is classified into three native subtypes, designated α_{1A}, α_{1B} and α_{1D} (the clones of which are α_{1a}, α_{1b} and α_{1d}, respectively) (Bylund et al., 1994; Ford et al., 1994; Hieble et al., 1995). On the basis of affinity for prazosin, the α_1-adrenoceptors can be pharmacologically classified into two subtypes α_{1H} ($pA_2 > 9$) and α_{1L} ($pA_2 < 9$) (Muramatsu et al., 1990, 1995). In the present study, prazosin pA_2 values in rabbit prostate were found to be 7.62 ± 0.24. Thus according to the latter classification, α_{1L}-adrenoceptors are functionally dominant in this tissue. We previously reported that JTH-601 had a higher affinity for α_{1L}-adrenoceptors and a lower affinity

for α_{1H}-adrenoceptors (except α_{1A}-adrenoceptors) than prazosin. Our results also seem to indicate that JTH-601 inhibits phenylephrine-induced prostatic contraction mainly via an α_{1L}-adrenoceptor blocking effect and partly via an α_{1A}-adrenoceptor blocking effect (Muramatsu et al., 1995, 1996). As JTH-601 also antagonized phenylephrine-induced contraction of bladder trigon and since the pA_2 value of prazosin in rabbit bladder trigon was 8.02 ± 0.18, α_{1L}-adrenoceptors may also be involved in bladder (neck) contraction via sympathetic nerves. In this study, prazosin was found to have a pA_2 value of 8.51 ± 0.09 in rabbit urethra, suggesting that both α_{1L}- and α_{1H}-adrenoceptors are present. JTH-601 inhibited phenylephrine-induced contraction in the urethra ($pA_2 = 8.74 \pm 0.09$) with the same potency as in the prostate ($pA_2 = 8.59 \pm 0.14$), therefore α_{1L}-adrenoceptors may also be functionally important in this tissue. Van der Graaf et al. (1997) also demonstrated that the functional α_1-adrenoceptor in rabbit urethra is of the α_{1L}-subtype.

In this study, the α_2-adrenoceptor blocking effect of JTH-601 was examined against the inhibitory effect of clonidine, a selective prejunctional α_2-adrenoceptor agonist, on electrical transmural stimulation-induced contraction in rat vas deferens. Although JTH-601 competitively antagonized the inhibitory effect of clonidine with the same potency as tamsulosin, it was about 32 times less potent than yohimbine and about 200 times less potent than it was at α_1-adrenoceptors in rabbit prostate. Therefore, the α_2-adrenoceptor blocking effect of JTH-601 is thought to be much weaker than its α_1-adrenoceptor blocking effect.

All α_1-adrenoceptor antagonists evaluated in the present study antagonized the phenylephrine-induced increases in urethral pressure and decreased mean blood pressure in a dose-dependent manner, but the decrease in mean blood pressure produced by JTH-601 was smaller than that produced by prazosin or tamsulosin in the i.d. administration experiment. JTH-601 did not potentiate the orthostatic hypotensive effect in the rabbit model, although prazosin and tamsulosin augmented the effect. It has already been reported that JTH-601 has higher selectivity for prostate than artery in dogs (Suzuki et al., 1997) and in humans (Takahashi et al., 1999). Yamada et al. (1998) reported that [^{3}H]JTH-601 shows specific binding in prostate but not in aorta in vivo. Taken together, the above findings suggest that in the rabbit, JTH-601, compared with prazosin and tamsulosin, may have higher selectivity for prostate and urethra than for vascular tissues, but further studies are necessary to clarify the tissue selectivity of JTH-601. In the i.v. administration experiment, there were no significant differences in the potency to inhibit phenylephrine-induced urethral pressure elevation and reduction in mean blood pressure among the drugs tested. Although it is unclear why there is a difference in the effect on blood pressure between i.d. and i.v. administration of JTH-601, it may be related to the pharmacokinetics (distribution rate to tissues) and/or metabolites of JTH-601. In our preliminary data, one active metabolite (JTH-601-G1) demonstrated more uroselectivity than JTH-601 (unpublished observation).

It is unknown whether or not α_{1L}-adrenoceptors exist separately from α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors, because the α_{1L}-adrenoceptor gene has not been identified in spite of considerable effort. RS-17053, an α_{1A}-adrenoceptor antagonist, was found to have a 100-fold lower affinity for the α_{1A}-adrenoceptors mediating contraction of the human lower urinary tract (including the prostate) than for the α_{1a}-adrenoceptors. This suggests that multiple forms of the α_{1A}-adrenoceptor may exist in the human lower urinary tract (Ford et al., 1996). Williams et al. (1996) and Ford et al. (1997) reported that the human cloned α_{1A}-adrenoceptor expressed in Chinese hamster ovary (CHO-K1) cells revealed properties of both α_{1L}- or α_{1A} (α_{1H})-adrenoceptors under experimental conditions (temperature and cellular integrity) in binding studies. Both authors insisted that the genes of the α_{1L}- and α_{1A}-adrenoceptors are identical. The reason that α_{1A}-adrenoceptors in the lower urinary tract have the characteristics of α_{1L}-adrenoceptors in the physiological state is unknown. Recently, Hirasawa et al. (1997) reported on the subcellular localization of α_1-adrenoceptors and found that the α_{1A} subtype is predominantly localized intracellularly, whereas the α_{1B} subtype is localized on the cell surface. Therefore, the localization of α_{1A}-adrenoceptors may determine which characteristics are apparent, α_{1A} (α_{1H}) or α_{1L}.

In conclusion, JTH-601 was shown to antagonize α_1-adrenoceptor-mediated contractile responses more potently than prazosin and tamsulosin in rabbit lower urinary tract both in vitro and in vivo. The α_{1L}-adrenoceptor-selective character may be important for the development of a uroselective α_1-adrenoceptor antagonist. JTH-601 is therefore expected to be effective in the treatment of urinary outlet obstruction in benign prostatic hypertrophy.

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