ELSEVIER

European Journal of Pharmacology 315 (1996) 73–79

ejp

Effect of KMD-3213, an α_{1a}-adrenoceptor-selective antagonist, on the contractions of rabbit prostate and rabbit and rat aorta

Ryoichi Yamagishi, Katsuyoshi Akiyama, Shunji Nakamura, Masachiyo Hora, Naoyuki Masuda, Akane Matsuzawa, Satoshi Murata, Arao Ujiie, Yoshikazu Kurashina, Kinji Iizuka, Makio Kitazawa *

Central Research Laboratories, Kissei Pharmaceutical Co., Ltd., 4365-1, Kashiwabara, Hotaka, Nagano 399-83, Japan

Received 1 February 1996; revised 18 July 1996; accepted 23 July 1996

Abstract

KMD-3213, (−)-(*R*)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide, a newly synthesized α_1-adrenoceptor antagonist, has been shown to have potent action toward, and to be selective for human cloned and native α_1-adrenoceptors. In the present study, we characterized the inhibitory effect of KMD-3213 on the phenylephrine (α_1-adrenoceptor-selective agonist)-induced contraction of rabbit prostate, rabbit thoracic aorta and rat thoracic aorta to functionally confirm the tissue selectivity of KMD-3213. The mean pA_2 value for KMD-3213 for the inhibition of the rabbit prostatic contraction was 10.05, whereas the values for the rabbit and rat aortic contractions were 9.36 and 8.13, respectively. The order of mean pA_2 values for the inhibition of the rabbit prostatic contraction was KMD-3213 ≥ tamsulosin > > prazosin, whereas that for the rabbit and rat aortic contractions was tamsulosin > KMD-3213 > prazosin and tamsulosin ≥ prazosin > > KMD-3213, respectively. KMD-3213 produced a sigmoidal inhibition curve for single-dose phenylephrine-induced contractions of rabbit prostate, whereas it produced a non-sigmoidal curve for that of rabbit aorta. KMD-3213 had no effect on isoproterenol-induced chronotropic action in guinea-pig atria, and 5-hydroxytryptamine-, histamine- and acetylcholine-mediated contractions of rabbit aorta. These results indicate that the potency of the inhibitory activity of KMD-3213 depends on the tissue subtype expression and that KMD-3213 preferentially antagonizes prostatic contraction.

Keywords: KMD-3213; α_1-Adrenoceptor subtype; α_{1a}-Adrenoceptor; Prostate; Thoracic aorta

1. Introduction

Benign prostatic hyperplasia patients have been reported to have a significant increase in the number of α_1-adrenoceptors in the hypertrophied prostate (Yamada et al., 1987). The prostatic smooth muscle tone mediated by the α_1-adrenoceptor is, therefore, thought to be one of the important components of the bladder outlet obstruction caused by prostatic hyperplasia. Although therapeutic use of several α_1-adrenoceptor antagonists to relieve the bladder outlet obstruction has been successful (Caine, 1986; Kawabe et al., 1990; Jønlar et al., 1994), this therapy frequently induces orthostatic hypotension as a side-effect. This side-effect is thought to be caused by blockade of α_1-adrenoceptors in the peripheral artery.

In recent years, both pharmacological and molecular biological studies have identified multiple α_1-adrenoceptor subtypes (reviewed by Ford et al., 1994). α_1-Adrenoceptors were originally subclassified in pharmacological studies into two subtypes designated α_{1A} and α_{1B}. Molecular cloning of the α_1-adrenoceptor has revealed the existence of the genes of three distinct subtypes: α_{1a}, α_{1b} and α_{1d} (formerly termed α_{1c}, α_{1b} and α_{1a}, $\alpha_{1a/d}$ or α_{1d}, respectively, see Hieble et al. (1995), for a review of the nomenclature of α_1-adrenoceptors), corresponding to the pharmacologically defined α_{1A}, α_{1B} and $\alpha_{1A/D}$, respectively (Ford et al., 1994; Hieble et al., 1995; Pimoule et al., 1995). Each of these subtypes has been observed to have a distinct expression pattern in various tissues. In particular, the α_{1a}-adrenoceptor has been shown to be preferentially expressed in human prostate (Hirasawa et al., 1993; Price et al., 1993; Weinberg et al., 1994), whereas α_{1b} and α_{1d} are mainly expressed in human aorta (Price et al., 1994; Weinberg et al., 1994; Faure et al., 1995). This difference provides a possibility to develop an α_1-adrenoceptor antagonist that is specific to the prostate and useful for the treatment of benign prostatic hyperplasia.

* Corresponding author. Tel.: (81-263) 82-8820; Fax: (81-263) 82-8826.

PII S0014-2999(96)00589-4

Recently, we found a novel α_1-adrenoceptor antagonist, KMD-3213, (−)-(*R*)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide, the chemical structure of which is shown in Fig. 1. Shibata et al. (1995) demonstrated that KMD-3213 has a significantly higher affinity for the human cloned α_{1a}-adrenoceptor, having an inhibition constant (K_i) of 0.036 nM, than for α_{1b} and α_{1d} (583- and 56-fold higher K_i values, respectively) and it can identify the high (66%)- and low (34%)-affinity sites in human prostate (K_i values of 0.042 and 16 nM, respectively). These observations suggest that KMD-3213 is a highly selective antagonist of the human α_{1a}-adrenoceptor. However, to confirm selectivity of KMD-3213 for the prostate, one must examine the correlation between its binding properties with respect to the cloned or native α_1-adrenoceptor and its functional effect on α_1-adrenoceptor-mediated smooth muscular contractions.

For this purpose, the present study was designed to determine the tissue selectivity of KMD-3213 by conducting functional studies on contraction of isolated muscular preparations from rabbit and rat. The inhibitory activity of KMD-3213 on phenylephrine (an α_1-adrenoceptor selective agonist)-induced contraction of rabbit prostate, rabbit thoracic aorta and rat thoracic aorta was characterized. These contractions are thought to be mediated by pharmacologically defined α_{1A}- (Testa et al., 1993), α_{1A}- plus α_{1B}- (Suzuki et al., 1990; Takayanagi et al., 1991), and α_{1D}-adrenoceptors (Kenny et al., 1995; Testa et al., 1995; Buckner et al., 1996), respectively. We compared these α_1-adrenoceptor-blocking activities of KMD-3213 with those of tamsulosin and prazosin, which are known as a subtype-selective and a non-selective α_1-adrenoceptor antagonist, respectively (Yamada et al., 1994; Foglar et al., 1995). The effect of KMD-3213 on other receptor-mediated contractions of vascular muscles was also studied.

2. Materials and methods

2.1. Drugs

(−)-(*R*)-1-(3-Hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide (KMD-3213) (Kissei Pharmaceutical, Matsumoto, Japan). Prazosin HCl (Sigma, St. Louis, MO, USA). (−)-(*R*)-5-[2-[[2-(*o*-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide HCl (tamsulosin HCl) (synthesized in our laboratory). *l*-Phenylephrine HCl, isoproterenol HCl, histamine HCl and 5-hydroxytryptamine creatinine sulfate (5-HT) (Wako, Osaka, Japan). Acetylcholine HCl (Daiichiseiyaku, Tokyo, Japan). All other chemicals were purchased from Nacalai Tesque (Kyoto, Japan). KMD-3213 was dissolved in Hartmann's solution, with the following composition (mM): NaCl, 131; KCl, 4; $CaCl_2$, 3; and sodium lactate, 28 (Green Cross, Osaka, Japan), containing two equivalents of HBr and diluted with the same solution, and tamsulosin HCl and prazosin HCl were dissolved in dimethylsulfoxide and diluted with physiological saline to the appropriate concentrations.

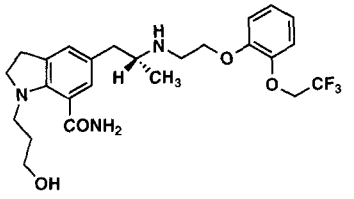

Fig. 1. Chemical structure of KMD-3213, (−)-(*R*)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]indoline-7-carboxamide.

2.2. Experimental procedure

The prostate and thoracic aorta were isolated from male Japanese White rabbits (2.5–3.5 kg, Nihon Clea, Osaka, Japan) and the thoracic aorta from male Sprague-Dawley rats (250–350 g, Japan SLC, Shizuoka, Japan) after cervical dislocation under anaesthesia with pentobarbital and ether, respectively. Endothelial cells were removed from the aorta by rubbing them with absorbent cotton. Tissue preparations from the prostate and helical strips from the aorta were prepared. Contractile responses were measured essentially as reported previously (Honda et al., 1985a,b). Each preparation was vertically suspended in a 10-ml organ bath at 37°C containing Krebs-Henseleit solution of the following composition (mM): NaCl, 118; KCl, 4.7; $CaCl_2$, 2.54; $MgSO_4$, 1.17, KH_2PO_4, 1.19; $NaHCO_3$, 25.0; and glucose 11.0. Each bath was continuously bubbled with a gas mixture consisting of 95% O_2 and 5% CO_2. The response to a given agonist was isometrically recorded under a resting tension of 1 g for all preparations. After an equilibration period of 60 min, the preparations were contracted by repeated doses of 10^{-5} M phenylephrine until constant responses were obtained. Cumulative concentration-response curves for the agonist were then obtained by increasing the concentration of the agonist by cumulative concentrations of the agonist. Antagonists were added to the bath after three successive concentration-response curves for phenylephrine had been obtained. Each tissue was equilibrated with the antagonist for 30 min before the next addition of phenylephrine.

In separate experiments, the effects of the antagonists on the single-dose phenylephrine-induced contraction of the rabbit prostate or aorta were assessed. Tissues were contracted with 10^{-5} M phenylephrine several times until a stable contraction was obtained under the same conditions as described before, and then contracted in the presence of various concentrations of antagonist added at least 30 min before the addition of 10^{-5} M phenylephrine.

The β_1-adrenoceptor blocking activity of KMD-3213 was evaluated as enhanced contraction of guinea pig atria

induced by 10^{-8} M isoproterenol. Blocking activity toward muscarinic, histamine or 5-HT receptors was examined using acetylcholine (10^{-6} M)-, histamine (10^{-6} M)- or 5-HT (10^{-6} M)-induced contraction of rabbit thoracic aorta. Experiments were performed as described above.

2.3. Data and statistical analysis

Experimental values were expressed as means ± S.E., or means with 95% confidence limits. The dose ratio was obtained from the ratio of EC_{50} values (concentration of agonist that produces half-maximal response) for each agonist in the presence or absence of an antagonist. Antagonist dissociation constants (K_B) were determined from the following equation: K_B = antagonist [M]/(dose ratio − 1).

The pA_2 values, which are expressed as the negative logarithm of K_B were estimated from Schild plots made by plotting the log of (dose ratio − 1) against the log of the molar concentration of antagonist (Arunlakshana and Schild, 1959). The statistical significance of differences between the calculated slopes and unity were tested by Student's *t*-test under the null hypothesis (slope = 1). In experiments with prostate, the dose-response curves for the agonist declined in the presence of high concentrations of KMD-3213 and tamsulosin. The potencies of these drugs for prostatic contraction were expressed as apparent pK_B values obtained at the antagonist concentrations used (Takayanagi et al., 1986).

3. Results

KMD-3213 did not cause relaxation of the resting tension of tissue preparations of rabbit prostate, rabbit aorta and rat aorta in the absence of any of the agonists tested (data not shown). Therefore, the inhibitory effect of KMD-3213 in each preparation should be due solely to its blocking activity toward each agonist.

Fig. 2 shows the effects of KMD-3213, tamsulosin and prazosin on the log concentration-response curve for phenylephrine-induced contraction of rabbit prostate. All drugs produced a shift to right in a concentration-dependent manner. However, KMD-3213 and tamsulosin at high concentrations reduced the maximum response. Fig. 3 shows the results for the rabbit thoracic aorta. KMD-3213 at concentrations over $10^{-8.5}$ M produced a non-parallel shift of the curve to the right. The other two drugs competitively antagonized the contraction. In contrast, in the case of inhibition of rat aortic contraction, as shown in Fig. 4, KMD-3213 as well as tamsulosin and prazosin in a concentration-dependent manner produced parallel shifts to the right without decreasing the maximum response.

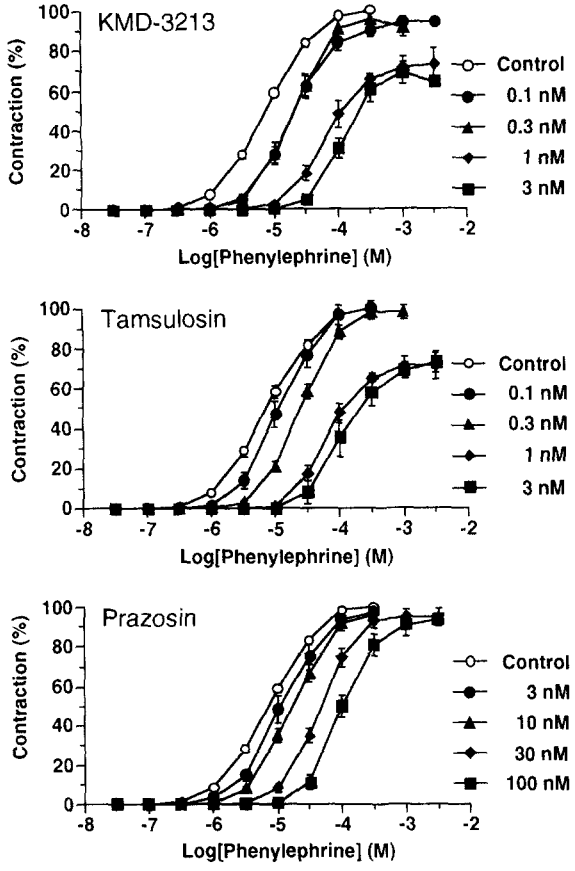

Fig. 2. Effects of KMD-3213, tamsulosin and prazosin on phenylephrine-induced rabbit prostatic contraction. Concentration-response curves, expressed as percentages of the maximum contraction elicited by phenylephrine, were obtained in the absence (open circles) or presence (closed symbols) of increasing concentrations (as indicated) of each antagonist equilibrated with the tissue for 30 min. Each point represents the mean ± S.E. of data from at least five preparations.

Table 1
pA_2 values and slopes for KMD-3213, tamsulosin and prazosin obtained with isolated rabbit prostate, rabbit aorta and rat aorta

Drug	Rabbit prostate		Rabbit aorta		Rat aorta	
	pA_2	Slope	pA_2	Slope	pA_2	Slope
KMD-3213	10.05 ± 0.05 [a]	–	9.36 ± 0.07	1.16 (1.02–1.30)	8.13 ± 0.07	0.98 (0.91–1.05)
Tamsulosin	9.99 ± 0.03 [a]	–	10.16 ± 0.07	1.16 (1.02–1.30)	10.03 ± 0.02	1.03 (0.99–1.07)
Prazosin	8.30 ± 0.03	0.90 (0.84–0.97)	9.05 ± 0.04	1.02 (0.95–1.10)	9.69 ± 0.04	1.01 (0.93–1.09)

Data are presented as the means ± S.E. (pA_2) or the means with 95% confidents limits (slope), $n \geq 20$.
[a] Apparent pK_B value, n = 23–26.

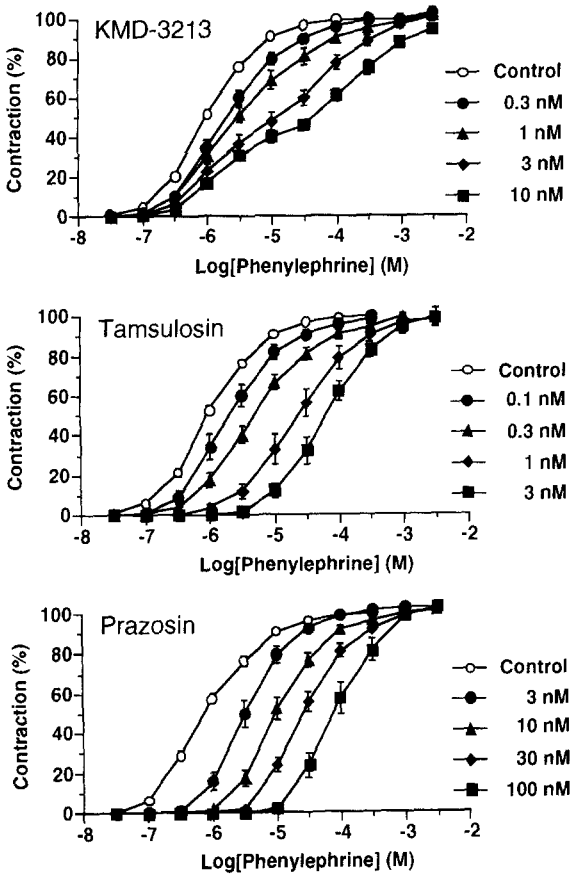

Fig. 3. Effects of KMD-3213, tamsulosin and prazosin on phenylephrine-induced rabbit aortic contraction. Concentration-response curves, expressed as percentages of the maximum contraction elicited by phenylephrine, were obtained in the absence (open circles) or presence (closed symbols) of increasing concentrations (as indicated) of each antagonist equilibrated with the tissue for 30 min. Each point represents the mean ± S.E. of data from at least five preparations.

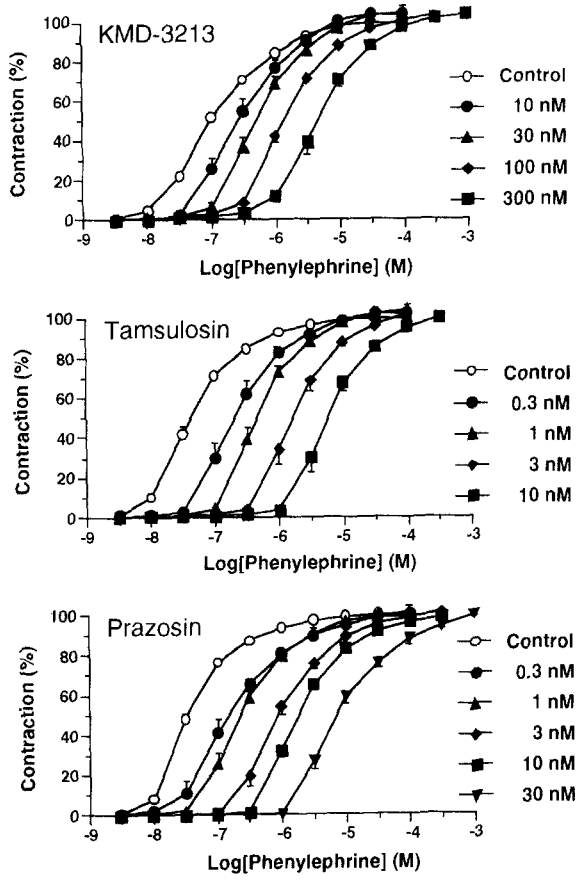

Fig. 4. Effects of KMD-3213, tamsulosin and prazosin on phenylephrine-induced rat aortic contraction. Concentration-response curves, expressed as percentages of the maximum contraction elicited by phenylephrine, were obtained in the absence (open circles) or presence (closed symbols) of increasing concentrations (as indicated) of each antagonist equilibrated with the tissue for 30 min. Each point represents the mean ± S.E. of data from at least five preparations.

Table 1 summarizes the mean pA_2 values and slopes determined from Schild plots for these antagonists determined from the experimental data of Fig. 2 and Fig. 3 and Fig. 4. The ratios of the apparent dissociation constant for KMD-3213 obtained on the rabbit prostate to that obtained on the rabbit aorta and on the rat aorta were 4.89 and 83.2, respectively. The corresponding ratios for tamsulosin were 0.68 and 0.91, respectively, and those for prazosin were 0.18 and 0.04, respectively. Although KMD-3213 produced a non-parallel shift to the right for the rabbit aortic contractile response curve, the slopes of the Schild plot were close to unity.

In the above experiments, the mode of action of KMD-3213 (unlike tamsulosin or prazosin) on rabbit aorta seemed to be different from that on prostate. To examine this difference, we investigated the effects of these antagonists on 10^{-5} M phenylephrine-induced rabbit prostatic and aortic contractions. Fig. 5 clearly shows that KMD-3213 produced a sigmoid inhibition curve for the prostatic contraction (upper panel) whereas it produced a biphasic non-sigmoid inhibition curve for the aortic contraction (lower panel). Tamsulosin and prazosin produced sigmoid inhibition curve for both muscle preparations.

Table 2 shows the antagonistic activity of KMD-3213 on isoproterenol-, acetylcholine-, 5-HT- and histamine-induced contractile responses of each isolated muscular strip. KMD-3213 had no effect on the isoproterenol-induced chronotropic action on guinea-pig atria, and 5-hydroxy-

Table 2
Effect of KMD-3213 on isoproterenol-, histamine- and acetylcholine-induced muscular contractions

Agonist	Tissue	IC_{50} (μM)
Isoproterenol (10 nM)	Guinea pig atria	> 100
5-HT (1 μM)	Rabbit aorta	> 10
Histamine (1 μM)	Rabbit aorta	> 10
Acetylcholine (1 μM)	Rabbit aorta	> 10

$n = 4$

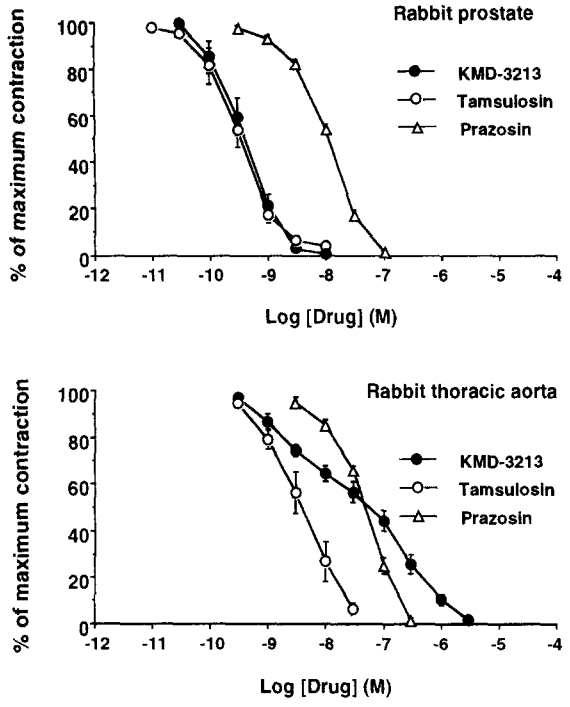

Fig. 5. Inhibition of 10^{-5} M phenylephrine-induced rabbit prostatic (upper) and rabbit aortic (lower) contraction by KMD-3213, tamsulosin and prazosin. Contractions are expressed as percentages of 10^{-5} M phenylephrine-induced contractile responses of each tissue in the absence of any antagonists. Tissues were equilibrated with increasing concentrations of each antagonist for 30 min before the addition of 10^{-5} M phenylephrine. Each point represents the mean ± S.E. of data from at least four preparations.

tryptamine-, histamine- and acetylcholine-mediated contractions of rabbit aorta.

4. Discussion

The results presented here indicate that the inhibitory potency of KMD-3213 for α_1-adrenoceptor-mediated muscular contractions of various tissues depends on the tissue expression pattern of the α_1-adrenoceptor subtypes and KMD-3213 preferentially inhibits prostatic contraction as compared to aortic contraction.

KMD-3213 showed a potent and competitive antagonistic activity toward the α_1-adrenoceptor-mediated rabbit prostatic contraction, with an apparent pK_B value of 10.05 (Table 1). The magnitude of this dissociation constant value is closer to the K_i value of KMD-3213 for the human α_{1a} subtype (Shibata et al., 1995) than to those for α_{1b} and α_{1d} subtypes. Fig. 5 suggests that the binding sites for KMD-3213 in the prostate are mostly of a single affinity type. These results indicates that the contraction of rabbit prostate is mediated mainly by a high-affinity binding site for KMD-3213, i.e., the α_{1a} (pharmacological α_{1A}) subtype. This is consistent with results of previous studies that showed the α_{1A} subtype to be the predominant subtype in human, dog, rabbit and rat prostate (Lepor et al., 1993; Goetz et al., 1994; Testa et al., 1993; Yazawa and Honda, 1993). KMD-3213 as well as tamsulosin reduced the maximum response of the prostatic contraction (Fig. 2). This phenomenon was previously observed for the inhibition by tamsulosin of the phenylephrine-induced contraction of rabbit femoral vein (Takayanagi et al., 1986) and was considered to reflect the hemi-equibrium state. In this state, the antagonist behaves as an irreversible blocker.

On the other hand, the present results shown in Fig. 3 and Fig. 5 suggest that at least two distinct binding sites for KMD-3213, i.e., high- and low-affinity sites, are involved in the inhibition by KMD-3213 of the rabbit aortic contraction. Both pharmacologically defined α_{1A} and α_{1B} subtypes have been shown to mediate rabbit aortic contraction (Suzuki et al., 1990; Takayanagi et al., 1991); there are high- and low-affinity sites for 2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane HCl (WB-4101) and 5-methyl-urapidil, both of which are known to be α_{1A}-selective antagonists (Ford et al., 1994; Hieble et al., 1995). Therefore, KMD-3213 might also functionally differentiate α_{1A} and α_{1B} subtypes in the rabbit aorta. The magnitude of the pA_2 value of KMD-3213 for the rabbit aortic contraction was, however, significantly different from those of the K_i values for the human α_{1a} or α_{1b} subtypes (Shibata et al., 1995). One possible explanation for this is that the data points used to obtain the Schild plot (50% of maximum contraction) were predominantly in the 'high-affinity area', and were partially affected by the 'low-affinity area' (Fig. 3), therefore, the pA_2 value of KMD-3213 for the rabbit aorta may apparently represent the intermediate of 'high'- and 'low'-affinity binding sites. However, it is unclear why the slope of the Schild plot was not significantly different from unity (Table 1). In contrast to its effect on the rabbit aortic contraction, KMD-3213 displayed competitive antagonistic activity toward the rat aortic contraction, showing a dissociation constant of 8.13, which was 83.2-fold lower than that for rabbit prostatic contraction. This potential ratio is in good agreement with the ratio of K_i values for KMD-3213 for the binding between the cloned human α_{1a} and α_{1d} subtypes (56-fold, Shibata et al., 1995). This result is consistent with the recent reports that the α_{1D} (α_{1d}) subtype is involved in the α_1-adrenoceptor-induced contraction of rat aorta (Kenny et al., 1995; Testa et al., 1995; Buckner et al., 1996). Therefore, KMD-3213 is expected to have a less marked effect on the vascular system. The absence of antagonistic effect of KMD-3213 on the other receptor-mediated contractions of guinea pig atria or rabbit aorta (Table 2) might further support this prediction.

In the functional study in human tissues, Forray et al. (1994) and Marshall et al. (1995) showed that the pharmacological properties of the human cloned α_{1a}-adrenoceptor (formerly α_{1c}) are similar to those of the α_1-adrenoceptor that mediates contraction of the prostate, whereas Hatano et al. (1994) showed that α_{1B}-adrenoceptors mediate contraction of human peripheral arteries. Therefore, the

tissue selectivity of KMD-3213 observed in the present study should also be observable in human tissues.

In the present study, the pA_2 values of tamsulosin and prazosin for the rabbit prostate, and rabbit and rat aorta which were in good agreement with those previously reported (Honda et al., 1985a,b; Honda and Nakagawa, 1986; Takayanagi et al., 1986; Kenny et al., 1995; Testa et al., 1995) were obtained. Tamsulosin could not differentiate between two affinity sites for the inhibition of the rabbit aorta contraction (Fig. 3). This may have been due to its selectivity for α_{1a} being lower than that of KMD-3213 (Shibata et al., 1995). On the other hand, Yamada et al. (1994) showed that the affinity of tamsulosin for native human prostate tissue is 12-fold greater than that for the human artery, whereas prazosin has equipotent affinities for both tissues. Foglar et al. (1995) showed that tamsulosin has a higher affinity for the α_{1a}-adrenoceptor than for the α_{1b} and α_{1d} (approximately 20 and 7 times, respectively). These studies suggest that tamsulosin is selective for blocking prostatic contraction. However, in spite of the α_{1a} selectivity of tamsulosin, the studies on contraction, from the present and previous reports (Honda et al., 1985a,b; Honda and Nakagawa, 1986), indicate that tamsulosin (as well as prazosin) has an equivalent or lower dissociation constant value for the rabbit prostate than for the rabbit or rat aorta. The reason for this discrepancy between the binding and the results of functional studies on the α_1-adrenoceptor blocking activity of tamsulosin is presently unclear.

In conclusion, because of its higher selectivity for blocking contraction of the prostate than of the aorta, KMD-3213 is expected to be a useful drug for the treatment of benign prostatic hyperplasia with much less effect on the vascular system.

References

Arunlakshana, O. and H.O. Schild, 1959, Some quantitative uses of drug antagonists, Br. J. Pharmacol. 14, 48.

Buckner, S.A., K.W. Oheim, P.A. Morse, S.M. Knepper and A.A. Hancock, 1996, α_1-Adrenoceptor-induced contractility in rat aorta is mediated by the α_{1D} subtype, Eur. J. Pharmacol. 297, 241.

Caine, M., 1986, The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy, J. Urol. 136, 1.

Faure, C., C. Gouhier, S.Z. Langer and D. Graham, 1995, Quantification of α_1-adrenoceptor subtypes in human tissues by competitive RT-PCR analysis, Biochem. Biophys. Res. Commun. 213, 935.

Foglar, R., K. Shibata, K. Horie, A. Hirasawa and G. Tsujimoto, 1995, Use of recombinant α_1-adrenoceptors to characterize subtype selectivity of drugs for the treatment of prostatic hypertrophy, Eur. J. Pharmacol. Mol. Pharmacol. Sect. 288, 201.

Ford, A.P.D.W., T.J. Williams, D.R. Blue and D.E. Clarke, 1994, α_1-adrenoceptor classification: sharpening Occam's razor, Trends Pharmacol. Sci. 15, 167.

Forray, C., J.A. Bard, J.M. Wetzel, G. Chiu, E. Shapiro, R. Tang, H. Lepor, P.R. Hartig, R.L. Weinshank, T.A. Branchek and C. Gluchowski, 1994, The α_1-adrenergic receptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned human α_{1C} subtype, Mol. Pharmacol. 45, 703.

Goetz, A.S., M.W. Lutz, T.J. Rimele and D.L. Saussy, Jr., 1994, Characterization of alpha-1 adrenoceptor subtypes in human and canine prostate membranes, J. Pharmacol. Exp. Ther. 271, 1228.

Hatano, A., H. Takahashi, M. Tamaki, T. Komeyama, T. Koizumi and M. Takeda, 1994, Pharmacological evidence of distinct α_1-adrenoceptor subtypes mediating the contraction of human prostatic urethra and peripheral artery, Br. J. Pharmacol. 113, 723.

Hieble, J.P., D.B. Bylund, D.E. Clarke, D.C. Eikenburg, S.Z. Langer, R.J. Lefkowitz, K.P. Minneman and R.R. Ruffolo Jr., 1995, International union of pharmacology X. Recommendation for nomenclature of α_1-adrenoceptors: consensus update, Pharmacol. Rev. 47, 267.

Hirasawa, A., K. Horie, T. Tanaka, K. Takagaki, M. Murai, J. Yano and G. Tsujimoto, 1993, Cloning, functional expression and tissue distribution of human cDNA for the α_{1C}-adrenergic receptor, Biochem. Biophys. Res. Commun. 195, 902.

Honda, K. and C. Nakagawa, 1986, Alpha-1 adrenoceptor antagonist effects of the optical isomers of YM-12617 in rabbit lower urinary tract and prostate, J. Pharmacol. Exp. Ther. 239, 512.

Honda, K., A. Miyata-Osawa and T. Takenaka, 1985a, α_1-adrenoceptor subtype mediating contraction of the smooth muscle in the lower urinary tract and prostate of rabbits, Naunyn-Schmiedeberg's Arch. Pharmacol. 330, 16.

Honda, K., T. Takenaka, A. Miyata-Osawa, M. Terai and K. Shiono, 1985b, Studies on YM-12617: a selective and potent antagonist of postsynaptic α_1-adrenoceptors, Naunyn-Schmiedeberg's Arch. Pharmacol. 328, 264.

Jønlar, M., M. Riehmann and R.C. Bruskewitz, 1994, Benign prostatic hyperplasia: current pharmacological treatment, Drugs 47, 66.

Kawabe, K., A. Ueno, Y. Takimoto, Y. Aso and H. Kato, 1990, Use of an α_1-blocker, YM-12617, in the treatment of benign prostatic hypertrophy. YM617 clinical study group, J. Urol. 144, 908.

Kenny, B.A., D.H. Chalmers, P.C. Philpott and A.M. Naylor, 1995, Characterization of an α_{1D}-adrenoceptor-mediating the contractile response of rat aorta to noradrenaline, Br. J. Pharmacol. 115, 981.

Lepor, H., R. Tang, S. Meretyk and E. Shapiro, 1993, Alpha$_1$ adrenoceptor subtypes in the human prostate, J. Urol. 149, 640.

Marshall, I., R.P. Burt and C.R. Chapple, 1995, Noradrenaline contractions of human prostate mediated by α_{1A}- (α_{1c}-) adrenoceptor subtype, Br. J. Pharmacol. 115, 781.

Pimoule, C., S.Z. Langer and D. Graham, 1995, Further evidence that the classical α_{1A}- and cloned α_{1c}-adrenoceptors are the same subtype, Eur. J. Pharmacol. Mol. Pharmacol. Sect. 290, 49.

Price, D.T., D.A. Schwinn, J.W. Lomasney, L.F. Allen, M.G. Caron and R.J. Lefkowitz, 1993, Identification, quantification, and localization of mRNA for three distinct alpha-1 adrenergic receptor subtypes in human prostate, J. Urol. 150, 546.

Price, D.T., R.J. Lefkowitz, M.G. Caron, D. Berkowitz and D.A. Schwinn, 1994, Localization of mRNA for three distinct α_1-adrenergic receptor subtypes in human tissues: implications for human α-adrenergic physiology, Mol. Pharmacol. 45, 171.

Shibata, K., R. Foglar, K. Horie, K. Obika, A. Sakamoto, S. Ogawa and G. Tsujimoto, 1995, KMD-3213, a novel, potent α_{1a}-adrenoceptor-selective antagonist: characterization using recombinant human α_1-adrenoceptors and native tissues, Mol. Pharmacol. 48, 250.

Suzuki, E., G. Tsujimoto, K. Tamura and K. Hashimoto, 1990, Two pharmacologically distinct α_1-adrenoceptor subtypes in the contraction of rabbit aorta: each subtype couples with a different Ca^{2+} signaling mechanism and plays a different physiological role, Mol. Pharmacol. 38, 725.

Takayanagi, I., F. Konno, T. Toru and R. Takahashi, 1986, Difference in mode of action of alpha$_1$-adrenoceptor antagonists on some vascular smooth muscles and efficacy, Jpn. J. Pharmacol. 42, 237.

Takayanagi, I., M. Harada, K. Koike and M. Satoh, 1991, Differences in α_1- adrenoceptor mechanisms for phenylephrine and tizanidine in rabbit thoracic aorta and common liliac artery, Can. J. Physiol. Pharmacol. 69, 1819.

Testa, R., L. Guarneri, M. Ibba, G. Strada, E. Poggesi, C. Taddei, I.

Simonazzi and A. Leonardi, 1993, Characterization of α_1-adrenoceptor subtypes in prostate and prostatic urethra of rat, rabbit, dog and man, Eur. J. Pharmacol. 249, 307.

Testa, R., C. Destefani, L. Guarneri, E. Poggesi, I. Simonazzi, C. Taddei and A. Leonardi, 1995, The α1d-adrenoceptor subtype is involved in the noradrenaline-induced contractions of rat aorta, Life Sci. 57, PL159.

Weinberg, D.H., P. Trivedi, C.P. Tan, S. Mitra, A. Perkins-Barrow, D. Borkowski, C.D. Strader and M. Bayne, 1994, Cloning, expression and characterization of human α adrenergic receptors α_{1A}, α_{1B} and α_{1C}, Biochem. Biophys. Res. Commun. 201, 1296.

Yamada, S., N. Ashizawa, H. Ushijima, K. Nakayama, E. Hayashi and K. Honda, 1987, Alpha-1 adrenoceptors in human prostate: characterization and alteration in benign prostatic hypertrophy, J. Pharmacol. Exp. Ther. 242, 326.

Yamada, S., M. Suzuki, C. Tanaka, R. Mori, R. Kimura, O. Inagaki, K. Honda, M. Asano, T. Takenaka and K. Kawabe, 1994, Comparative study on α_1-adrenoceptor antagonist binding in human prostate and aorta, Clin. Exp. Pharmacol. Physiol. 21, 405.

Yazawa, H. and K. Honda, 1993, α_1-adrenoceptor subtype in the rat prostate is preferentially the α_{1A} type, Jpn. J. Pharmacol. 62, 297.