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Pharmacological evidence of distinct α_1-adrenoceptor subtypes mediating the contraction of human prostatic urethra and peripheral artery

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1 The α_1-adrenoceptor subtypes mediating contractions of the smooth muscle in human prostatic urethra and branches of internal iliac artery were characterized in isometric contraction experiments.

2 Phenylephrine produced concentration-dependent contractions in both the urethra and artery. These responses were competitively inhibited by prazosin, WB4101 and 5-methyl-urapidil, and the slopes of Schild plots for all these antagonists were close to unity.

3 The pA_2 values for prazosin were not significantly different between the urethra (9.42 ± 0.11; mean ± s.d.) and artery (9.50 ± 0.27), while the pA_2 values for WB4101 and 5-methyl-urapidil in the human prostatic urethra (8.94 ± 0.19 and 8.42 ± 0.14, respectively) were significantly greater than in the branches of human internal iliac artery (7.94 ± 0.21 and 7.43 ± 0.22, respectively; $P<0.01$).

4 Pretreatment with chlorethylclonidine (CEC) at concentrations ranging from 0.1 μM to 100 μM attenuated the maximum contraction to phenylephrine in a concentration-dependent manner in both the urethra and artery. However, the urethra was significantly less affected by CEC than the artery. The pD'_2 values (negative logarithm of the molar concentration of antagonist which reduced the maximum contraction to one half) in the urethra and artery were 4.35 ± 0.27 and 5.20 ± 0.37, respectively ($P<0.01$).

5 The present results indicate that there are distinct populations of α_1-adrenoceptor subtypes in the human prostatic urethra and branches of the internal iliac artery. The α_1-adrenoceptors responsible for the contraction of the human internal iliac artery branches are predominantly α_{1B}-subtype, whereas those in the human prostatic urethra are considered to be not α_{1B}, but α_{1C} or possibly α_{1A} or $\alpha_{1A/D}$-subtype.

Keywords: α_1-Adrenoceptor subtype; human urethra; human artery; phenylephrine-induced contraction; prazosin; WB4101; 5-methyl-urapidil; chlorethylclonidine

Introduction

α_1-Adrenoceptors have been subclassified according to their pharmacological properties into two receptor subtypes designated α_{1A} and α_{1B}. The α_{1A}-subtype shows high affinity for WB4101, benoxathian and 5-methyl-urapidil, and has little sensitivity to an irreversible alkylating agent, chlorethylclonidine (CEC), whereas the α_{1B}-subtype exhibits low affinity for the above-mentioned competitive antagonists and is potently inactivated by CEC (Morrow & Creese, 1986; Han *et al.*, 1987a,b; Minneman *et al.*, 1988; Gross *et al.*, 1988).

In recent years, molecular biological studies have revealed the existence of three genes encoding α_1-adrenoceptor subtypes, α_{1A} (rat: Lomasney *et al.*, 1991), α_{1B} (hamster: Cotecchia *et al.*, 1988) and α_{1C} (bovine: Schwinn *et al.*, 1990). In addition, another gene coding for a novel α_{1D}-subtype has been cloned (rat: Perez *et al.*, 1991). Identification of α_1-adrenoceptor subtypes in human various tissues is difficult. As regards the subtypes of α_1-adrenoceptors in human prostatic smooth muscles, several pharmacological and molecular biological studies have been reported (Chapple *et al.*, 1991; Lepor *et al.*, 1993a,b; Testa *et al.*, 1993; Price *et al.*, 1993). However, subclassification of α_1-adrenoceptors in human urethra and blood vessels has received little attention (Chapple *et al.*, 1991; Testa *et al.*, 1993).

The clinical effect of α_1-adrenoceptor antagonists for bladder outlet obstruction has already been established. Caine *et al.* (1975) first reported the pharmacological evidence that the human prostatic capsule and prostatic adenoma were rich in α-adrenoceptors. Subsequently, the efficacy of nonselective α-adrenoceptor antagonists, such as phenoxybenzamine and phentolamine, for the treatment of symptomatic bladder outlet obstruction was reported (Caine *et al.*, 1976; McGuire *et al.*, 1976; Awad *et al.*, 1976). In patients with benign prostatic hypertrophy, it was found that phentolamine reduced the intraurethral pressure in all portions of the urethra and inhibited noradrenaline-induced contraction of the isolated prostate, prostatic capsule and prostatic urethra (Furuya *et al.*, 1982). More recently, the α-adrenoceptors in these tissues were characterized as α_1- and α_2-adrenoceptors (Lepor & Shapiro, 1984; Kunisawa *et al.*, 1985; Gup *et al.*, 1990), and the selective α_1-adrenoceptor antagonists, such as prazosin or terazosin, have been reported as superior to nonselective α-blockers in safety and efficacy (Hedlund *et al.*, 1983; Kawabe *et al.*, 1990; Lepor *et al.*, 1990; Jardin *et al.*, 1991). The clinical effects of these antagonists are dose-dependent, but the development of systemic side effects restricts the maximum therapeutic dose. The most common adverse events associated with current selective α_1-antagonists are light-headedness, weakness and dizziness (Lepor *et al.*, 1990), which may be mediated by vascular and cerebral α_1-adrenoceptors. To avoid such adverse events, differentiation of α_1-adrenoceptor subtypes between human urethra and artery, as well as development of α_1-blockers selective for the human urethra, is essential. Consequently, this study was designed to identify α_1-adrenoceptor subtypes mediating contraction of the smooth muscle in human prostatic urethra and peripheral artery by isometric contraction technique.

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Methods

Human prostatic urethra in the region from the bladder neck to the proximal end of the colliculus seminalis and branches of the internal iliac artery, such as the superior vesical artery or obturator artery, were used. These tissues were obtained at the time of surgery from 19 males, aged 51 to 83 years (65.9 average), undergoing total cystectomy and pelvic lymph node dissection for urinary bladder tumour. Patients who had symptomatic bladder outlet obstruction, macroscopically obvious benign prostatic hyperplasia, urethral involvement of urinary bladder tumour, or prostatic cancer were excluded from this study. No patient had received irradiation, anticancer chemotherapy, or α_1-blocker administration prior to the surgery. Informed consent was obtained from each patient. These resected tissues were preserved at 4°C in oxygenated Krebs-Henseleit solution just after excision, and were used for the experiments within 24 h.

Preparation of tissue specimens

Urethral mucosa and prostate were removed from the smooth muscle layer of the normal prostatic urethra, and the artery was cleaned of adherent fatty and connective tissues. Then transverse smooth muscle strips measuring approximately 10 × 3 mm were prepared from the prostatic urethra, and ring media preparations, approximately 2 mm in diameter and 5 mm in length, were obtained from the branches of internal iliac artery. In order to avoid the possible involvement of endothelium-derived relaxing factor in the mechanical response (Furchgott, 1981), the endothelium of each segment of the artery was removed by rubbing them with a metal sound. Each preparation was suspended in an organ bath containing 10 ml modified Krebs-Henseleit buffer (mM): NaCl 111.0, KCl 5.9, $CaCl_2$ 2.5, $MgCl_2$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 25.0 and glucose 11.5. The baths were maintained at 37°C, pH 7.4 and continuously aerated with a gas mixture consisting of 95% O_2 and 5% CO_2. A resting tension of 1 g was applied and the isometric contraction was recorded through a force-displacement transducer (T-7, Orientec, Japan) coupled to an amplifier unit (1829, Nihon Denki San-ei, Japan) and ink oscillographs (Servocorder, SR6211-2L, Graphtec, Japan). The preparations were equilibrated for at least 60 min before starting the experiments.

Phenylephrine concentration-response experiments

We used phenylephrine as an agonist in both tissues in order to eliminate the involvement of postjunctional α_2-adrenoceptors. Concentration-response curves for phenylephrine were obtained by direct administration of the drug into the bathing media in a cumulative fashion (10 nM–10 mM). Propranolol (1 μM) and atropine (1 μM) were added to the bathing solution 10 min before the phenylephrine concentration-response experiments in order to block β-adrenoceptors and muscarinic receptors, respectively.

In preliminary experiments, we confirmed the reproducibility of the concentration-response curves in each preparation. After determination of control concentration-response curves, the preparations were washed 3 times with a drug-free buffer and allowed to equilibrate for about 60 min prior to the next cumulative dose experiments. Competitive antagonists of α_1-adrenoceptors, prazosin (1–30 nM), WB-4101 (10–300 nM), and 5-methyl-urapidil (10–300 nM) were applied 30 min before the contractile response to phenylephrine in the presence of each antagonist. This procedure was repeated with 3 or 4 different but increasing concentrations of the antagonist in the same preparation. The competitive antagonistic activities were expressed as pA_2 values which were calculated according to the method of Arunlakshana & Schild (1959).

Chlorethylclonidine-pretreatment

Effects of chlorethylclonidine (CEC), an irreversible antagonist of α_1-adrenoceptors were also investigated. After determination of control concentration-response curves, the preparations were repetitively treated with CEC (at final concentrations ranging from 0.1 to 100 μM) for a total of 80 min; following the initial application, CEC was renewed 3 times every 20 min, because previous reports (Minneman *et al.*, 1988; Suzuki *et al.*, 1990) and our preliminary experiments showed that the incomplete access of the highly water-soluble CEC to α_1-adrenoceptor-binding sites could be overcome by repetitive treatments. After CEC pretreatment, the preparations were extensively washed with fresh Krebs-Henseleit solution for 30 min (7 repeats at 5 min intervals, 5 times each repeat), and then cumulative concentration-response curves for phenylephrine were obtained. The antagonistic activities of CEC were expressed as pD'_2 values (negative logarithm of the molar concentration of antagonist which reduce the maximum contraction to one half; Ariëns & van Rossum, 1957).

Drugs

Phenylephrine hydrochloride, prazosin hydrochloride, WB4101 hydrochloride (N-[2-(2,6-dimethoxy-phenoxy)ethyl]-2,3-dihydro-1,4-benzodioxin-2-methanamine hydrochloride), 5-methyl-urapidil, chlorethylclonidine and (±)-propranolol hydrochloride were purchased from Research Biochemicals Inc. (Natick, MA, U.S.A.). Atropine sulphate monohydrate was purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan).

Statistical analyses

Experimental values are given as a mean ± standard deviation (s.d.). Results were analysed by Student's *t* test for unpaired observation and a probability of less than 0.05 was considered significant.

Results

Effects of the competitive antagonists on phenylephrine-induced contraction

α_1-Adrenoceptor stimulation by phenylephrine produced concentration-dependent contractions in the human urethra and branches of the internal iliac artery. These contractile responses were antagonized by prazosin, WB4101 and 5-methyl-urapidil, resulting in rightward parallel shifts of the concentration-response curves (Figures 1, 2 and 3). The slopes of Schild plots for all antagonists tested were close to unity (Table 1), suggesting that these antagonists competitively inhibited the contractile responses elicited by phenylephrine in both tissues. Prazosin inhibited the phenylephrine responses at lower concentrations than WB4101 or 5-methyl-urapidil in both the urethra and the artery, thus resulting in higher pA_2 values. The pA_2 values for prazosin in the urethra and artery were 9.42 ± 0.11 and 9.50 ± 0.27, respectively (Table 1), and there was no significant difference in the pA_2 values between the two tissues. The pA_2 values for WB4101 in the urethra and artery were 8.94 ± 0.19 and 7.94 ± 0.21, respectively, and those for 5-methyl-urapidil were 8.42 ± 0.14 and 7.43 ± 0.22 (Table 1). Thus the pA_2 values for WB4101 and 5-methyl-urapidil in the urethra were significantly greater than those in the artery ($P<0.01$).

Effects of chlorethylclonidine on phenylephrine-induced contractions

Chlorethylclonidine (CEC) which is an irreversible alkylating agent of α_1-adrenoceptors (LeClerc *et al.*, 1980) attenuated

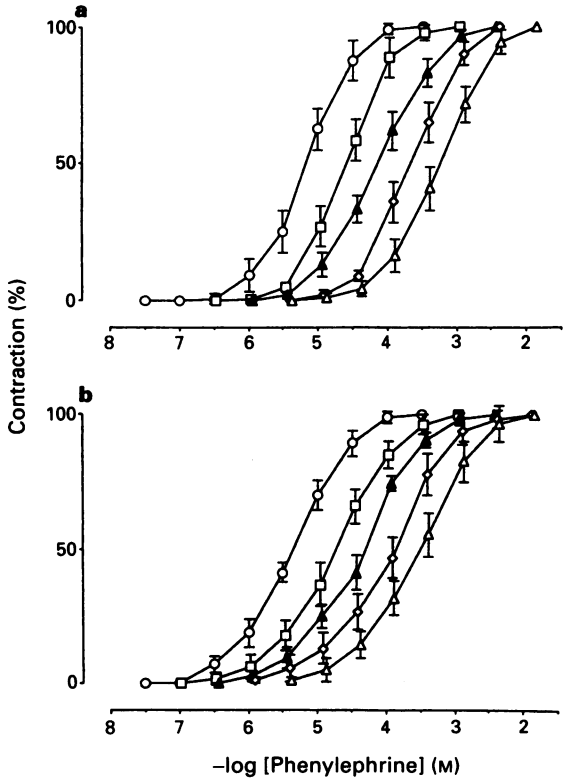

Figure 1 Effects of prazosin on the concentration-response curves for phenylephrine in the human prostatic urethra (a) and branches of the internal iliac artery (b). (○) Control; (□) 1 nM prazosin; (▲) 3 nM prazosin; (◇) 10 nM prazosin; (△) 30 nM prazosin. Each value is presented as the mean ± s.d. (bar) of 8 experiments.

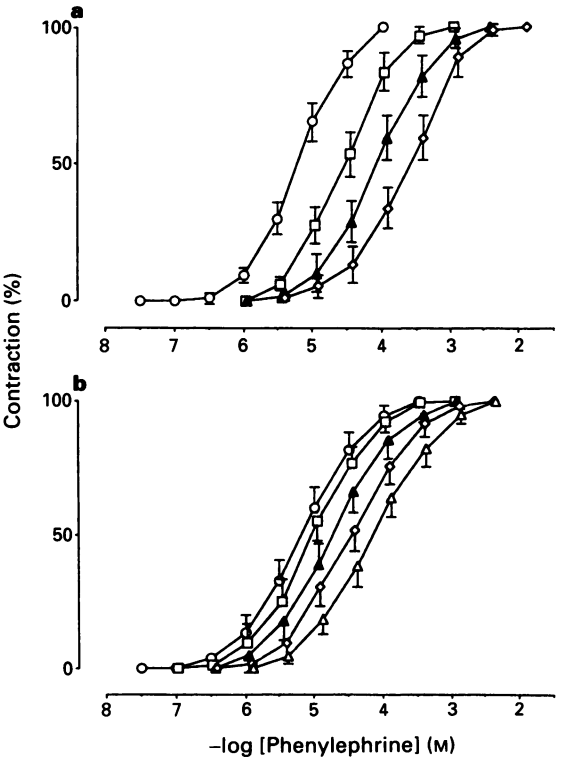

Figure 3 Effects of 5-methyl-urapidil (5-MeU) on the concentration-response curves for phenylephrine in the human prostatic urethra (a) and branches of the internal iliac artery (b). (○) Control; (□) 10 nM 5-MeU; (▲) 30 nM 5-MeU; (◇) 100 nM 5-MeU; (△) 300 nM 5-MeU. Each value is presented as the mean ± s.d. of 7 (a) and 9 (b) experiments.

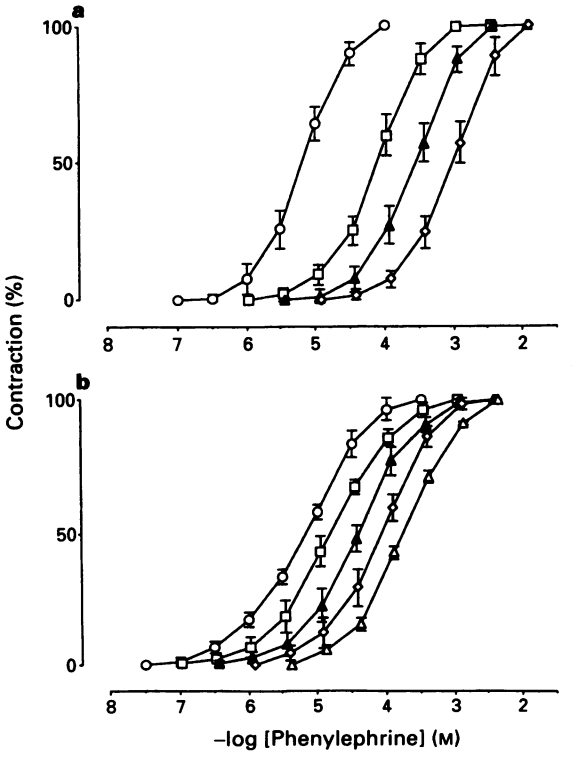

Figure 2 Effects of WB4101 on the concentration-response curves for phenylephrine in the human prostatic urethra (a) and branches of the internal iliac artery (b). (○) Control; (□) 10 nM WB4101; (▲) 30 nM WB4101; (◇) 100 nM WB4101; (△) 300 nM WB4101. Each value is presented as the mean ± s.d. of 11 (a) and 8 (b) experiments.

the maximum contractile responses induced by phenylephrine in both tissues in a concentration-dependent manner (Figure 4). However, the urethra was less affected by CEC than was the artery. Pretreatment with 10 μM and 100 μM CEC abolished about 55% and 90%, respectively, of the contractile response elicited by phenylephrine in the artery, while it abolished about 30% and 60% in the urethra. The pD'_2 value for CEC in the branches of the internal iliac artery (5.20 ± 0.37) was significantly greater than that in the prostatic urethra (4.35 ± 0.27) ($P<0.01$; Table 2).

Discussion

In this study, we have confirmed the distinction of α_1-adrenoceptor subtypes in the smooth muscle between the human prostatic urethra and branches of the internal iliac artery by the isometric contraction technique using WB4101, 5-methyl-urapidil and chlorethylclonidine as selective antagonists. This is the first report on the comparison of the α_1-adrenoceptor subtypes mediating the contraction of the smooth muscle in the human urethra and peripheral artery.

Originally, α_1-adrenoceptors which have high affinity for prazosin were subdivided into α_{1A}- and α_{1B}-adrenoceptor subtypes based on the affinities of WB4101, benoxathian (Morrow & Creese, 1986; Han *et al.*, 1987a) and 5-methyl-urapidil (Gross *et al.*, 1988) and sensitivities to the Ca^{2+} channel blocker, nifedipine (Han *et al.*, 1987a) in various tissues of rat, and also based on the ability of the alkylating agent CEC to inactivate the α_{1B} but not the α_{1A}-subtype (Han *et al.*, 1987b; Minneman *et al.*, 1988).

In the present study, the pA_2 values for WB4101 and 5-methyl-urapidil, which were thought to be α_{1A}-selective antagonists, were significantly higher in the urethra than in the artery, and the pD'_2 values for CEC were significantly

Table 1 pA_2 values of prazosin, WB4101 and 5-methyl-urapidil (5-MeU) in the human prostatic urethra and branches of the internal iliac artery

Antagonist	n	Urethra pA_2	Slope	n	Artery pA_2	Slope	Student's t test
Prazosin	8	9.42 ± 0.11	0.98	8	9.50 ± 0.27	0.90	NS
WB4101	11	8.94 ± 0.19	1.07	8	7.94 ± 0.21	0.97	$P<0.01$
5-MeU	7	8.42 ± 0.14	1.07	9	7.43 ± 0.22	1.06	$P<0.01$

Data shown are mean ± standard deviation, n = number of experiments. NS = not significant.

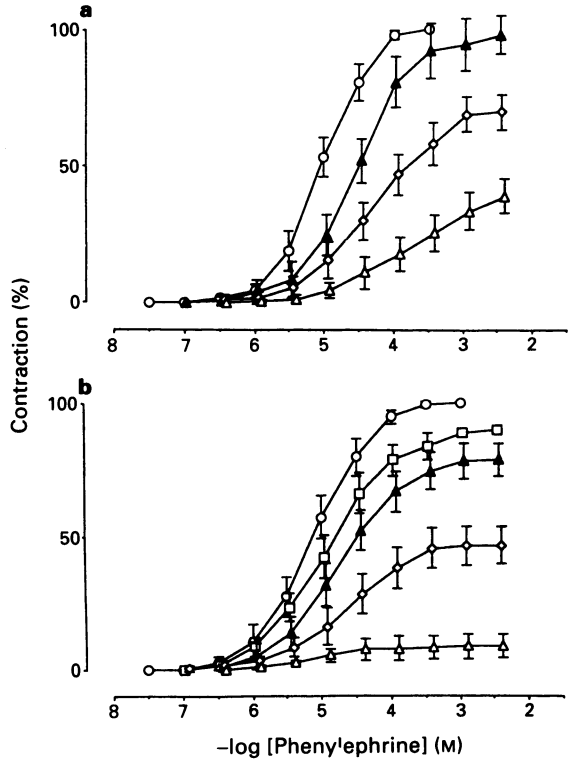

Figure 4 Effects of pretreatment with chlorethylclonidine (CEC) on phenylephrine-induced contraction of the human prostatic urethra (a) and branches of the internal iliac artery (b). (○) Control; (□) 0.1 μM CEC; (▲) 1 μM CEC; (◇) 10 μM CEC; (△) 100 μM CEC. Each value is expressed as % maximal response to phenylephrine is the mean ± s.d. (bar) of 6 (a) and 5 (b) experiments.

Table 2 pD'_2 values of chlorethylclonidine (CEC) in the human prostatic urethra and branches of the internal iliac artery

Antagonist	n	Urethra pD'_2	n	Artery pD'_2	Student's t test
CEC	6	4.35 ± 0.27	5	5.20 ± 0.37	$P<0.01$

Data shown are mean ± standard deviation, n = number of experiments. pD'_2: negative logarithms of the molar concentration of antagonist which reduce the maximum contraction to one half.

higher in the artery than in the urethra. Thus, the artery showed low affinities for WB4101 and 5-methyl-urapidil, and high susceptibility to inactivation by CEC. The α_1-adrenoceptor subtype responsible for the contraction of smooth muscles of human peripheral arteries therefore should be considered to belong to the α_{1B}-subtype. On the other hand, the human prostatic urethra showed higher affinities for WB4101 and 5-methyl-urapidil, which suggested that the α_1-subtype mediating the contraction of the human urethral smooth muscles might be the α_{1A}-subtype. However, the urethra displayed a considerable degree of sensitivity to inactivation by CEC, although it was significantly less than in the artery. This result does not agree with the fact that the pretreatment with CEC produced no effect on the contractile response of rat vas deferens (Han *et al.*, 1987b) which is considered to be mediated predominantly by α_{1A}-adrenoceptors (Aboud *et al.*, 1993). Thus, the α_1-adrenoceptors in the human prostatic urethra may be a mixture of α_{1A}- and α_{1B}-subtypes. In rat mesenteric artery and portal vein, α-adrenergic contractile responses are supposed to be mediated by a mixture of both α_{1A}- and α_{1B}-subtypes because both CEC and nifedipine partially attenuated noradrenaline-induced contractions, and WB4101 had moderate potencies in those tissues (Han *et al.*, 1990). Takayanagi *et al.* (1991) showed that, in rabbit common iliac artery, the concentration-response curve for phenylephrine was shifted by a lower concentration of WB4101, with no further shift being evident when a higher concentration of WB4101 was used, and demonstrated that, in rabbit aorta, two pA_2 values for WB4101 could be estimated according to computer-assisted analysis of the nonlinear Schild plot for an antagonism between phenylephrine and WB4101. Consequently, it was suggested that the rabbit aorta and the common iliac artery contained both α_{1A}- and α_{1B}-subtypes. In the present experiments, however, phenylephrine-induced concentration-responses curves in the urethra were shifted by WB4101 and 5-methyl-urapidil in a parallel manner and the Schild plots for both antagonists were linear with the slope close to unity. Thus, we could not obtain evidence of involvement of more than two adrenoceptor subtypes in the contraction of the human prostatic urethra by functional experiments.

Recent molecular biological studies revealed the existence of at least three distinct genes coding for α_1-adrenoceptors of mammals, namely α_{1A}- (Lomasney *et al.*, 1991), α_{1B}- (Cotecchia *et al.*, 1988) and α_{1C}-receptors (Schwinn *et al.*, 1990). Moreover, the clone of a novel α_{1D}-subtypes has been reported (Perez *et al.*, 1991). It is now widely accepted that CEC inactivates all of these cloned α_1-adrenoceptor subtypes, whereas the classical 'pharmacological' α_{1A}-subtype is considered resistant to this alkylating agent (Han *et al.*, 1987b; Minneman *et al.*, 1988) and it has not yet been identified by molecular cloning techniques. The cloned rat α_{1A}-adrenoceptor is now regarded as identical to rat α_{1D}-adrenoceptor (the DNA sequences of these two receptors were identical, except for two codons), and thus Schwinn & Lomasney (1992) have proposed designating it as the $\alpha_{1A/D}$-adrenoceptor. Pharmacological properties of the cloned α_1-adrenoceptor subtypes (α_{1B}, α_{1C} and $\alpha_{1A/D}$) have been studied by ligand binding experiments using membranes from COS-7 or HeLa cells transfected with the expression vector containing each cDNA (Schwinn *et al.*, 1990; Lomasney *et al.*, 1991; Perez *et al.*, 1991; Schwinn & Lomasney, 1992). Testa *et al.* (1993) evaluated the affinities of diverse α_1-antagonists for the α_1-adrenoceptor subtypes by a receptor binding technique using membranes of rat hippocampus pretreated with CEC (classical α_{1A}), rat liver (α_{1B}) and rabbit liver (α_{1C}). According to these reports, the pK_i values for prazosin were 9.03 in rat classical α_{1A} (Testa *et al.*, 1993), 9.25–9.60 in hamster and rat α_{1B} (Schwinn *et al.*, 1990; Lomasney *et al.*, 1991; Perez *et al.*,

1991; Testa *et al.*, 1993), 9.00–9.57 in bovine and rat α_{1C} (Schwinn *et al.*, 1990; Lomasney *et al.*, 1991; Testa *et al.*, 1993), and 9.48–9.49 in rat $\alpha_{1A/D}$ (Lomasney *et al.*, 1991; Perez *et al.*, 1991), all of which showed almost equivalent values. The pA_2 values for prazosin in our study were 9.42 in the urethra and 9.50 in the artery, being close to the above-mentioned pK_i values. The pK_i values for WB4101 derived from those binding studies were 8.89 in classical α_{1A} (Testa *et al.*, 1993), 7.54–8.23 in α_{1B} (Schwinn *et al.*, 1990; Lomasney *et al.*, 1991; Perez *et al.*, 1991; Testa *et al.*, 1993), 8.89–9.26 in α_{1C} (Schwinn *et al.*, 1990; Lomasney *et al.*, 1991; Testa *et al.*, 1993), and 8.67–8.72 in $\alpha_{1A/D}$ (Lomasney *et al.*, 1991; Perez *et al.*, 1991). The pK_i values for 5-methyl-urapidil were 8.33 in classical α_{1A} (Testa *et al.*, 1993), 6.47–7.39 in α_{1B} (Perez *et al.*, 1991; Schwinn & Lomasney, 1992; Testa *et al.*, 1993), 7.76–8.16 in α_{1C} (Schwinn & Lomasney, 1992; Testa *et al.*, 1993), and 6.48–7.82 in $\alpha_{1A/D}$ (Perez *et al.*, 1991; Schwinn & Lomasney, 1992). It is noteworthy that WB4101 has high affinity for α_{1C} and $\alpha_{1A/D}$ subtypes, and 5-methyl-urapidil has high affinity for the α_{1C}-subtype and low affinity for the $\alpha_{1A/D}$-subtype as well as the α_{1B}-subtype, although they have been regarded as α_{1A}-selective antagonists. The pA_2 values of the human artery for WB4101 and 5-methyl-urapidil found in this study were 7.94 and 7.43, which were comparable to the pK_i values of hamster and rat α_{1B}-receptors. On the other hand, the pA_2 value of the human urethra for WB4101 (8.94) and 5-methyl-urapidil (8.42) were close to the pK_i values of rat classical α_{1A}- and bovine and rat α_{1C}-receptors. These findings suggest that the human peripheral artery contains predominantly the α_{1B}-adrenoceptor subtype, and the human prostatic urethra primarily α_{1A} or α_{1C}; however it is unknown which receptor is the chief one in the urethra.

In the binding study of transfected COS-7 cells, pretreatment with 100 μM CEC for 10 min inactivated 98% of the cloned hamster α_{1B}-receptor, while 72% of the rat $\alpha_{1A/D}$-receptor was inactivated by the same pretreatment (Perez *et al.*, 1991). Exposure to 100 μM CEC for 20 min also inactivated 95% of the cloned hamster α_{1B}-receptor and 68% of the bovine α_{1C}-receptor (Schwinn *et al.*, 1990). In our study, preincubation of the artery with 10 μM and 100 μM CEC for 80 min caused 55% and 90% decrease in maximum contraction, respectively, and thus high susceptibility of the human artery to CEC was demonstrated. Accordingly, it is strongly suggested that the α_1-adrenoceptor subtype mediating the contraction of the branches of human internal iliac artery is mainly the α_{1B}-subtype. In the human urethra in our study, preincubation with 10 μM and 100 μM CEC for 80 min elicited 30% and 60% reduction in maximum contraction, respectively; thus a fairly high susceptibility of the urethra to blockade by CEC was demonstrated. In the light of these findings, we consider the α_1-adrenoceptor subtype responsible for the contraction of the human prostatic urethra may be primarily the α_{1C}- or $\alpha_{1A/D}$-subtype rather than the classical α_{1A}-subtype. In contrast to our results, Testa *et al.* (1993) reported that the number of specific [^{3}H]-prazosin binding sites in the human prostatic urethral membranes was not affected by pretreatment with CEC for 30 min, and they concluded that the α_{1A}-subtype is the main α_1-adrenoceptor present in the urethra. This discrepancy may be due to the difference in the method of CEC-pretreatment. Also in our preliminary experiments, a single pretreatment with CEC up to 10 μM for 10–30 min hardly affected the contractile responses in both the urethra and artery.

It is clear from this study that it is at present difficult to identify definitively functional α_1-adrenoceptors with the materials available. But we have confirmed that the α_1-adrenoceptors in the human prostatic urethra are apparently different from those in the human peripheral artery, and our findings have important clinical implications for the possibility that an α_1-adrenoceptor antagonist with low affinity for the α_{1B}-subtype may attain a therapeutic response to bladder outlet obstruction with fewer side effects. To determine the exact adrenoceptor subtypes in the human urethra and artery, application of molecular biological techniques to the human tissues are essential.

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