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Investigation of the effects of some alkaloidal α_1-adrenoceptor antagonists on human hyperplastic prostate

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Abstract

The effects of *N*-allylsecoboldine, (−)-discretamine, (±)-govadine and [(±)-2,3,10,11-tetrahydroxytetrahydroproto-berberine HBr] ((±)-THP) on contractile responses were investigated in human hyperplastic prostate. They all inhibited, concentration dependently, the tension responses to phenylephrine and electrical field stimulation, and the pA_2 and pIC_{50} values were calculated. The relative potencies of these four agents with reference to prazosin were obtained. The results showed that *N*-allylsecoboldine exhibited greater potency (4.1-fold), whereas (−)-discretamine, (±)-govadine and (±)-THP had similar potencies, against contractions elicited by electrical field stimulation and against contractions elicited by phenylephrine in human hyperplastic prostate. In addition, the potency ratios of *N*-allylsecoboldine, (−)-discretamine, (±)-govadine and (±)-THP against phenylephrine-induced contractions in rat vas deferens/spleen were 7.78, 0.89, 0.57, and 0.96, respectively. In the presence of prazosin (0.3 μM) to block α_1-adrenoceptor-mediated responses, nifedipine (10 μM), but not the above four agents, significantly blocked KCl (60 mM)-induced tension responses in human hyperplastic prostate. It is suggested that *N*-allylsecoboldine exhibits greater potency against nerve-mediated contraction than against phenylephrine-induced contraction in human hyperplastic prostate and that this antagonistic effect is due mainly to its high affinity for the α_{1A}-adrenoceptor subtype.

Keywords: α_1-Adrenoceptor antagonist; α_1-Adrenoceptor subtype; Electrical field stimulation; Hyperplastic prostate; Human

1. Introduction

Benign prostatic hyperplasia, a progressive enlargement of the prostate, is a well-recognized age-related phenomenon among aging men, leading to outflow obstruction and acute retention of urine. The contractile properties of human prostate adenoma are mediated primarily by α_1-adrenoceptors (Hieble et al., 1985; Kitada and Kumazawa, 1987; Marshall et al., 1996; Langer, 1998). Additionally, endogenous adrenergic stimulation plays an important role in human prostate since the tone of prostatic smooth muscle regulated by the autonomic nervous system is thought to be the 'dynamic' component of bladder outlet obstruction due to benign prostatic hyperplasia (Caine, 1986). Furthermore, a rather dense network of adrenergic nerve fibers has been found within the smooth muscle layer of the prostatic glandular stroma (Vaalasti and Hervonen, 1980). Therefore, one of the major medical treatments for benign prostatic hyperplasia is targeted toward reducing bladder outlet obstruction by α-adrenoceptor blockade to relax the smooth muscle tone of the prostate (Wilde and McTavish, 1996; Andersson et al., 1997).

Recently, selective α_{1A}-adrenoceptor antagonists have been developed to optimize the therapeutic effectiveness of α-adrenoceptor blockade in the prostate, as there is accumulating evidence suggesting that α_{1A}-adrenoceptors are the predominant α_1-adrenoceptor subtypes in the prostate (Guh et al., 1995; Beduschi et al., 1998). Moreover, the use of an α_{1A}-adrenoceptor antagonist in the management of benign prostatic hyperplasia could reduce the side effects associated with α-adrenoceptor blockade in other areas of the body, such as the vascular system (Lee and Lee, 1997; Lepor, 1998). Accordingly, the development of selective α_{1A}-adrenoceptor antagonists is now an important issue in the management of benign prostatic hyperplasia.

Recently, in a large scale screening test, we found that *N*-allylsecoboldine, (−)-discretamine, (±)-govadine and

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[(±)-2,3,10,11-tetrahydroxytetrahydroproto-berberine HBr] ((±)-THP) (Ko et al., 1994, 1996; Vargas and Gorman, 1995) all have antagonistic effects at α_1-adrenoceptors, although they are less potent than prazosin. This study seeks to evaluate the effects of these four agents on muscle contractions in response to phenylephrine and electrical field stimulation in human hyperplastic prostate, in order to elucidate their action mechanisms and to establish a study model for the development of selective α_{1A}-adrenoceptor antagonist in the prostate.

2. Materials and methods

2.1. Human prostatic tissues

Human hyperplastic prostates were obtained at operations from symptomatic BPH patients, aged 52–81 years, by transurethral resection of the prostate or open prostatectomy. All these patients were diagnosed to have benign prostatic hyperplasia by the combination of prostatism symptoms, digital rectal examination, transrectal ultrasonography, histopathology of the prostate, and urodynamic studies (including uroflowmetry, cystometry, and urethral pressure profile). The protocol of this study complies with the Declarations of Helsinki and Tokyo for humans.

Immediately after removal, the specimens were cut into strips (3×15 mm^2) and mounted in a thermostatically controlled organ bath (37°C) containing Krebs solution (5 ml) of the following composition (mM, pH 7.4): NaCl 118.2, KCl 4.7, $CaCl_2$ 1.9, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0 and glucose 11.7. The tissue bath solution was bubbled with a mixture of CO_2 (5%) and O_2 (95%). Tissues were equilibrated for 90 min with four changes of solution and maintained under an optimal tension of 1 g before specific experimental protocols were initiated. Contractions were recorded isometrically via a force-displacement transducer (Grass, model 7DAG) connected to a Grass polygraph. Cumulative concentration–response curves for phenylephrine-induced contractions were determined in the absence or presence of the indicated antagonists. Tissues were allowed to equilibrate with each antag-

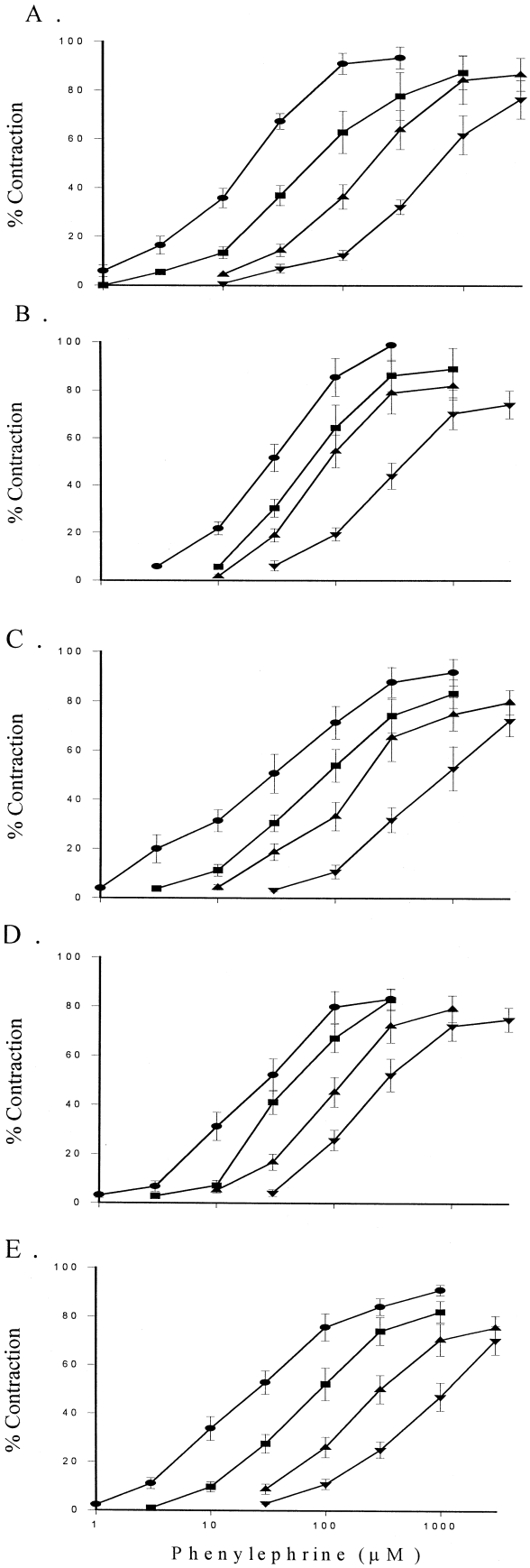

Fig. 1. Effects of prazosin, *N*-allylsecoboldine, (−)-discretamine, (±)-govadine, and (±)-THP on phenylephrine-induced contractions of human hyperplastic prostate. Tissues were pre-treated with 0.1% dimethylsulfoxide (●), or with: (A) prazosin (10^{-9} M, ■; 3×10^{-9} M, ▲; 10^{-8} M, ▼), (B) (−)-discretamine (3×10^{-7} M, ■; 10^{-6} M, ▲; 3×10^{-6} M, ▼), (C) *N*-allylsecoboldine (3×10^{-6} M, ■; 10^{-5} M, ▲; 3×10^{-5} M, ▼), (D) (±)-govadine (10^{-6} M, ■; 3×10^{-6} M, ▲; 10^{-5} M, ▼), or (E) (±)-THP (3×10^{-6} M, ■; 10^{-5} M, ▲; 3×10^{-5} M, ▼), and then concentration–response curves for phenylephrine were determined. Each point is the means ± S.E.M. of six experiments.

onist for 20 min before each cumulative concentration–response was measured. However, different antagonist incubation times (15–30 min) have been examined before 20 min was chosen for the present experiments. Four reproducible concentration–response curves were made in this study. For electrical field stimulation, tissues were mounted vertically between two parallel platinum ring electrodes in organ baths. Intramural nerve stimulation was performed by means of an electronic stimulator (Grass model S88) delivering square pulses of 0.3 ms duration at supramaximum voltage (80 V over the electrodes) and 20 Hz for 5 s. The almost complete inhibition of the response by tetrodotoxin (0.1 μM) confirmed that the contractions induced by transmural stimulation were nerve-mediated.

The contractile effect of calcium was measured in a high K^+ (60 mM) solution without Ca^{2+}. The high K^+ solution was prepared by substituting an equimolar amount of KCl for NaCl. The tissues were incubated in KCl (60 mM)/Ca^{2+}-free medium in the presence of prazosin (0.3 μM) to block α_1-adrenoceptor-mediated responses, and then incubated in the absence or presence of the indicated agents or nifedipine (10 μM) at 37°C for 20 min. Cumulative concentrations of Ca^{2+} (0.1 to 3 mM) were then used to evoke contraction.

2.2. Rat vas deferens

The protocol of this study complies with the European Community guidelines for animals. Both vas deferens were removed from Male Wistar rats (250–300 g). The tissues were mounted and equilibrated under the same conditions as prostatic strips for 90 min under a resting tension of 0.5 g. After the equilibration period, rat vas deferens were contracted twice with 10 μM phenylephrine and then washed and equilibrated for a further 30 min. Non-cumulative concentration–response curves for phenylephrine-induced contractions were determined in the absence or presence of the indicated antagonists and four reproducible concentration–response curves were made.

2.3. Rat spleens

Rat spleens were hemisected and equilibrated under the same conditions as prostatic strips at a resting tension of 1 g and a concentration–response curve for phenylephrine was obtained in a cumulative manner in the absence or presence of the indicated antagonists. Four reproducible concentration–response curves were made.

2.4. Materials

N-allylsecoboldine (the gift from Dr. S.S. Lee, School of Pharmacy, College of Medicine, National Taiwan Uni-

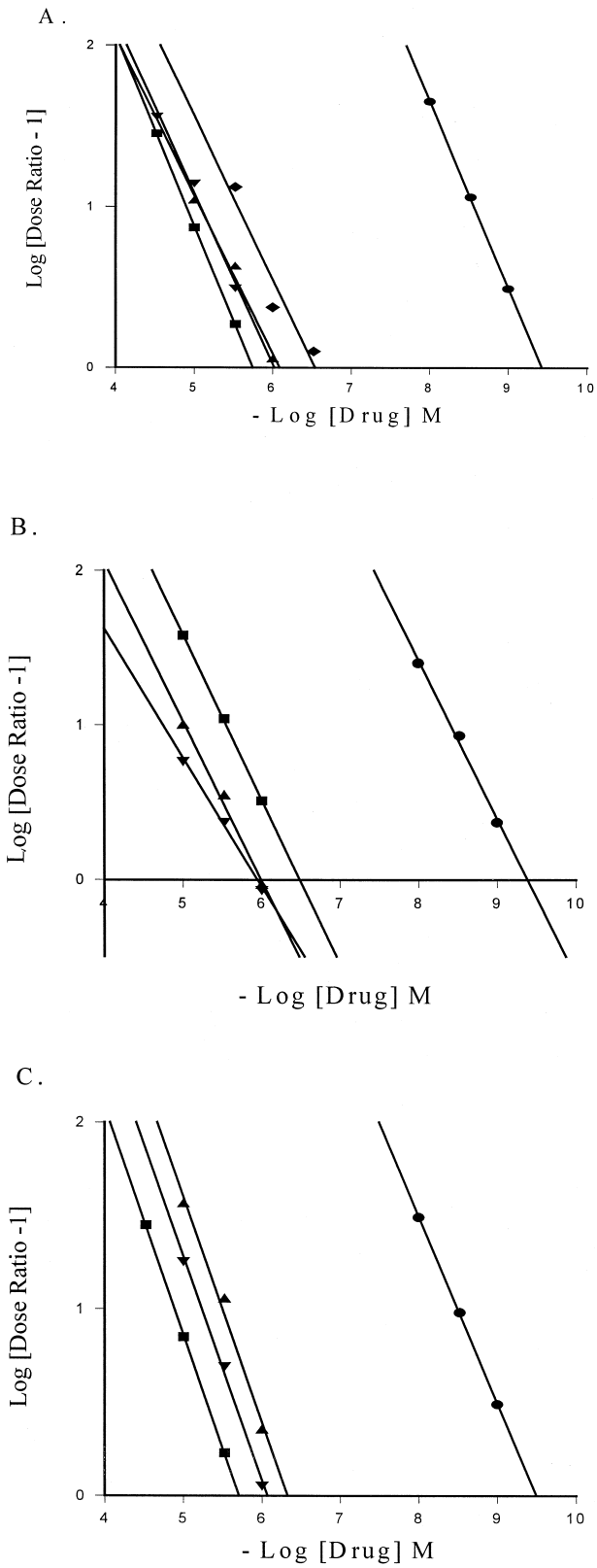

Fig. 2. Schild plots of the inhibition by prazosin (●), (−)-discretamine (♦), *N*-allylsecoboldine (■), (±)-govadine (▲), or (±)-THP (▼) of the phenylephrine-induced muscle contraction in human hyperplastic prostate (A), rat vas deferens (B), and spleens (C). The Schild plots were constructed from Figs. 1, 4 and 5, respectively.

versity) was prepared from boldine, (−)-discretamine (the gift from Dr. Y.C. Wu, Graduate Institute of Natural Products, Kaohsiung Medical College) was isolated from the plant *Fissistigma glaucescens* (Lu et al., 1985), and (±)-govadine and (±)-THP [(±)-2,3,10,11-tetrahydroxy-tetrahydroproto-berberine HBr] (the gift from Dr. C.M. Chen, School of Pharmacy, Taipei Medical College) are two tetrahydroprotoberberine alkaloids; their purity (> 99%) was confirmed by mass spectrometry, nuclear magnetic resonance (NMR), infrared (IR) and proton spectroscopy. Prazosin HCl, nifedipine, phenylephrine HCl and boldine were obtained from Sigma (St. Louis, MO, USA). Drugs were dissolved in dimethylsulfoxide and the final concentration of dimethylsulfoxide in the bathing solution did not exceed 0.1% and had no effect on this study.

2.5. Data analysis

Agonist-elicited concentration–response curves in the presence of the indicated concentrations of each antagonist were related to the control concentration–response curves, of which the maximal response was taken as 100%. The concentration of agonist necessary to give a half-maximal response in the presence of each concentration of antagonist was divided by the concentration giving a half-maximal response in the absence of antagonist, to determine the dose ratio (DR). Data were plotted by the method of Arunlakshana and Schild (1959) as the −log (antagonist concentration) (M) vs. the log (DR — 1). When DR was 2, the −log (antagonist concentration) was taken as the pA_2 value from the Schild plot (Mackay, 1978).

The experimental results are expressed as means ± S.E.M. and accompanied by the number of observations. Statistical significance was assessed by Student's t-test and a P-value less than 0.05 was considered significant.

3. Results

3.1. Effects of various α_1-adrenoceptor antagonists on phenylephrine-induced contractions of human hyperplastic prostate

Phenylephrine induced a contractile response in human hyperplastic prostate in a concentration-dependent manner; the maximum contraction in response to phenylephrine was 0.91 ± 0.04 g ($n = 30$). Prazosin, *N*-allylsecoboldine, (−)-discretamine, (±)-govadine and (±)-THP all caused concentration-dependent parallel rightward shifts of the concentration–response curve of phenylephrine in human hyperplastic prostate (Fig. 1). The slopes of these regressions did not differ significantly from negative unity (Fig. 2A). The pA_2 values were calculated and the relative potencies of *N*-allylsecoboldine, (−)-discretamine, (±)-govadine and (±)-THP with reference to prazosin were examined (Table 1).

3.2. Effects of various α_1-adrenoceptor antagonists on electrical field stimulation-induced contraction of human hyperplastic prostate

Electrical field stimulation (20 Hz, 0.3 ms duration, 80 V) induced a significant contractile response (0.52 ± 0.04 g, $n = 18$) in human hyperplastic prostate. This response was concentration dependently blocked by prazosin (0.3 to 10 nM), *N*-allylsecoboldine (0.3 to 10 μM), (−)-discretamine (0.1 to 10 μM), (±)-govadine (0.3 to 30 μM), and (±)-THP (0.3 to 30 μM) (Fig. 3). The pIC_{50} values of these α_1-adrenoceptor antagonists were calculated and the relative potencies of *N*-allylsecoboldine, (−)-discretamine, (±)-govadine and (±)-THP with reference to prazosin were also determined (Table 1).

From the above results, the potency ratios of *N*-allylsecoboldine, (−)-discretamine, (±)-govadine and (±)-THP against electrical field stimulation/phenylephrine-induced contractions were 4.1, 1.0, 1.1, and 1.1, respectively.

3.3. Effects of various α_1-adrenoceptor antagonists on phenylephrine-induced contractions in rat vas deferens and spleens

Prazosin, *N*-allylsecoboldine, (±)-govadine and (±)-THP all inhibited the phenylephrine-induced contractions in rat vas deferens (Fig. 4) and spleens (Fig. 5). Schild plots were constructed from the effects of the above

Table 1
Potencies of various α_1-adrenoceptor antagonists against contractions elicited by phenylephrine and electrical field stimulation (0.2 ms duration, 80 V and 20 Hz) in human hyperplastic prostate. Values are expressed as means ± S.E.M., n = number of individual experiments

Drugs	Phenylephrine			Electrical field stimulation		
	pA_2	Relative potency	n	pIC_{50}	Relative potency	n
Prazosin	9.44 ± 0.06	1	6	8.87 ± 0.06	1	6
N-allylsecoboldine	5.74 ± 0.11	2.00×10^{-4}	6	5.78 ± 0.07	8.13×10^{-4}	3
(−)-Discretamine	6.57 ± 0.07	1.35×10^{-3}	6	5.99 ± 0.02	1.32×10^{-3}	3
(±)-Govadine	6.07 ± 0.07	4.27×10^{-4}	6	5.53 ± 0.10	4.57×10^{-4}	3
(±)-THP	6.02 ± 0.05	3.80×10^{-4}	6	5.50 ± 0.03	4.27×10^{-4}	3

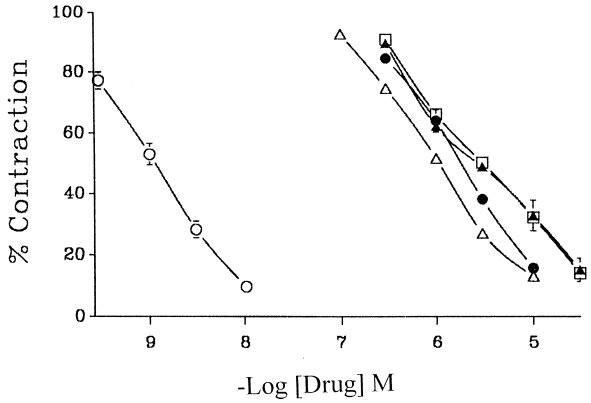

Fig. 3. Effects of prazosin (○), *N*-allylsecoboldine (●), (−)-discretamine (△), (±)-govadine (▲) and (±)-THP (□) on contractile responses to electrical field stimulation of human hyperplastic prostate. Tissues were pre-treated with the indicated drug for 15 min and then a contractile response was elicited by electrical field stimulation (0.2 ms duration, 80 V and 20 Hz). Each point is the means ± S.E.M. of three to six experiments.

α_1-adrenoceptor antagonists at various concentrations (Fig. 2B and C). The pA_2 values were calculated and the relative potencies of *N*-allylsecoboldine, (±)-govadine and (±)-THP with reference to prazosin were also determined (Table 2). Additionally, in our previous study, the relative potencies of (−)-discretamine with reference to prazosin were 8.71×10^{-4} and 9.77×10^{-4}, respectively (Ko et al., 1994).

3.4. Effects of various α_1-adrenoceptor antagonists and nifedipine on high K^+-induced Ca^{2+}-dependent contraction in human hyperplastic prostate

In the presence of prazosin (0.3 μM) to block α_1-adrenoceptor responses, the cumulative addition of Ca^{2+} (0.1 to 3 mM) caused a stepwise increase of muscle tension in human hyperplastic prostate pre-depolarized with 60 mM K^+ in Ca^{2+}-free medium. The maximal tension attained at 3 mM Ca^{2+} was 0.57 ± 0.03 g and was taken to be 100%. *N*-allylsecoboldine (10 μM), (−)-discretamine (10 μM), (±)-govadine (30 μM) and (±)-THP (30 μM) all had little effect on this Ca^{2+}-induced muscle contraction under the above conditions (Fig. 6); however, nifedipine (10 μM) almost completely abolished this Ca^{2+}-induced contraction in human hyperplastic prostate (Fig. 6).

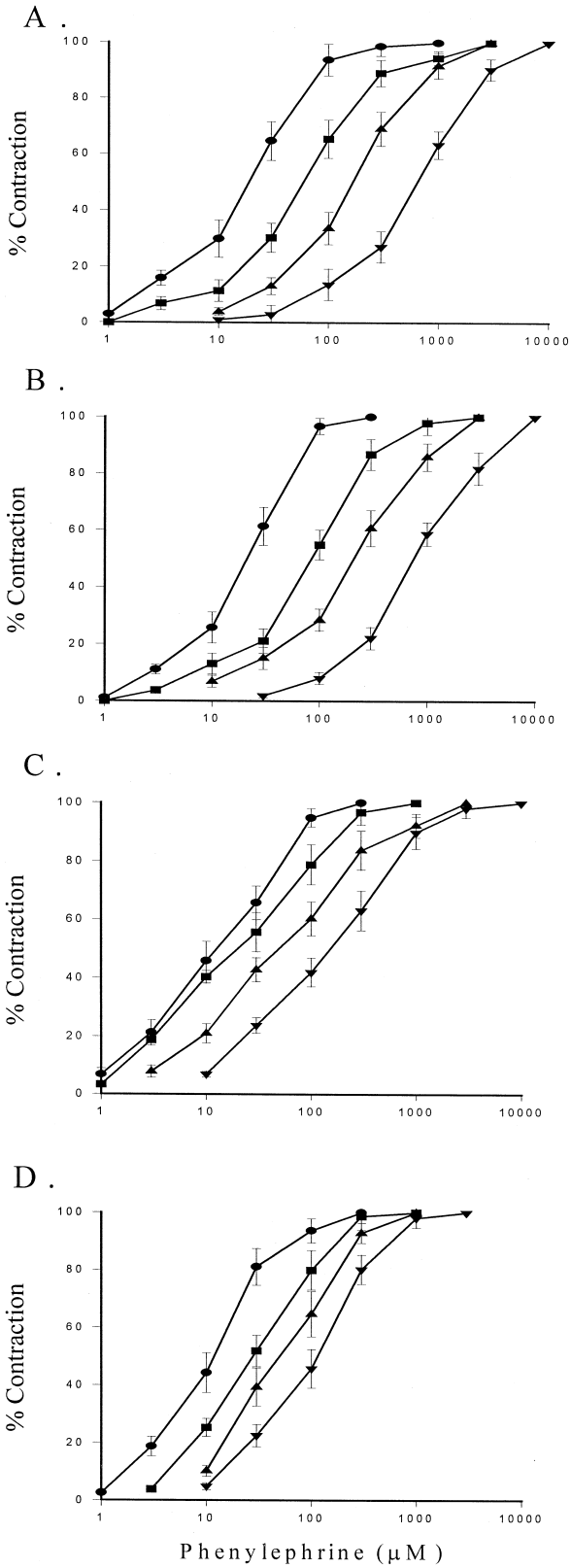

Fig. 4. Effects of prazosin, *N*-allylsecoboldine, (±)-govadine, and (±)-THP on phenylephrine-induced contractions of rat vas deferens. Tissues were pre-treated with 0.1% dimethylsulfoxide (●), or with: (A) prazosin (10^{-9} M, ■; 3×10^{-9} M, ▲; 10^{-8} M, ▼), (B) *N*-allylsecoboldine (10^{-6} M, ■; 3×10^{-6} M, ▲; 10^{-5} M, ▼), (C) (±)-govadine (10^{-6} M, ■; 3×10^{-6} M, ▲; 10^{-5} M, ▼), or (D) (±)-THP (10^{-6} M, ■; 3×10^{-6} M, ▲; 10^{-5} M, ▼), and then concentration–response curves for phenylephrine were determined. Each point is the means ± S.E.M. of six experiments.

4. Discussion

N-allylsecoboldine, (−)-discretamine, (±)-govadine and (±)-THP were shown to exhibit an antagonistic effect at α_1-adrenoceptors in rat thoracic aorta (Ko et al., 1994, 1996; Vargas and Gorman, 1995). However, their effects on endogenous adrenergic stimulation have not been documented in human hyperplastic prostate. This study examined the effects of these four agents on contractile responses elicited by phenylephrine and electrical field stimulation in human hyperplastic prostate and the results showed that all of these four agents were α_1-adrenoceptor antagonists in this tissue. However, it was difficult to obtain pA_2 values for these α_1-adrenoceptor antagonists against contractions in response to electrical field stimulation; the $p\mathrm{IC}_{50}$ values were thus calculated and the relative potencies with reference to prazosin were determined, since prazosin exhibits no selectivity for α_1-adrenoceptor subtypes (Hanft and Gross, 1989). The results of this study showed that *N*-allylsecoboldine had greater potency (4.1-fold) against contractions elicited by electrical field stimulation than against those elicited by phenylephrine. However, (−)-discretamine, (±)-govadine and (±)-THP exhibited similar potencies against contractions elicited by the above two stimuli. In our previous study (Teng et al., 1994; Guh et al., 1995), we suggested that the major subtypes mediating contractions in response to neuronally released noradrenaline in human prostate were the α_{1A}-adrenoceptor subtypes, and that contractions elicited by phenylephrine were mediated by both α_{1A}- and α_{1B}-adrenoceptor subtypes. It is likely that the greater potency against nerve-mediated contractions in human hyperplastic prostate is due mainly to the high affinity of *N*-allylsecoboldine for the α_{1A}-adrenoceptor subtypes. To investigate this hypothesis, two working models were used in this study. It has been suggested that contractions in response to exogenously applied noradrenaline are mediated predominantly by α_{1A}-adrenoceptor subtypes in rat vas deferens (Han et al., 1987; Gross et al., 1988; Hanft and Gross, 1989), and by α_{1B}-adrenoceptor subtypes in rat spleens (Han et al., 1987; Minneman, 1988). In this study, the contractions in rat vas deferens and spleens elicited by phenylephrine were used as models for α_{1A}- and α_{1B}-adrenoceptor subtypes, respectively. Table 2 shows that *N*-allylsecoboldine exhibited greater potency (7.8-fold) against phenylephrine-induced contractions in rat vas deferens than in rat spleens; however, (−)-discretamine, (±)-govadine and (±)-THP all had similar potencies in

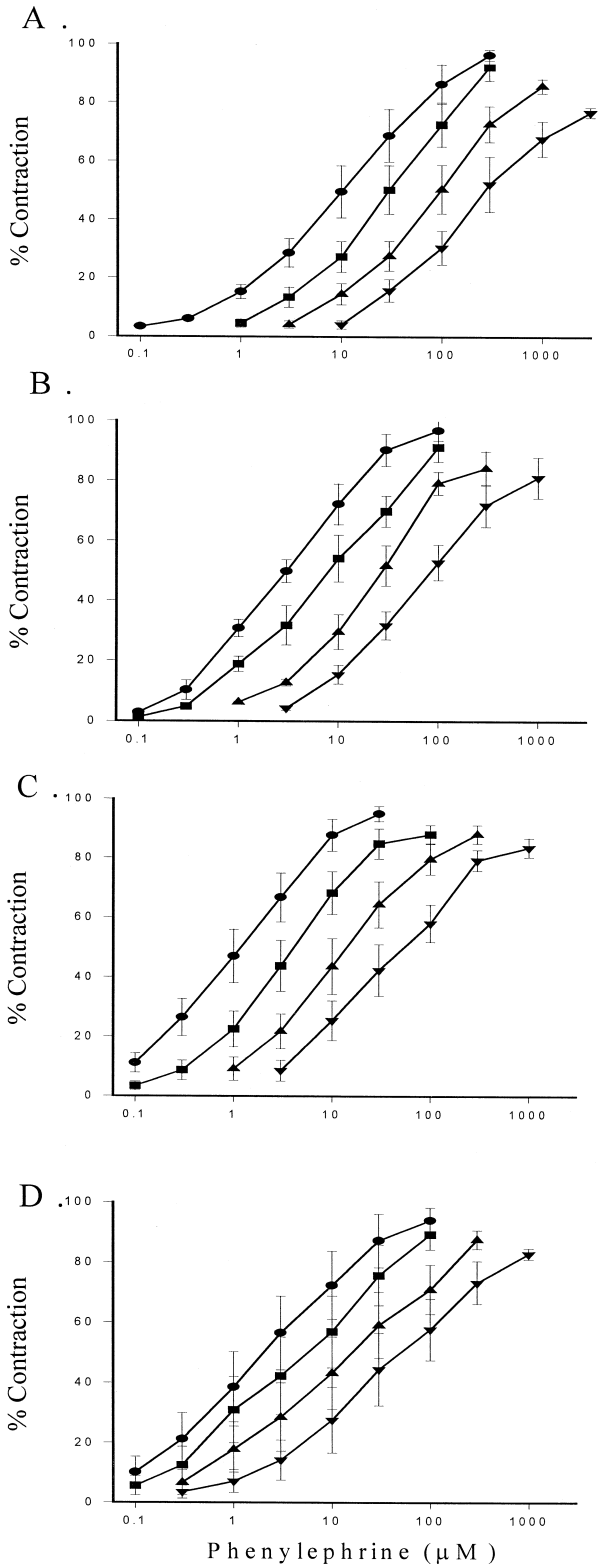

Fig. 5. Effects of prazosin, *N*-allylsecoboldine, (±)-govadine, and (±)-THP on phenylephrine-induced contractions of rat spleens. Tissues were pre-treated with 0.1% dimethylsulfoxide (●), or with: (A) prazosin (10^{-9} M, ■; 3×10^{-9} M, ▲; 10^{-8} M, ▼), (B) *N*-allylsecoboldine (3×10^{-6} M, ■; 10^{-5} M, ▲; 3×10^{-5} M, ▼), (C) (±)-govadine (10^{-6} M, ■; 3×10^{-6} M, ▲; 10^{-5} M, ▼), or (D) (±)-THP (10^{-6} M, ■; 3×10^{-6} M, ▲; 10^{-5} M, ▼), and then concentration–response curves for phenylephrine were determined. Each point is the means ± S.E.M. of six experiments.

Table 2
Effects of various α_1-adrenoceptor antagonists on tension responses to phenylephrine in rat vas deferens and spleen. Values are expressed as means ± S.E.M. of six individual experiments

Drugs	Vas deferens (α_{1A})		Spleen (α_{1B})	
	pA_2	Relative potency	pA_2	Relative potency
Prazosin	9.38 ± 0.08	1	9.49 ± 0.11	1
N-allylsecoboldine	6.48 ± 0.09	1.26×10^{-3}	5.70 ± 0.05	1.62×10^{-4}
(±)-Govadine	5.99 ± 0.11	4.07×10^{-4}	6.34 ± 0.09	7.08×10^{-4}
(±)-THP	5.94 ± 0.06	3.63×10^{-4}	6.07 ± 0.09	3.80×10^{-4}

these two preparations (0.89-, 0.57-, and 0.96-fold, respectively), suggesting that *N*-allylsecoboldine had higher affinity for the α_{1A}-adrenoceptor subtype than for the α_{1B}-adrenoceptor subtype. However, the inhibition by these alkaloids was not proven to be competitive, even though the alkaloids shifted the phenylephrine concentration–contraction curve in parallel to higher concentrations, and the slope of the Schild plot was unity.

The α_{1A}-adrenoceptor subtype requires the influx of extracellular Ca^{2+} through dihydropyridine-sensitive channels to cause smooth muscle contraction (Minneman, 1988). In the presence of prazosin (0.3 μM) to block the α_1-adrenoceptor-mediated response, *N*-allylsecoboldine, (−)-discretamine, (±)-govadine and (±)-THP all had no effect on high K^+ (60 mM)-depolarized Ca^{2+}-induced contractions in human hyperplastic prostate. These results suggested that the above four agents had no direct effect on the voltage-operated calcium channels in this tissue.

In conclusion, these results suggest that *N*-allylsecoboldine has a greater antagonistic effect on nerve-mediated than on phenylephrine-mediated contractions in human hyperplastic prostate and this is due mainly to its high affinity for the α_{1A}-adrenoceptor subtype.

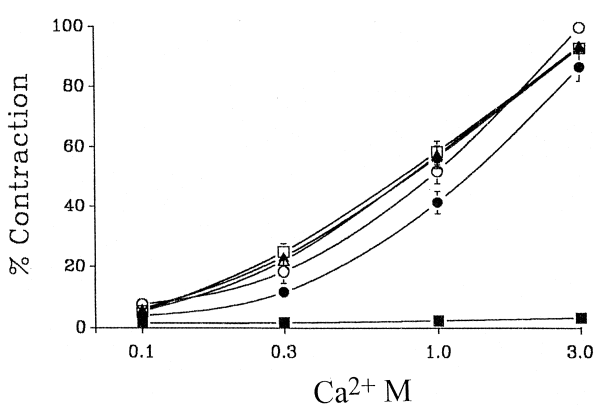

Fig. 6. Effects of various α_1-adrenoceptor antagonists and nifedipine on the Ca^{2+}-dependent contraction of human hyperplastic prostate induced by KCl. In a Ca^{2+}-free medium containing KCl (60 mM) and 0.3 μM prazosin, tissues were pre-incubated with 0.1% dimethylsulfoxide (○), *N*-allylsecoboldine (10 μM, ●), (−)-discretamine (10 μM, △), (±)-govadine (30 μM, ▲), (±)-THP (30 μM, □) or nifedipine (10 μM, ■) for 15 min, and then cumulative concentrations of Ca^{2+} (0.1 to 3 mM) were used to evoke contraction. Each point is the means ± S.E.M. of six experiments.

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