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Characterization of some novel α_1-adrenoceptor antagonists in human hyperplastic prostate

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Abstract

We synthesized some quinazoline-based compounds, such as FH-71 (ethyl 4-(3-(4-(2-methoxyphenyl)piperazinyl)aminoquinazolin-2-carboxylate), EW-65 (4-(3-(4-(2-methoxyphenyl)piperazinyl)propyl)aminoquinazolin-2-carboxamide) and EW-154 (2-(4-(4-(2-methoxyphenyl)piperazinyl)butyl)amino-4-cyclohexylamino-quinazolin), and then characterized their pharmacological properties in several tissues. All of these compounds produced potent inhibition of phenylephrine but not high K^+ or U46619 (11α,9α-epoxymethano-15*S*-hydroxy-prosta-5*Z*,13*E*-dienoic acid)-induced contractions in rat aorta, suggesting α_1-adrenoceptor antagonist properties. With rat vasa deferentia and spleens as the functional α_{1A}- and α_{1B}-adrenoceptor models, respectively, FH-71 exhibited greater antagonistic potency in rat vas deferens, EW-154 in rat spleen, and EW-65 had similar effects in both tissues. The potency ratios of terazosin, FH-71, EW-65 and EW-154 against phenylephrine-induced contractions in rat vas deferens/spleen were 1, 19.04, 0.39 and 0.09, respectively. The results suggest that FH-71 is a selective α_{1A}-adrenoceptor antagonist, whereas EW-154 exhibits more antagonistic selectivity against α_{1B}-adrenoceptors. FH-71 also showed a greater potency than EW-65 and EW-154 against phenylephrine-induced contraction in human hyperplastic prostate. The pA_2 values were 8.34, 7.44 and 7.05, respectively. Furthermore, FH-71 and EW-65 were not cytotoxic whereas EW-154 (all in 10 μM) had a massive toxic effect (more than 80%) in human prostatic smooth muscle cells. These data show FH-71 to be a potent and selective α_{1A}-adrenoceptor antagonist with activity in human hyperplastic prostate.

Keywords: α_1-Adrenoceptor antagonist; α_1-Adrenoceptor subtype; Hyperplastic prostate, human

1. Introduction

Benign prostatic hyperplasia is common among men older than 50, and its prevalence increases with age. Its symptoms interfere with normal daily activities, reduce the sense of well-being and can also be progressive, with a risk of urinary retention, urinary tract infection, bladder calculi and even renal failure (Garraway et al., 1991). Endogenous adrenergic stimulation plays an important "dynamic" role in the pathophysiology of bladder outlet obstruction in humans since the tone of prostatic smooth muscle is significantly increased by α-adrenergic agonists and decreased by α-adrenoceptor antagonists (Caine, 1986). Additionally, a dense network of adrenergic nerve fibers has been found within the smooth muscles of the prostatic stromal tissues (Vaalasti and Hervonen, 1980). The contractile properties of human prostate adenoma are mediated primarily by α_1-adrenoceptors (Hieble et al., 1985; Langer, 1998). Therefore, one of the major medical treatments for benign prostatic hyperplasia is targeted toward reducing bladder outlet obstruction by blocking α-adrenoceptors to relax the tone of prostatic smooth muscles (Andersson et al., 1997; Narayan et al., 1998). As there is more evidence that α_{1A}-adrenoceptors are the predominant α_1-adrenoceptor subtypes in the prostate (Guh et al., 1995; Beduschi et al., 1998), selective α_{1A}-adrenoceptor antagonists have been developed to optimize the therapeutic effectiveness of relieving bladder outlet obstruction in benign prostatic hyperplasia and to reduce the adverse effects (e.g. postural hypotension, dizziness, aesthenia) associated with systemic α-adrenoceptor blockade (Lee and Lee, 1997; Narayan et al., 1998). Accordingly, we focused our research on the development of novel and more selective α_{1A}-adrenoceptor antagonists.

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Recently, we synthesized several quinazoline-based compounds. After the pharmacological characterization, we found that most of these compounds showed α_1-adrenoceptor antagonistic properties. In the present work, we examined their α_1-adrenoceptor blocking potency and selectivity for α_1-adrenoceptor subtypes. Furthermore, the therapeutic potential in the treatment of benign prostatic hyperplasia was also determined in human hyperplastic prostates.

2. Materials and methods

2.1. Human prostatic tissues

Human hyperplastic prostates were obtained at operation from patients with symptomatic benign prostatic hyperplasia, aged 53–79 years, by open prostatectomy or transurethral resection of the prostate. All these patients had a history of lower urinary tract symptoms (international prostatic symptom scores $\geqq$13) and were diagnosed to have benign prostatic hyperplasia by the combination of rectal digital examination, transrectal sonography of prostate, uroflowmetry and histopathology of the prostatic specimens. The protocol of this study complied with the Declarations of Helsinki and Tokyo for humans. The specimens were used for in vitro isometric tension experiments.

Immediately after removal, the prostatic tissues were placed in gassed Krebs solution. The specimens were cut into strips (3×15 mm) and mounted in a thermostatically controlled organ bath (37 °C) containing 5 ml of Krebs solution, which was continuously bubbled with a mixture of O_2 (95%) plus CO_2 (5%). Tissues were equilibrated for 90 min with five changes of solution and maintained under a resting 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. Tissues were allowed to equilibrate with each antagonist for 20 min before each cumulative concentration–response was measured. Four reproducible concentration–response curves were made for a given antagonist.

2.2. Rat aortae

The protocol of this study complied with the European Community guidelines for animals. Male Wistar rats (250–300 g) were killed and then the thoracic aorta was isolated and excess fat and connective tissues were removed. The vessels were denuded and then cut into rings of about 5 mm in length, mounted and equilibrated under the same conditions as human hyperplastic prostates for 90 min under a resting tension of 1 g. Similar protocols as for human prostates were carried out to evaluate the potency of the indicated inhibitors in rat aorta.

2.3. Rat vas deferens

Both vasa deferentia were removed from male Wistar rats, and 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 vasa deferentia were contracted twice with 10 μM phenylephrine and then washed and equilibrated for a further 30 min. Noncumulative concentration–response curves for phenylephrine-induced contractions were determined in the absence or presence of the indicated concentrations of antagonists. Four reproducible concentration–response curves were made for a given antagonist.

2.4. 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 for a given antagonist.

2.5. Human prostatic smooth muscle cells

Prostatic tissue explants were handled and cultured cells were obtained as previously described (Guh et al., 1998). Isolated human prostatic cells were identified by the following criteria: the cultured cells exhibited positive immunofluorescence staining for vimentin and smooth muscle α-actin, but showed negative immunostaining for epithelial cytokeratins; the culture morphology was characterized by the formation of nodules of cells, that is ‘hills and valleys’.

2.6. Cytotoxic assays

The cytotoxic effect of the mentioned agents was evaluated with the MTT assay. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was dissolved in PBS at a concentration of 5 mg/ml and Millipore filtered. From the stock solution, 10 μl per 100 μl of medium was added to each well, and plates were gently shaken and incubated at 37 °C for 4 h. Treatment of living cells with MTT produces a dark blue formazan product, whereas no such staining is observed in dead cells. After loading with MTT, the medium was replaced with 100 μl acidified β-isopropanol and was left for 20–30 min at room temperature for color development, and then the 96-well plate was read with an enzyme-linked immunosorbent assay reader (570 nm) to obtain the absorbance density values.

Necrotic cell death was measured by the release of lactate dehydrogenase into the culture medium, which indicates the loss of membrane integrity and cell necrosis. Lactate dehydrogenase activity was measured using a commercial assay kit (Cytotoxicity assay kit, Promega, Madison, WI, USA), where the released lactate dehydrogenase in culture super-

natants is measured with a coupled enzymatic assay, which results in the conversion of a tetrazolium salt into a red formazan product. The necrotic percentage is expressed as (sample value/maximal release)×100%, where the maximal release was obtained following the treatment of control cells with 0.5% Triton X-100 for 10 min at room temperature.

2.7. Materials

The composition of the Krebs solution (pH 7.4) used was (mM): NaCl 118.2, KCl 4.7, $MgSO_4$ 1.2, $CaCl_2$ 1.9, KH_2PO_4 1.2, $NaHCO_3$ 25.0 and glucose 11.7. A series of quinazoline derivatives was designed and synthesized as potential α_{1A}-adrenoceptor antagonists by Dr. Ji-Wang Chern (unpublished results) and FH-71 (ethyl 4-(3-(4-(2-methoxyphenyl) piperazinyl) aminoquinazolin-2-carboxylate), EW-65 (4-(3-(4-(2-methoxyphenyl) piperazinyl) propyl) aminoquinazolin-2-carboxamide) and EW-154 (2-(4-(4-(2-methoxyphenyl)piperazinyl)butyl)amino-4-cyclohexylaminoquinazolin), (Fig. 1) were studied in the present work. The following drugs were used: phenylephrine HCl, terazosin HCl, MTT, U46619 (11α,9α-epoxymethano-15*S*-hydroxy-prosta-5*Z*,13*E*-dienoic acid), testosterone, mouse anti-vimentin, anti-cytokeratin, anti-mouse α-actin, anti-desmin and fluorescein-conjugated goat anti-mouse immunoglobulin (Sigma, St. Louis, MO, USA). RPMI-1640 medium and all other tissue culture reagents (GIBCO, Grand Island, NY). Drugs were dissolved in dimethylsulfoxide. The final concentration of dimethylsulfoxide in the bathing solution and culture medium did not exceed 0.1% and had no effect on the muscle contraction and cell viability.

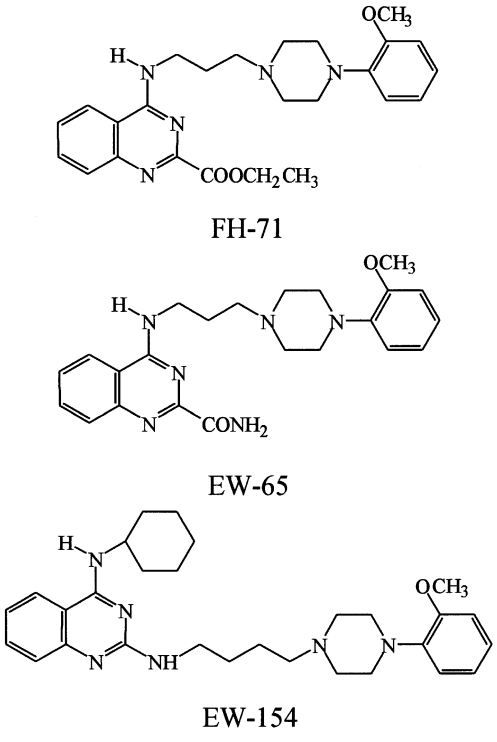

Fig. 1. Chemical structures of FH-71, EW-65, and EW-154.

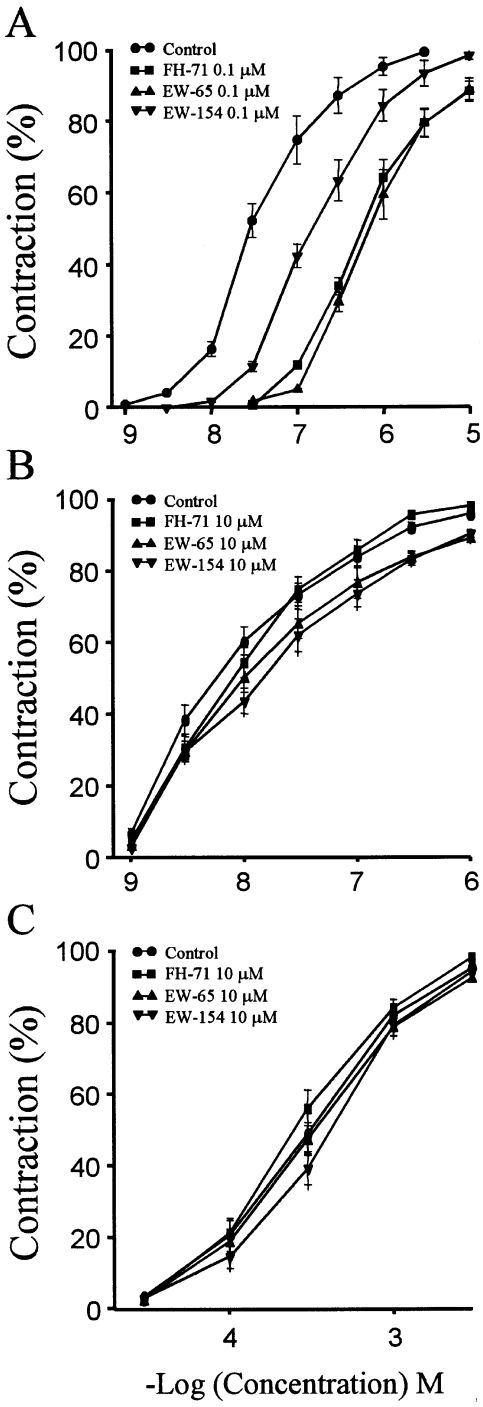

Fig. 2. Effects of FH-71, EW-65 and EW-154 on the contractions in response to phenylephrine, U46619 or high K^+ in rat aorta. Tissues were pre-incubated in the absence (control) or presence of the indicated compound in normal Krebs solution (A and B) or in a Ca^{2+}-free medium containing KCl (60 mM) for 20 min. Then, cumulative concentrations of the agonist were added to evoke muscle contractions. Each point is the mean±S.E.M. of three to five experiments.

2.8. 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 the 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

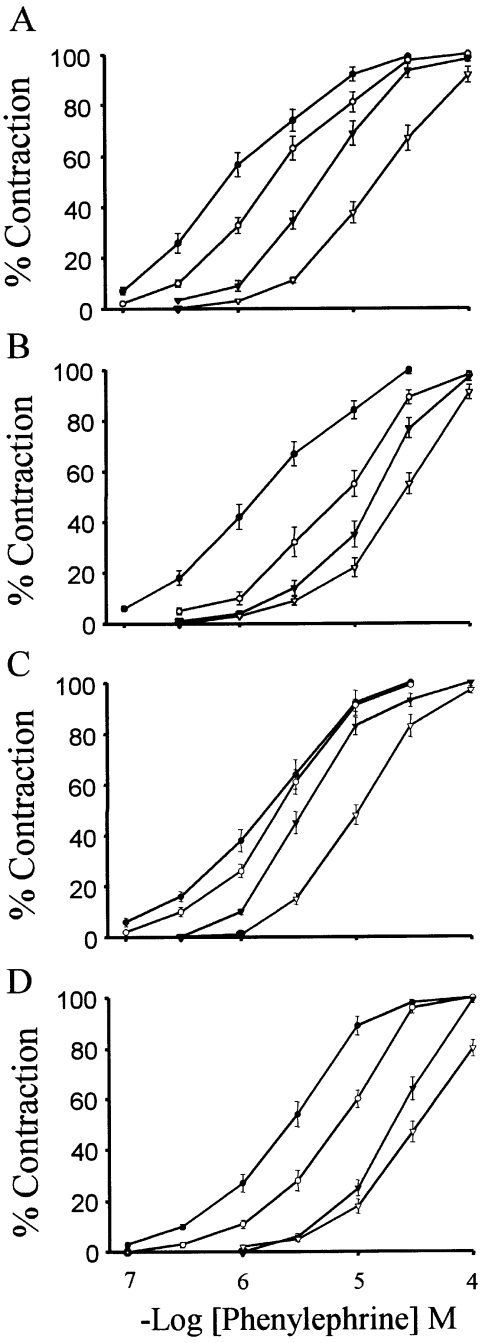

Fig. 3. Effects of FH-71, EW-65, and EW-154 on phenylephrine-induced contractions of rat vas deferens. Tissues were pretreated with 0.1% dimethylsulfoxide (●), or with (A) terazosin (10^{-8} M, ○; 3×10^{-8} M, ▼; 10^{-7} M, ▽), (B) FH-71 (10^{-8} M, ○; 3×10^{-8} M, ▼; 10^{-7} M, ▽), (C) EW-65 (3×10^{-8} M, ○; 10^{-7} M, ▼; 3×10^{-7} M, ▽) or (D) EW-154 (3×10^{-7} M, ○; 10^{-6} M, ▼; 3×10^{-6} M, ▽) for 20 min, and then concentration–response curves for phenylephrine were determined. Each point is the mean±S.E.M. of four experiments.

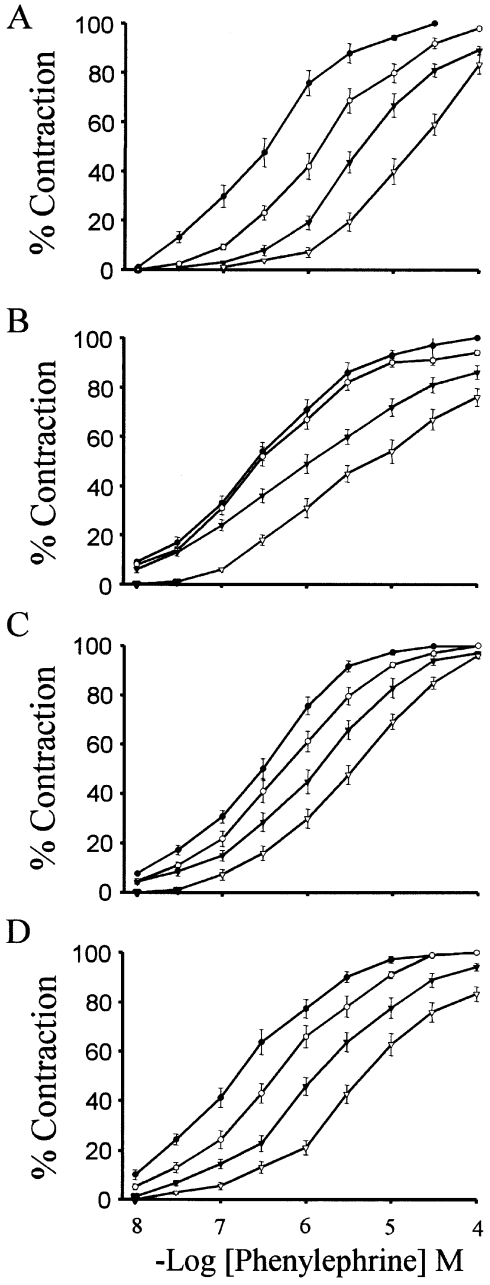

Fig. 4. Effects of FH-71, EW-65, and EW-154 on phenylephrine-induced contractions of rat spleen. Tissues were pretreated with 0.1% dimethylsulfoxide (●), or with (A) terazosin (10^{-8} M, ○; 3×10^{-8} M, ▼; 10^{-7} M, ▽), (B) FH-71 (10^{-8} M, ○; 3×10^{-8} M, ▼; 10^{-7} M, ▽), (C) EW-65 (10^{-8} M, ○; 3×10^{-8} M, ▼; 10^{-7} M, ▽) or (D) EW-154 (10^{-8} M, ○; 3×10^{-8} M, ▼; 10^{-7} M, ▽) for 20 min, and then concentration–response curves for phenylephrine were determined. Each point is the mean±S.E.M. of four experiments.

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. Examination of the selectivity on α1-adrenoceptors

The α_1-adrenoceptor antagonistic properties of FH-71, EW-65 and EW-154 were evaluated against phenylephrine-induced contractions in rat thoracic aorta. As demonstrated in Fig. 2A, at a low concentration (0.1 μM) all of these compounds reversibly shifted the concentration−response curves for phenylephrine, whereas they had little influence on those for U46619 (a thromboxane A_2 receptor agonist) and high K^+ even with a high concentration of 10 μM (Fig. 2B and C), suggesting selectivity on α_1-adrenoceptors. The potency of these compounds against phenylephrine-induced contraction in rat aorta was determined. The results showed that FH-71, EW-65 and EW-154 all caused concentration-dependent parallel rightward shifts of the concentration–response curves for phenylephrine in a competitive manner (data not shown). Schild plots were constructed and the pA_2 values were calculated to be 8.22, 8.37 and 7.16, respectively.

3.2. Determination of α_1-adrenoceptor subtype potency in rat vas deferens and spleen

There are several lines of evidence suggesting that contractions in response to noradrenaline are mediated predominantly by α_{1A}-adrenoceptor subtypes in rat vas deferens, and by α_{1B}-adrenoceptor subtypes in rat spleen (Han et al., 1987; Hanft and Gross, 1989). In the present work, the contractions in rat vas deferens and spleen elicited by phenylephrine were used as models for α_{1A}- and α_{1B}-adrenoceptor subtypes, respectively. The results showed that terazosin, FH-71, EW-65 and EW-154 all caused concentration-dependent parallel rightward shifts of the concentration−response curves for phenylephrine in a competitive manner without diminishing the maximal contraction in rat vas deferens (Fig. 3) and spleen (Fig. 4). Schild plots were constructed from the effects of the above α_1-adrenoceptor antagonists at various concentrations; the pA_2 values were calculated and the relative potencies of FH-71, EW-65 and EW-154 with reference to terazosin were also determined (Table 1). The data showed that FH-71 was the most potent against the action of phenylephrine in rat vas deferens, whereas it was the least effective against that in rat spleen. In contrast, EW-154 was much more potent in rat spleen than in vas deferens (Table 1). The potency ratios of these compounds against α_{1A}- and α_{1B}-adrenoceptor subtypes were also calculated. With reference to terazosin (as 1), FH-71 showed a 19-fold selectivity for α_{1A}- than for α_{1B}-adrenoceptor subtypes; in contrast, EW-154 exhibited a 11-fold selectivity for α_{1B}- than for α_{1A}-adrenoceptor subtypes (Table 2). We also determined the effects of these compounds against α_{1A}- and α_{1B}-adrenoceptor subtypes using a radio-ligand binding test with rat submaxillary gland and liver, respectively. The data were obtained and the binding affinity for α_{1A}- and α_{1B}-adrenoceptor subtypes was calculated. The pK_i values of FH-71, EW-65 and EW-154 are 8.97, 7.72 and 7.21 in rat submaxillary gland, respectively, and 7.75, 7.79 and 7.93 in rat liver, respectively.

Table 2
Potency ratio of FH-71, EW-65 and EW-154 against α_{1A}- and α_{1B}-adrenoceptors

Drugs	α_{1A}/α_{1B}	α_{1B}/α_{1A}
Terazosin	1.00	1.00
FH-71	19.04	0.05
EW-65	0.39	2.55
EW-154	0.09	11.11

3.3. Examination of α_1-adrenoceptor antagonistic potency in human hyperplastic prostate

Phenylephrine induced a contractile response in human hyperplastic prostate in a concentration-dependent manner; the maximum contraction was 0.82±0.06 g (n=16). Terazosin, FH-71, EW-65 and EW-154 all caused concentration-dependent parallel rightward shifts of the concentration–response curve for phenylephrine in hyperplastic prostate, and the Schild plots were constructed (figures not shown). The pA_2 values were calculated from the Schild plots and

Table 1
Effect of FH-71, EW-65 and EW-154 on tension responses to phenylephrine in rat vas deferens and spleen

Drugs	Vas deferens (α_{1A})		Spleen (α_{1B})	
	pA_2	Relative potency	pA_2	Relative potency
Terazosin	8.12±0.10	1	8.40±0.09	1
FH-71	8.62±0.06	3.16	7.62±0.06	0.17
EW-65	7.15±0.06	0.11	7.84±0.07	0.28
EW-154	6.68±0.04	0.04	8.02±0.06	0.42

Values are expressed as means±S.E.M. of four experiments.

Table 3
Effect of FH-71, EW-65 and EW-154 on tension responses to phenylephrine in human hyperplastic prostates

Drugs	pA_2
Terazosin	8.17±0.05
FH-71	8.34±0.04
EW-65	7.44±0.03
EW-154	7.05±0.03

Values are expressed as means±S.E.M. of four experiments.

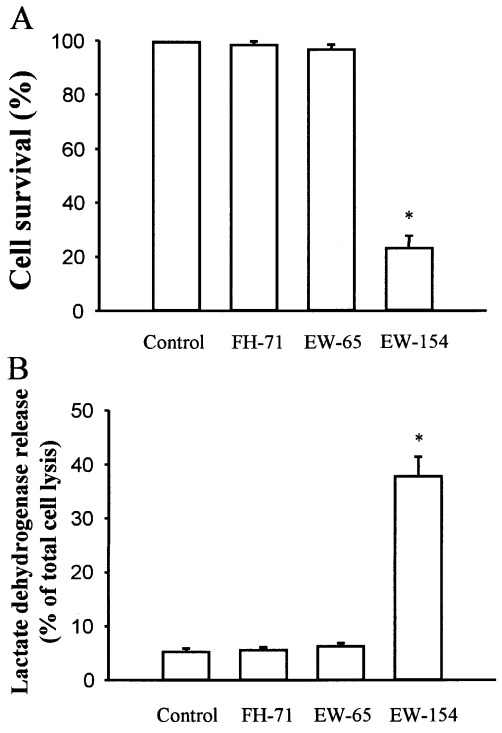

Fig. 5. Effects of FH-71, EW-65, and EW-154 on cytotoxic reactions in human prostatic smooth muscle cells. Cells were incubated without (control) or with the indicated compound (10 μM) for 24 h. After the incubation period, the cytotoxic effects were assayed by the MTT assay method (A) or the culture medium was obtained for the measurement of lactate dehydrogenase release (B) as described in Materials and methods. Results are expressed as percent cell survival of control (A) or percent of total cell lysis (B). Data are expressed as means±S.E.M. of four experiments. *$P<0.001$ compared with control.

the data showed that FH-71 was the most potent compound against the contraction elicited by phenylephrine (Table 3).

3.4. Determination of the cytotoxic effect in human prostatic smooth muscle cells

We also determined the cytotoxic effect of these compounds in cultured human prostatic smooth muscle cells. As demonstrated in Fig. 5A, FH-71 and EW-65 had little cytotoxic effect using MTT assay methods; however, EW-154 (10 μM) induced significant cytotoxicity in these cells. Furthermore, using the lactate dehydrogenase release assay, we also found that EW-154 but not FH-71 and EW-65 induced a profound increase in lactate dehydrogenase release (Fig. 5B), suggesting that EW-154 had a necrotic rather than apoptotic effect.

4. Discussion

In our laboratory, we are interested in the development of drugs for the treatment of benign prostatic hyperplasia. The selective α_1-adrenoceptor antagonist is an important target because a substantial body of experimental evidence shows that the contractile properties of human prostate adenoma are mediated primarily by α_1-adrenoceptors (Hedlund et al., 1985; Hieble et al., 1985), and 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). Additionally, endogenous adrenergic stimulation plays an important role in the human prostate since the tone of prostatic smooth muscle, which is regulated by the autonomic nervous system, is thought to be the dynamic component of bladder outlet obstruction in benign prostatic enlargement (Caine, 1986). We synthesized some quinazoline-based compounds and found that FH-71, EW-65 and EW-154 are three representatives. The present work demonstrated that FH-71, EW-65 and EW-154 inhibited phenylephrine-induced contractile responses in rat aorta. All of these compounds shifted the concentration–response curves for phenylephrine in parallel and without diminishing the maximum contraction, suggesting reversible antagonistic effects at α_1-adrenoceptors. Furthermore, at a high concentration (10 μM) all of these compounds showed no effect on the contractions elicited by high K^+ and U46619, revealing that they had little influence on voltage-operated Ca^{2+} channels and thromboxane A_2 receptors. Taken together, the data showed that FH-71, EW-65 and EW-154 were selective α_1-adrenoceptor antagonists.

On the basis of functional and binding studies, at least three α_1-adrenoceptor subtypes have been found, such as the α_{1A}-, α_{1B}- and α_{1D}-adrenoceptor subtypes (Ford et al., 1994). Recently, selective α_{1A}-adrenoceptor antagonists have been developed to optimize the therapeutic efficacy of the treatment of benign prostatic hyperplasia, since there is accumulating evidence that α_{1A}-adrenoceptors are the predominant α_1-adrenoceptor subtype in the prostate (Guh et al., 1995; Beduschi et al., 1998). Moreover, the use of α_{1A}-adrenoceptor antagonists could reduce the side effects associated with α-adrenoceptor blockade in other tissues or organs of the body, such as the vascular system (Lepor, 1998). Thus, the development of selective α_{1A}-adrenoceptor antagonists is now an important issue in the management of benign prostatic hyperplasia. To examine the selectivity for α_1-adrenoceptor subtypes, rat vas deferens and spleen, for the functional determination of α_{1A}- and α_{1B}-adrenoceptor subtypes, respectively, were used and the nonselective α_1-adrenoceptor antagonist, terazosin, was used for comparison. The functional data showed that FH-71 exhibited a 19-fold selectivity for α_{1A}- rather than α_{1B}-adrenoceptor subtypes, whereas EW-154 showed a 11-fold selectivity for α_{1B}- rather than α_{1A}-adrenoceptor subtypes. The effects of these compounds against α_{1A}- and α_{1B}-adrenoceptor subtypes have also been determined using a radio-ligand binding test with rat submaxillary gland and liver, respectively, in our laboratory. The data were obtained and the binding affinity for α_{1A}- and α_{1B}-adrenoceptor subtypes was calculated. The data showed that FH-71 had a 17-fold selectivity for α_{1A}- rather than α_{1B}-adrenoceptor subtypes, whereas EW-154 showed a fivefold selectivity for α_{1B}- rather than

α_{1A}-adrenoceptor subtypes. In the functional tension study, we found that FH-71 was the most potent α_1-adrenoceptor antagonist among the mentioned compounds in human hyperplastic prostate. It showed a potency 8- and 19-fold higher than that of EW-65 and EW-154, respectively. These results demonstrated the potential of FH-71 as treatment of benign prostatic hyperplasia. Furthermore, we also examined the effects of these compounds against α_2-adrenoceptors using a radio-ligand binding assay in the rat cortex. The pK_i values were 7.87, 7.64 and 7.22, for FH-71, EW-65 and EW-154, respectively. The blockade of α_2-adrenoceptors by FH-71 may be beneficial to its development.

In the present study, we also determined the cytotoxic effects of these compounds. At first, we examined the cytotoxicity using the MTT assay method and found that only a high concentration of EW-154 (10 μM) caused cell death in human prostatic smooth muscle cells. It seems that prostatic cell death plays a beneficial role in the restriction of prostate size. However, in the lactate dehydrogenase release assay, EW-154 also induced a significant increase in lactate dehydrogenase release, suggesting that necrosis rather than apoptosis occurred in response to EW-154. EW-154 caused cell death not only in the prostatic cells, but also in human umbilical vein endothelial cells, evaluated using the above two assay methods (data not shown). These results demonstrated that high concentrations of EW-154 may exert a broad cytotoxic effect in several types of cells. We speculate that the cytotoxic activity of EW-154 could be a result of the guanidine group present in the structure of this compound. In conclusion, we suggest that FH-71 is a selective α_{1A}-adrenoceptor antagonist against muscle contractions in human hyperplastic prostate and that it possesses potential as a therapeutic agent for clinical symptomatic benign prostatic hyperplasia.

Acknowledgements

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