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Pharmacological Activity of DC-015, a Novel Potent and Selective α_1-Adrenoceptor Antagonist

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Abstract

The pharmacological activity of 3-((4-(2-methoxyphenyl)piperazin-1-yl)methyl)-2,3-dihydroimidazo(1,2-*c*)quinazolin-5(6H)-one (DC-015), a newly synthesized quinazoline derivative, was determined in rat isolated thoracic aorta and pressor responses were determined in spontaneously hypertensive rats (SHR).

Experimental results indicated that DC-015 is an α_1-adrenoceptor-blocking agent in rat thoracic aorta as revealed by its competitive antagonism of phenylephrine-induced vasocontraction ($pA_2 = 10{\cdot}54 \pm 0{\cdot}55$). These effects still persisted in denuded aorta. It was as potent as prazosin ($pA_2 = 10{\cdot}04 \pm 0{\cdot}63$). At higher concentrations (1·0 μM), DC-015 also expressed 5-hydroxytryptamine (5-HT) receptor competitive antagonism, but this 5-HT blocking effect was not found in the prazosin-administration group. [^{3}H]Inositol monophosphate formation stimulated by phenylephrine (30 μM) in rat thoracic aorta was diminished by DC-015 (3 and 10 nM) and prazosin (10 nM); whereas the cAMP content of rat thoracic aorta was not altered by DC-015 and prazosin. Furthermore, intravenous administration of DC-015 and prazosin (both at 0·01, 0·05 and 0·1 mg kg^{-1}) induced a dose-dependent reduction of mean arterial pressure which reached a maximal effect at 5 min after injection and persisted over 2 h in SHR. A higher dose of DC-015 (0·1 mg kg^{-1}, i.v.) did not cause any significant changes in heart rate, whereas, the same dose of prazosin (0·1 mg kg^{-1}, i.v.) produced a decrease which seems to parallel the time course of the hypotensive response.

We can conclude that the DC-015 is a potent, highly selective α_1-adrenoceptor antagonist in vascular smooth muscle.

Although the role played by α-adrenoceptors in hypertensive disease remains unclear, the blockade of α-adrenoceptors by appropriate antagonistic drugs is effective in lowering blood pressure, particularly with the selective α_1-antagonists such as prazosin (Stanaszek et al 1983; Timmermans & Van Zwieten 1984; Young & Brogden 1988). Several antihypertensive agents such as prazosin and doxazosin, a structural analogue of prazosin (Young & Brogden 1988) contain quinazoline ring systems. Other 3-substituted quinazolinones have been found to have antihypertensive activities mediated via α-adrenoceptor and 5-hydroxytyptamine-(5-HT) receptor antagonism. Recently, during the course of our synthetic studies on the antihypertensive effects of the fused quinazolinone ring system, we found that DC-015, 3-[[4-(2-ethoxyphenyl) piperazin-1-yl] methyl]-2,3-dihydroimidazo [1,2-*c*] quinazolin-5(6H)-one (Fig. 1), possesses selective α_1-adrenoceptor antagonistic action (Chern et al 1993). In this study, we have evaluated the antihypertensive effect in spontaneously hypertensive rats (SHR) and its mechanisms.

Materials and Methods

Measurement of blood pressure in SHR

Male SHR of body weight 250–350 g (12–16 weeks) (mean arterial pressure (MAP): 182 ± 12 mmHg; heart rate: 360 ± 15 beats min^{-1}) were used in this study. Rats were anaesthetized with sodium pentobarbitone (40–50 mg kg^{-1}, i.p.). Both right femoral artery and vein were cannulated with PE-50 tubing to monitor blood pressure and for drug administration (DC-015 and prazosin). The body temperature was maintained at 37·5°C with a heating pad and monitored with a rectal thermometer. Blood pressure was measured with a pressure transducer (Statham P23D) via a polyethylene cannula placed in the right femoral artery. The heart rate was measured through a tachograph preamplifier (Grass Model 7B) triggered with pulses of arterial blood pressure. All data were recorded on a polygraph (Grass Model 7B).

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Rat aortic contraction

Sprague-Dawley rats of both sexes, 270–350 g, were used. The animals were anaesthetized with urethane (1·2 g kg^{-1}, i.p.). The thoracic aorta was isolated and excess fat and connective tissue were removed. Vessels were cut into rings about 4 mm in length and mounted in organ baths containing Krebs solution of the following composition (mM): NaCl, 118; KCl, 4·7; $NaHCO_3$, 25; KH_2PO_4, 1·2; $MgCl_2$, 1·2; $CaCl_2$, 2·5 and glucose, 11. The tissue bath solution was maintained at 37°C and gassed with 95% O_2–5% CO_2. Two stainless-steel hooks were inserted into the aortic lumen in tissue organ baths containing 20 mL Krebs solution. That is, one was fixed while the other was connected to a transducer (Grass FT03). Aorta was equilibrated in the medium for 90 min with three changes of Krebs solution. Each ring was progressively stretched to the optimal point on its length-tension curve as determined by the active tension developed to phenylephrine (1 μM) and maintained under an optimal resting tension before specific experimental processes were initiated. Vasocontractions were recorded isometrically via

a force-displacement transducer connected to a Grass Model 7D polygraph. Aorta was pretreated with various concentrations of DC-015 and prazosin for 30 min before generating the cumulative concentration-response curves with vascocontractors (phenylephrine and 5-HT) for 15–30 min at 3–5 min intervals. In other experiments, the endothelium was removed by rubbing with a cotton ball and the absence of relaxation induced by acetylcholine was taken to show the vessels were denuded completely; the activity of endothelium by acetylcholine-induced vasorelaxation was detected as an indicator to ensure the function of endothelium remained intact in thoracic aorta before each experiment. Results obtained in this study were expressed as percentage of the maximal control response for each agonist.

[^{3}H]Inositol monophosphate

The procedure previously described by Hirata et al (1990) was used. Briefly, thoracic aorta of rats was exposed to Krebs solution containing 10 μCi mL^{-1} [^{3}H]myo-inositol for 3 h and gassed with 95% O_2–5% CO_2. Tissues were then transferred to tubes containing fresh Krebs solution with solvent (distilled water), DC-015 (3, 10 nM) and prazosin (10 nM); the mixture was incubated for 30 min. Normal saline or phenylephrine (30 μM) was added to trigger vasocontraction and the mixture was incubated for another 15 min. LiCl (10 mM) was added 5 min before phenylephrine to inhibit metabolism of inositol monophosphates (Berridge et al 1982). Aorta was then immediately frozen in liquid nitrogen and homogenized in 1·3 mL 10% trichloroacetic acid. Samples of supernatant (1 mL) after centrifugation (10 000 g, 4 min) were transferred to the test-tubes. Trichloroacetic acid was removed by extraction with 10 mL diethyl ether three times, and the mixture was incubated at 80°C to remove the residual diethyl ether. The inositol phosphates were separated on Dowex-1 anion exchanger (50%, w/v, 1 mL) as described by Berridge et al (1982) and Neylon & Summers (1987). In this experiment, only [^{3}H]inositol monophosphate was measured as an index of the total inositol phosphate formation because the levels of inositol bisphosphate and inositol trisphosphate were very low. The pellets of the precipitate were resuspended in 0·1 M NaOH and assayed for protein by Bio-Rad protein assay kits using bovine serum albumin as standard (Lowry et al 1951).

cAMP in rat aorta

cAMP in the preparations was assayed as described previously (Itoh et al 1982; Kauffman et al 1987). The aortic rings were pre-equilibrated in an organ bath containing 5 mL Krebs solution and aerated with 95% O_2–5%CO_2 at 37°C for 60 min. After incubation of aortic rings with solvent (distilled water), DC-015 (3, 10 nM) or forskolin (2 mM) for 2 min, the aortic rings were rapidly frozen in liquid nitrogen and stored at −80°C until homogenized in 1·3 mL 10% trichloracetic acid and 4 mM EDTA using a homogenizer (Glas-Col 099C K44). The homogenate was centrifuged at 10 000 g for 5 min and the supernatant was removed and extracted with 4 × 3 vol diethyl ether; cAMP was assayed using EIA kits. The precipitable protein was determined using Bi-Rad protein assay kits with bovine serum albumin as standard. cAMP values are presented as pmol mg protein^{-1}.

Data analysis

Agonist dose-response curves in the presence of DC-015 or prazosin were related to the control dose-response curve, of which the maximal response was taken as 100%. In all experiments, each concentration of DC-015 or prazosin was tested and the slopes of the resulting Schild plots were used to evaluate the competitive antagonism. The pA_2 values were calculated for each concentration of DC-015 and prazosin according to: $pA_2 = -\log$ ([antagonist]/[dose ratio-1]) (Mackay 1978). The MAP was calculated as [(systolic pressure − diastolic pressure)/3 + diastolic pressure]. The experimental results are expressed as the mean ● s.e.m. and accompanied by the number of observations. Statistical significance was assessed by Student's t-test and P values less than 0·05 were considered significant.

Materials

DC-105 (Fig. 1) was synthesized according to the method

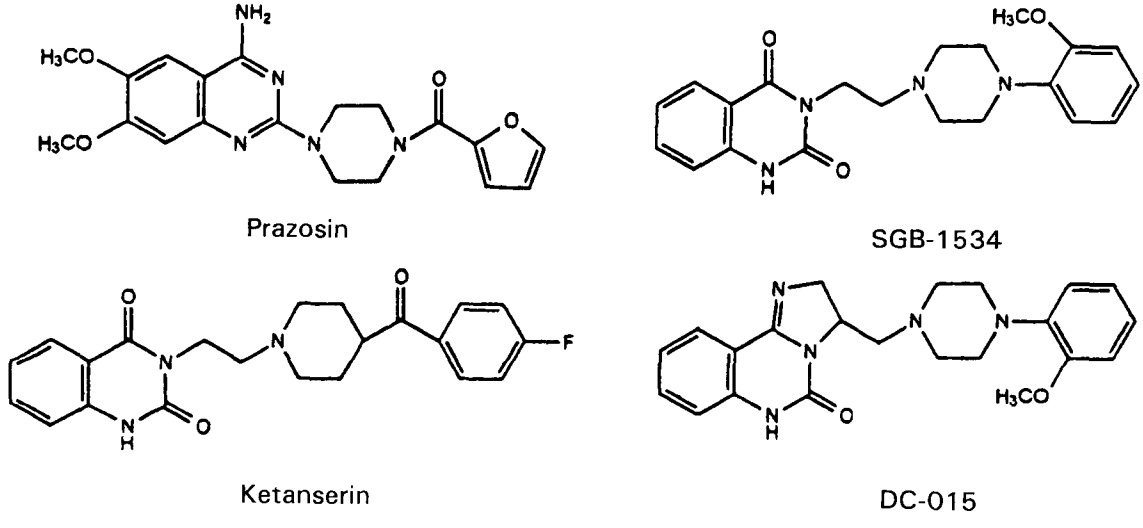

FIG. 1. Chemical structures of prazosin, SGB-1534, ketanserin and DC-015.

described previously (Chern et al 1993). Phenylephrine, prazosin, angiotensin II, calcium chloride, magnesium sulphate, glucose, indomethacin, myo-inositol, trichloroacetic acid, Dowex-1 resin (100–200 mesh; ×8, chloride), acetylcholine, 5-HT, forskolin, sodium formate, ammonium formate, formic acid, sodium tetraborate, lithium chloride, ethylenediaminetetraacetic acid (EDTA, disodium salt), ethylene glycol bis-9(b-aminoethyl ether) *N, N, N′, N′*-tetra-acetic acid (EGTA) were obtained from Sigma Chemical Co., USA. Myo-[2-^{3}H]inositol was from Amersham, UK. cAMP EIA kits were purchased from Cayman Chemical Co., USA.

Results

Antihypertensive effects of DC-015 and prazosin in anaesthetized SHR

Administration of DC-015 (0·01, 0·05, 0·1 and 0·5 mg kg^{-1}, i.v. bolus) produced a dose-related reduction of MAP which reached a maximal effect at 5 min after injection and persisted over 2 h (Fig. 2A). Relationships between the dose of DC-015 and MAP or heart rate responses in anaesthetized rats are depicted in Fig. 2A & B. Control solvent (distilled water) did not exert any significant effects on MAP or heart rate (data not shown). Effects of DC-015 on heart rate were not significant in SHRs, with a slight bradycardia (not achieving statistical significance) occurring during the initial 5 min after injection of DC-015 and then returned to baseline values (Fig. 2B). Intravenous administration of prazosin (0·01, 0·05 and 0·1 mg kg^{-1}) caused a similar dose-related reduction of MAP (Fig. 2C). Peak responses were observed within 5 min after prazosin injection (Fig. 2C). At the highest dose of prazosin (0·1 mg kg^{-1}), there was an obvious decrease in heart rate ($P < 0·05$) which paralleled its hypotensive effect (Fig. 2C & D).

α_1-Adrenoceptor antagonism in rat aorta

In rat thoracic aorta, phenylephrine caused a phasic contraction and then a tonic contraction maintained for at least 30 min. Pretreatment of DC-015 (0·3–10 nM) or prazosin (0·3–10 nM) with aorta for 30 min inhibited phenylephrine (10 μM)-induced vasocontraction in a dose-dependent manner (data not shown). At 10 nM, DC-015 and prazosin almost completely abolished vasocontraction; yohimbine (3 μM) did not significantly affect phenylephrine-induced vasocontraction (data not shown). Noradrenaline (3 μM) produced a similar tracing to phenylephrine but displayed a more potent tension than phenylephrine. DC-015 also significantly inhibited noradrenaline-induced vasocontraction in a dose-dependent manner (data not shown).

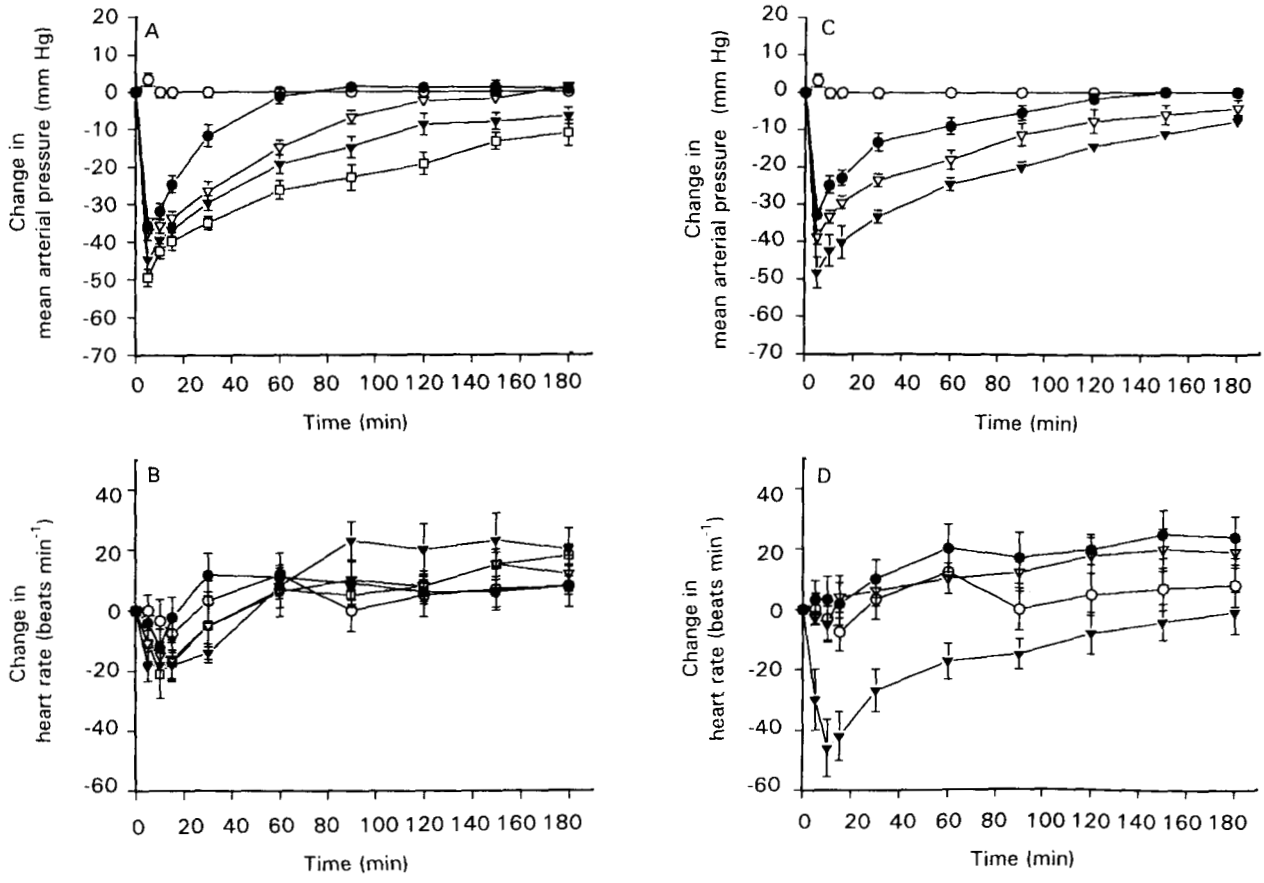

FIG. 2. Effects of DC-015 and prazosin (i.v. bolus) on hypotensive effect and heart rate in SHR. Changes in (A) MAP and (B) heart rate caused by intravenous injection of various doses of DC-015. Changes in (C) MAP and (D) heart rate caused by intravenous injection of various doses of prazosin. Data are presented as mean ± s.e.m. (n = 8). ○, control; ●, 0·01 mg kg^{-1}; ▽, 0·05 mg kg^{-1}; ▼, 0·1 mg kg^{-1}; □ 0·5 mg kg^{-1}.

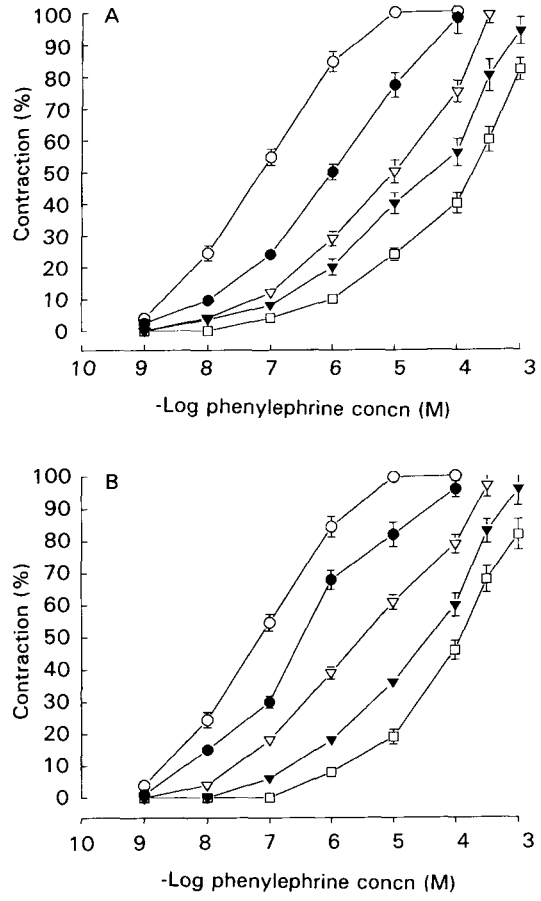

FIG. 3. Antagonism of the concentration-response curves to phenylephrine by 15 min pretreatment of thoracic aorta with (A) DC-015 (○, control; ●, 0·3 nM; ▽, 1·0 nM; ▼, 3·0 nM; □, 10·0 nM) and (B) prazosin (○, control; ●, 0·3 nM; ▽, 1.0 nM; ▼, 3·0 nM; □, 10·0 nM). Data are presented as mean ±s.e.m. (n = 15).

Analysis of the concentration-response curve of phenylephrine-induced contraction of rat thoracic aorta was performed for the α_1-adrenoceptor antagonism by DC-015 in comparison with prazosin. DC-015 (0·3–10 nM) produced a parallel rightward shift of the curve consistent with competitive blockade (Fig. 3A). This concentration-related shift of DC-015 was also observed without significant affect in rat aorta from which the endothelium had been removed (data not shown). Figure 3B shows that prazosin (0·3–10 nM) also produced a parallel rightward shift of the curve. The pA_2 of DC-015 and prazosin against phenylephrine (10 μM) were 10·54 ± 0·55 (slope range: 0·91 ~ 1·18) and 10·04 ± 0·63 (slope range: 0·89 ~ 1·20), respectively (Table 1). These results indicated that DC-015 has a similar potency to prazosin in

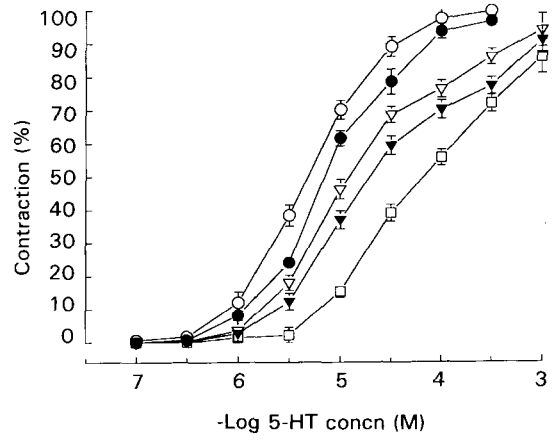

FIG. 4. Antagonism of the concentration-response curves to 5-HT by 30 min pretreatment of thoracic aorta with DC-015 (○, control; ▽, 1·0 μM; ▼, 3·0 μM; □, 10·0 μM) and prazosin (●, 10 μM). Data presented as mean ± s.e.m. (n = 15).

phenylephrine-induced contraction of rat thoracic aorta. In this case, the Schild slopes were not significantly different from 1·0.

Quinazoline derivatives SGB-1534 and ketanserin have an appreciable affinity for α_1-adrenceptor and 5-HT receptors (Fozard 1982; Imagawa & Sakai 1986). DC-015 is also a quinazoline derivative (Fig. 1), therefore, DC-015 was further evaluated against vasocontraction stimulated by 5-HT in thoracic aorta. As shown in Fig. 4, DC-015 (1·0–10 μM) exhibited a significant parallel rightward shifting of the curve consistent with competitive blockade (Fig. 4). The pA_2 was 6·80 ± 0·24 (slope range: 0·85 ~ 1·25) (Table 1). However, prazosin significantly inhibited 5-HT-induced vasocontraction only at higher concentrations (10 μM) than DC-015 (Fig. 4). The maximal contractions (E_{max}) induced by 5-HT and phenylephrine were not significantly different from each other (Table 1); however, the EC50 of 5-HT-induced vasocontraction was higher than that of phenylephrine (5·62 ± 0·3 μM vs 52·5 ± 3·0 nM) (Table 1). Therefore, we concluded that DC-015 had an equivalent potency to prazosin against phenylephrine, but showed a greater potency than prazosin against 5-HT in thoracic aorta. In all cases, the Schild plot slopes were not significantly different from 1·0.

A high concentration of DC-015 (20 μM) was used to evaluate its antagonism against the effect on rat thoracic aorta caused by vasoactive agents other than α-adrenoceptor agonists. Vasocontraction of aorta was challenged with angiotensin II (1 μM), U-46619 (1 μM), KCl (60 mM) or carbachol (3 μM); DC-015 (20 μM) did not inhibit the increase in tension by these vasoconstrictors (data not shown).

Table 1. Comparison of the responses of rat aorta to phenylephrine and 5-HT, and the pA_2 values of DC-015 and prazosin against phenylephrine and 5-HT.

Agonist	E_{max} (g)	EC50	Antagonist	pA_2
Phenylephrine (10 μM)	2·48 ± 0·08	52·50 ± 3·0 nM	DC-015	10·54 ± 0·55
			prazosin	10·04 ± 0.63
5-HT (30 μM)	2·64 ± 0·09	5·62 ± 0·3 μM	DC-015	6·80 ± 0·24

E_{max}, maximum developed tension. Results are given as mean ±s.e.m. (n = 15).

Effect of DC-015 on the phosphoinositide breakdown in rat thoracic aorta by phenylephrine

To observe whether signal transduction after α_1-adrenoceptor activation was blocked by DC-015, rat thoracic aorta was labelled with [^{3}H]myoinositol. In this study, only the [^{3}H]inositol phosphate formation was measured as an index of the total inositol phosphate formation. As summarized in Table 2, phenylephrine (30 μM) caused a 3-fold rise of inositol monophosphate formation as compared with the resting thoracic aorta (4601 ± 426 counts min^{-1}, phenylephrine-treated vs 1522 ± 281 counts min^{-1}, resting control). This increase was significantly suppressed by prazosin (10 nM) or DC-015 (3 or 10 nM) (Table 2). These results indicated that DC-015 and prazosin interfere with the phosphoinositide breakdown via α_1-adrenoceptors stimulated by phenylephrine of aortic muscle.

Effect of DC-015 on the cAMP formation in rat aorta

The cAMP content of the aorta was measured by EIA kits. As shown in Table 3, forskolin (2 μM) markedly elevated cAMP levels in rat aorta. DC-015 (3 or 10 nM) had no effect on cAMP.

Table 2. Effects of prazosin and DC-015 on the accumulation of [^{3}H]inositol monophosphate in rat thoracic aorta by phenylephrine.

Treatment	[^{3}H]inositol monophosphate (counts min^{-1} (mg protein)$^{-1}$)
Resting	1522 ± 281
Phenylephrine (30 μM)	4601 ± 426
+ Prazosin (10 nM)	2025 ± 262**
+ DC-015 (3 nM)	3023 ± 276**
+ DC-015 (10 nM)	2391 ± 210**

Data are presented as total inositol monophosphates accumulated and expressed as means ± s.e.m., (n = 4). *P < 0·01, **P < 0·001 compared with the control value.

Discussion

Our results have demonstrated that DC-015 inhibited the contractile responses of rat thoracic aorta to the selective α_1-adrenoceptor agonist phenylephrine, acting as a selective α_1-adrenoceptor antagonist without affecting the contraction of rat aorta induced by the prostaglandin endoperoxides (U46619), angiotensin II, high-potassium depolarization or the muscarinic receptor agonist (carbachol). Comparison of the α_1-adrenoceptor antagonism of DC-015 with prazosin in thoracic aorta clearly revealed that DC-015 is a selective α_1-adrenoceptor antagonist with a pA_2 10·54 ± 0·55 for competitive antagonism of phenylephrine. The potency of DC-015 is equivalent to prazosin at inhibiting vasocontraction stimulated by phenylephrine. Furthermore, we have previously reported (Chern et al 1993), that DC-015 had a higher binding affinity for α_1-adrenoceptors (K_i 0·27 ± 0·02 nM), but had a lower affinity for α_2-adrenoceptors (K_i 593 ± 6 nM).

Vascular endothelium plays a crucial role in the regulation of vascular tone. It responds to a variety of neurochemical and physical stimuli to release endothelium-derived relaxing factor (EDRF) and prostaglandin (PGI_2) (Jaffe 1985; Vanhoutte et al 1986). Endothelium modulates the vasocontractor responses to many agonists, and EDRF is primarily responsible for these effects (Palmer et al 1987). The relaxant effect of DC-015 persisted in denuded aorta. Thus, the vasorelaxation induced by DC-015 was independent of the endothelium and was not mediated by either EDRF or PGI_2 (data not shown). Furthermore, DC-015 also possessed 5-HT receptor blocking activity in a competitive manner (Fig. 4), since Schild plot slope was not far from unity (range 0·85–1·25). However, its potency for blocking 5-HT receptors is roughly one-five hundredth that for blocking α_1-adrenoceptors. On the other hand, it was more potent than prazosin for blocking 5-HT receptors. The activity profile of DC-015 resembles that of the structurally similar agent ketanserin in possessing both α-adrenoceptor- and 5-HT receptor-blocking properties (Van Neuten et al 1981; Kalkman et al 1982). These agents quantitatively differ in that DC-015 is more selective for α_1-adrenoceptors while ketanserin shows roughly a 10-fold selectivity for 5-HT receptors.

Activation of α_1-adrenoceptors leads to alterations in intracellular free Ca^{2+} secondary to hydrolysis of membrane phosphoinositides (Berridge 1984). In most cases, α_2-adrenoceptors are coupled to adenylate cyclase by a guanine nucleotide binding regulatory protein and a subsequent decrease in cAMP production by the cell (Bylund & U'Pritchard 1983). Cyclic nucleotides are very important for relaxing vascular smooth muscle (Murad 1986). For example, forskolin has been shown to be a potent relaxing agent via activation of adenylate cyclase resulting in increasing cAMP levels in vascular smooth muscle (Ousterhout & Sperelankis 1987). In our study, phosphoinositide breakdown stimulated by phenylephrine and 5-HT of the thoracic aorta was inhibited by DC-015 (Table 2). In contrast, the cAMP content was not significantly altered by DC-015 (Table 3). This indicates that α_1-adrenoceptor and 5-HT receptor antagonistic effects of DC-015 are mainly mediated by phosphoinositide breakdown but unrelated to increase of cellular cAMP concentration. Analysis of the concentration-response curves of DC-015 revealed a competitive antagonism against phenylephrine and 5-HT in thoracic aorta (Figs 3, 4). In addition, our preliminary studies indicated that oral administration of DC-015 causes more significant reduction of hyperlipidaemia than prazosin in SHR fed a high-fat cholesterol diet (unpublished data).

The present experiments demonstrated that DC-015 is an effective antihypertensive agent when applied as intravenous

Table 3. Effects of DC-015 on the cAMP formation of rat thoracic aorta.

	cAMP (pmol (mg protein)$^{-1}$)	n
Control	3·56 ± 0·42	4
DC-015 (3 nM)	4·38 ± 0·34	4
DC-015 (10 nM)	4·52 ± 0·62	4
Forskolin (2 μM)	18·42 ± 2·65*	4

After pre-incubation of aortic rings in Krebs solution for 1 h, solvent (control), DC-015 (3, 10 nM) or forskolin was added for another 2 min and the reaction was stopped by immersing the tissue into liquid nitrogen. Results are expressed as the means ± s.e.m. *P < 0·001 as compared with the respective control.

bolus in anaesthetized SHR. When DC-015 (0·1 mg kg^{-1}) was administered intravenously to SHR, it caused a decrease in blood pressure of similar magnitude to that caused by prazosin (0·1 mg kg^{-1}). Several classic α-adrenceptor antagonists, such as phentolamine, phenoxybenzamine, tolazoline and hydrogenated ergot alkaloids have not proven useful for ideal blood pressure control in hypertensive patients (Graham & Pettinger 1979; Van Zwieten 1990). The administration of these drugs is accompanied by marked reflex tachycardia, triggered by the cardioreceptor reflex system and autonomic nervous system. At maximal hypotensive doses of prazosin (0·1 mg kg^{-1}, i.v.) a significant decrease in heart rate was noted (Fig. 2D). Constantine et al (1978) have reported that prazosin does not cause reflex tachycardia in conscious dogs due perhaps to reduction in baroreceptor modulation, since prazosin depresses the baroreflex function in cats (Cambridge et al 1977), dogs (Hardey & Lokhandwala 1979) and rats (Person et al 1981). Furthermore, with DC-015 treatment, there was no significant change in heart rate at the dose employed (Fig. 2B); it can be shown that the reflex tachycardia is suppressed as a result of anaesthetic in SHR. The hypotensive effect of prazosin is mainly due to interference with peripheral sympathetic function as a result of vascular α_1-adrenoceptor blockade, and is devoid of direct vasodilator activity (Graham et al 1977; Van Zwieten 1990). Intravenous administration of DC-015 to rats pretreated with prazosin did not induce any further decrease in MAP (data not shown). Furthermore, DC-015 and prazosin both failed to impair the pressor response of angiotensin II even at maximal hypotensive dose (0·1 mg kg^{-1}) (data not shown). Thus, on the basis of in-vitro and in-vivo studies, we conclude that the antihypertensive action of DC-015 is mainly mediated by blocking of α_1-adrenoceptors.]

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