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Characterization of FR 172357, a new non-peptide bradykinin B_2 receptor antagonist, in human, pig and rabbit preparations

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Abstract

FR 172357, a new non-peptide antagonist of the kinin B_2 receptor was tested in three isolated vessels, the human umbilical vein, the rabbit jugular vein, and the pig coronary artery, to evaluate its antagonistic activities against bradykinin. FR 172357 displaced to the right the concentration–response curves of bradykinin. The displacements were parallel to the controls without reduction of the maximum effect in the human umbilical vein and in the rabbit jugular vein, but not in the pig coronary artery. Schild plots confirmed that FR 172357 acts as a competitive antagonist in the human umbilical vein (pA_2 8.65) and in the rabbit jugular vein (pA_2 9.07), and as a non-competitive antagonist in the pig coronary artery (pK_B 10.14). FR 172357 is selective for the kinin B_2 receptor since it does not influence the effects of Lys-des-Arg^9-bradykinin in the human umbilical vein, in the rabbit aorta, and in the pig renal vein. It is specific because it does not affect the contractions induced by angiotensin II, noradrenaline, 5-hydroxytryptamine, or endothelin-1 in the human umbilical vein. It, however, interacts with the tachykinin NK_1 receptor of the rabbit jugular vein and pig coronary artery. Compared to other bradykinin B_2 receptor antagonists, FR 172357 emerges as a very potent compound, which may represent a choice for experimental (and clinical?) applications.

Keywords: Bradykinin B_2 receptor; Antagonist; Vessel, isolated; (Human); (Pig); (Rabbit)

1. Introduction

Attempts were made by investigators at Fujisawa to improve the pharmacological features of FR 173657, the first potent and selective non-peptide antagonist for the kinin B_2 receptor (Asano et al., 1996; Inamura et al., 1997). Modifications at the N and C-terminal ends of FR 173657 ((*E*)-3-(6-acetamido-3-pyridyl)-*N*-(*N*-[2,4-dichloro-3-[(2-methyl-8-quinoinyl)oxymethtyl]phenyl] *N*-methylaminocarbonylmethyl]acrilamide) led to a new compound (3-bromo-8-[2,6-dichloro-3-[*N*-[(*E*)-4-(*N*,*N*-dimethylcarbamoyl)cinnamidoacetyl]-*N*-methylamino]benzyloxy]-2-methylimidazo[1,2-a]pyridine), which was obtained as HCl (FR 167344) and as CH_3SO_3H (FR 172357) salt (Inamura, N., personal communication). Biochemical and biological data obtained with FR 167344 were compared with those of FR 173657 by Aramori et al. (1997). It was found that FR 167344 is less potent than FR 173657 both as a competitor of [^{3}H]bradykinin binding to membranes from Chinese hamster ovary cells transfected with the human B_2 receptor (pIC_{50} 7.19 and 8.05, respectively), and as an antagonist of the phosphatidyl-inositol hydrolysis stimulated by bradykinin in the same cell type (pA_2 8.0 and 9.0, respectively).

In the present study, the pharmacologic spectrum and the potency of the sulphate salt of FR 167344 (compound FR 172357) were compared with those previously published on FR 173657 (Rizzi et al., 1997b) and of HOE 140 the standard B_2 receptor antagonist (Gobeil et al., 1996), using isolated vessels from three species and a recently developed binding assay (Gessi et al., 1997) for the native human B_2 receptor of the umbilical vein.

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2. Materials and methods

Handling of animals and experiments on human umbilical vein were made in accord with the guidelines of the Ethics Committee of the Medical School of the University of Ferrara (Italy).

2.1. Bioassay experiments

Human umbilical cords ($n = 7$) from healthy women of 25–38 years old were collected after spontaneous delivery at term. Immediately after the delivery, the cords were placed in cold (4°C) Krebs solution and were used for experiments within 12 h. In the laboratory, the middle segment of the cord (10–12 cm long) was cut and placed in Petri dishes containing Krebs solution at room temperature, and within 30–40 min, the vein was cannulated for removing surrounding connective tissues and was then cut into spiral strips (20 mm long, 3 mm wide). The endothelium was mechanically removed since the bradykinin B_2 receptor, which mediate contraction, is localized on the smooth muscle (Gobeil et al., 1996) of the human umbilical vein. Pig coronary arteries were obtained within 30 min after the death of adult pigs from the slaughterhouse at Negrini (Salara, Rovigo, Italy), and placed in cold Krebs solution. The left anterior descending coronary artery was cleaned of adherent connective tissues and fat, and then cut helically (20 mm long, 3 mm wide) with preserved endothelium, since the bradykinin B_2 receptor of the pig coronary artery, which is primarily a relaxing one, is localized on the endothelium (Pruneau et al., 1996). Pig renal vein was prepared according to the procedures described by Rizzi et al. (1997a). New Zealand white rabbits (1.3–1.8 kg) were killed by stunning and bleeding. Rabbit aorta and jugular vein were prepared according to the procedures previously described by Furchgott and Bhadrakom (1953) and Gaudreau et al. (1981), respectively.

All the tissues were suspended in 10-ml organ baths containing warm (37°C), oxygenated (95% O_2, 5% CO_2) Krebs solution of the following composition (in mM): NaCl 118.1; KCl 4.7; $CaCl_2$ 2.5; KH_2PO_4 1.2; $MgSO_4$ 1.2; $NaHCO_3$ 25; and glucose 10. The human umbilical vein and pig coronary artery were stretched to a resting tension of 2 g, while the rabbit jugular vein, the pig renal vein, and the rabbit aorta were loaded with 1 g. Changes of tension were measured isometrically with force transducers (FT03, Grass Instruments) and recorded on multichannel chart recorder (Linseis model L2005). In all experiments, the kininase II inhibitor captopril (Squibb, Montreal) was added to the Krebs solution at 1 μM concentration to prevent kinin degradation.

Before testing any agent, the pig coronary artery and rabbit jugular vein were equilibrated for 90–120 min, and the human umbilical vein for 150–180 min. During this time, fresh Krebs solution was applied and the tension readjusted every 20 min. The experiments began with the application of KCl 100 mM on the human umbilical vein and the rabbit jugular vein, and KCl 30 mM on the pig coronary artery to assess the responsiveness of the preparations. On the pig coronary artery stimulated by KCl 30 mM, substance P 100 nM was applied to test the presence of a functional endothelium. Experiments were started about 30 min later.

The B_2 receptor agonist bradykinin was used as standard agonist in the three tissues. While the rabbit jugular vein and pig coronary artery are B_2 mono-receptor systems, in the human umbilical vein the B_1 receptor is also present and it mediates contraction: this latter tissue was therefore treated with Lys-[Leu^8]-des-Arg^9-bradykinin 1 μM, according to Gobeil et al. (1996) to eliminate the interference by the B_1 receptor. Since the B_2 receptor of the pig coronary artery is primarily a relaxing one (Pruneau et al., 1996), this tissue was brought to contraction of about 3 g with U 46619 10 nM (a selective tromboxane prostanoid receptor agonist) before applying bradykinin.

The antagonistic activity of FR 172357 was evaluated on the three preparations, by measuring cumulative concentration–response curves of bradykinin in the absence and in the presence of increasing concentrations of the antagonist, in order to collect the experimental data for the Schild plot. FR 172357 was applied 15 min before the standard agonist.

To assess the selectivity and specificity of action of FR 172357 in the human umbilical vein, rabbit aorta, rabbit jugular vein, pig coronary artery, and pig renal vein, several contractile agents (Lys-des-Arg^9-bradykinin, noradrenaline, angiotensin II, 5-hydroxytryptamine, adenosine, substance P and, only in the human umbilical vein, endothelin-1) were used. The myotropic activity of each agent (given at a submaximal concentration) was challenged with 10 μM of FR 172357.

When testing FR 172357 on the B_1 receptor, the human umbilical vein was pretreated with HOE 140 1 μM to eliminate the interference of B_2 receptor according to Gobeil et al. (1996).

2.2. Binding experiments

Binding experiments were performed to determine the K_i value of FR 172357 in human umbilical vein smooth muscle membranes using [^{3}H]bradykinin as a radioligand, according to Gessi et al. (1997). The human umbilical vein membranes were prepared from the umbilical cords ($n = 10$) of healthy women (20–35 years old) after spontaneous delivery at term.

2.3. Agents and drugs

The B_2 receptor agonist bradykinin, the B_1 receptor agonist Lys-des-Arg^9-bradykinin, and the B_1 receptor antagonist Lys-[Leu^8]-des-Arg^9-bradykinin, were prepared by

solid-phase synthesis and purified by high pressure chromatography, as previously described by Drapeau and Regoli (1988). The non-peptide compounds FR 173657 and FR 172357 (Aramori et al., 1997) (see chemical structures in Fig. 1) are gifts of Fujisawa (Osaka, Japan). HOE 140 (D-Arg[Hyp^3, Thi^5, D-Tic^7, Oic^8]bradykinin) was made available by Hoechst (Frankfurt, Germany). U 46619 (1,5,5-hydroxy-11,9-(epoxymethano)prosta-5*z*,13E-dienoic acid) was obtained from Sigma (St. Louis, MO, USA). Captopril ([2*S*]-1-[3Mercapto-2-methyl-propionyl]-L-proline) was provided by Squibb Canada and was dissolved in isotonic saline. All reagents used for Krebs solution were from Sigma or E. Merck (Darmstadt, Germany). Concentrated solutions (1 mM) of peptides were made in bidistilled water and kept at −20°C. Solution of FR 172357 (10 mM) was made in dimethyl sulfoxide (DMSO), while U 46619 (1 mM) was dissolved in ethanol (final concentration in the organ baths not exceeding 0.1%). The highest concentration of DMSO used in all the experiments did not cause any effects per se.

2.4. Data analysis and terminology

All the data are expressed as means ± standard error of the mean. Data have been statistically analyzed using the Student's *t*-test for paired data, or one way analysis of variance followed by the Dunnett test as specified in Figs. 1–4 and Tables 1 and 2 via a software package (Tallarida and Murray, 1987). P values lower than 0.05 were considered as significant.

The pharmacological terminology adopted in this paper is in line with the recent IUPHAR recommendations (Jenkinson et al., 1995; Vanhoutte et al., 1996) The agonist apparent affinity is given as pEC_{50}, the negative logarithm to the base 10 of the molar concentration of an agonist that produces 50% of the maximal possible effect. Antagonist affinities are given in terms of pA_2 or pK_B, depending on the nature of the antagonism (competitive or non-competitive). For competitive antagonist, pA_2 (negative logarithm to base 10) of the molar concentration of an antagonist that

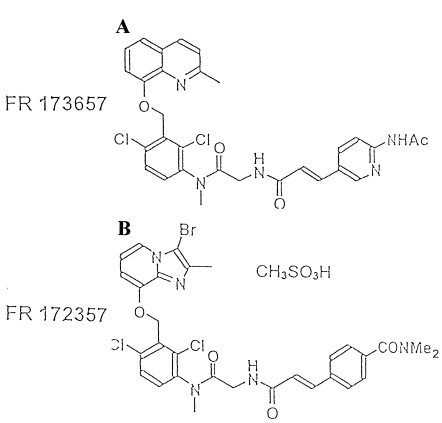

Fig. 1. Chemical structures of (A) FR 173657 and (B) FR 172357.

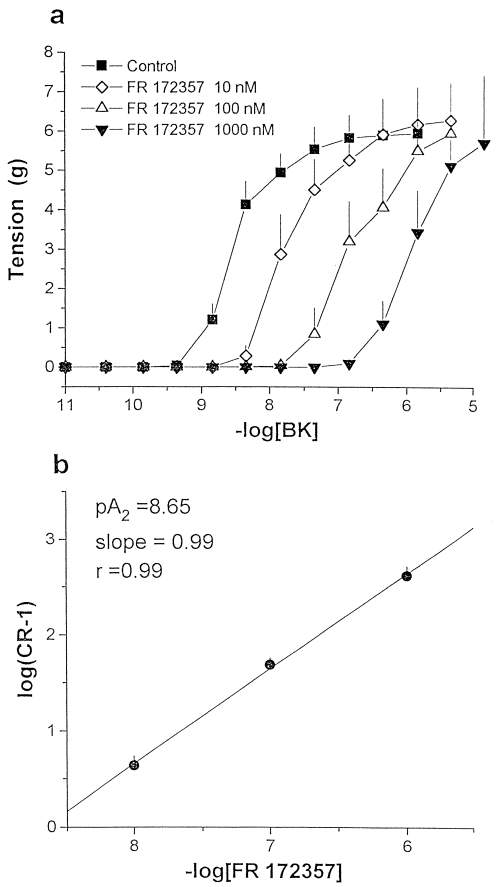

Fig. 2. (a) Concentration–response curves of bradykinin obtained in the human umbilical vein (E−), treated with 1 μM Lys-[Leu^8]-des-Arg^9-bradykinin, in the absence (■ indicated as control) and in the presence of increasing concentrations of FR 172357 (◇ 10 nM; △ 100 nM; and ▼ 1000 nM). Abscissa: negative log of the molar concentration of bradykinin (BK). Ordinate: tension in g. (b) Schild plot of FR 172357 obtained against bradykinin in the human umbilical vein. Abscissa: negative log of the molar concentration of FR 172357. Ordinate: log of the concentration ratio — 1. Values are means ± S.E.M. of at least five experiments. E− (without endothelium).

makes it necessary to double the concentration of agonist needed to elicit the original submaximal response (Schild, 1947; Jenkinson et al., 1995) was obtained from the Schild plot according to Arunlakshana and Schild (1959). For non-competitive antagonist, the equilibrium dissociation constant (K_B) was determined according to Kenakin (1993). In practice, a double-reciprocal plot of equieffective concentration of agonist (A) in the absence (1/A) and in presence (1/A′) of the antagonist (B) was constructed and pK_B was derived from the equation $pK_B = \log_{10}$-[(slope-1)/B].

3. Results

3.1. Control experiments

In the majority of experiments FR 172357 was compared either with HOE 140 or with FR 173657: results

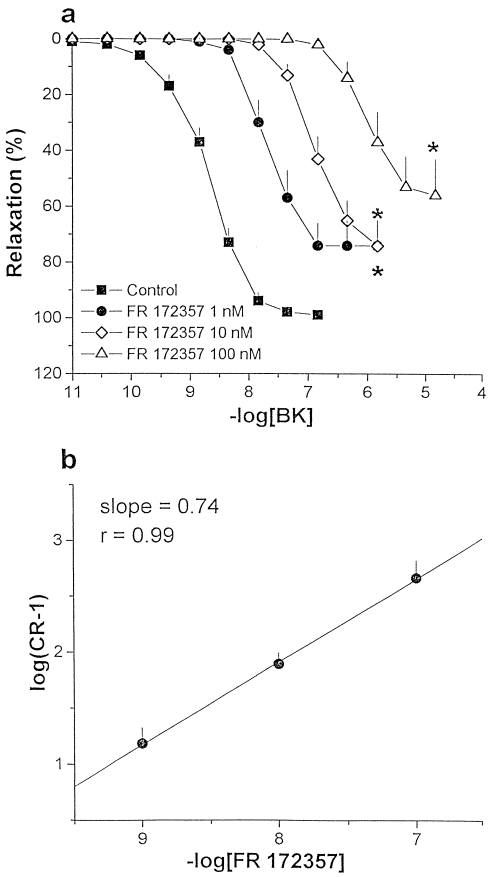

Fig. 3. (a) Concentration–response curves of bradykinin obtained in the pig coronary artery (E+), precontracted with U 46619 10 nM, in the absence (■ indicated as control) and in the presence of increasing concentrations of FR 172357 (● 1 nM; ◇ 10 nM; and △ 100 nM). * $p < 0.05$ vs. control, according to ANOVA followed by the Dunnett test for multiple comparison. (b) Schild plot of FR 172357 against bradykinin in pig coronary artery. Values are means ± S.E.M. of at least five experiments. Abscissa and ordinate for (a) and (b), as in Fig. 2. E+ (with endothelium).

(already known) obtained with these antagonists in the present study are identical with those previously published (Gobeil et al., 1996; Rizzi et al., 1997a) which are shown in Table 1.

3.2. Antagonistic potency of FR 172357

Concentration response curves, obtained with bradykinin, in the absence and in presence of increasing concentrations of FR 172357 in the three B_2-receptor systems are presented in Figs. 2–4. The antagonist (tested up to a concentration of 10 μM) is inactive (as a contractile or relaxing agent) in the three preparations (data not shown). The human umbilical vein responds to bradykinin with contractions that are initiated by a threshold concentration of 0.3–1 nM and reach the maximum of about 6 g at concentrations ranging from 100 to 1000 nM (Fig. 2a). The bradykinin apparent affinity, given as pEC_{50}, is 8.55, in accordance with Gobeil et al. (1996). The concentration–response curves of bradykinin, measured in the presence of FR 172357 (10,100 and 1000 nM), are displaced to the right in a concentration-dependent manner, maintain parallelism, and reach full maximal effect. The compound seems to act as competitive antagonist in this preparation. This is confirmed by the Schild plot (Fig. 2b), which is linear, showing a slope of 0.99, not significantly different from unity and correlation coefficient of 0.99. The extrapolated pA_2 value is 8.65.

FR 172357 acts as an antagonist also on the pig coronary artery. This preparation, stimulated by U 46619 10 nM, responds to bradykinin with a concentration dependent relaxation (Fig. 3a). The threshold concentration is 0.1–0.3 nM, while 100% of relaxation is obtained with 30–100 nM of bradykinin. In the pig coronary artery, the pEC_{50} value for bradykinin is 8.67. The concentration–response curves obtained in the presence of FR 172357 (1, 10 and 100 nM) are displaced to the right and the maximum effect is strongly depressed (about 50%), especially in the presence of high concentrations of the compound

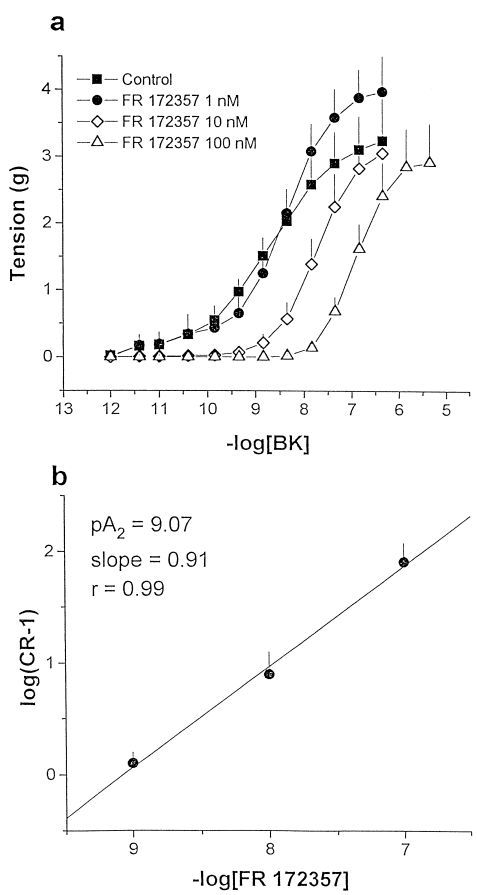

Fig. 4. (a) Concentration–response curves of bradykinin obtained in the rabbit jugular vein (E−) in the absence (■ indicated as control) and in the presence of increasing concentrations of FR 172357 (● 1 nM; ◇ 10 nM; and △ 100 nM). (b) Schild plot of FR 172357 measured against bradykinin in the rabbit jugular vein. Values are means ± S.E.M. of at least four experiments. Abscissa and ordinate for (a) and (b), as in Fig. 2. E− (as in Fig. 2).

Table 1
Apparent affinities of bradykinin and bradykinin B_2 receptor antagonists measured by bioassay in three isolated vessels of human, rabbit and pig origin as well as by receptor binding on plasma membranes of human umbilical vein smooth muscle [human umbilical vein treated with Lys-[Leu^8]-des-Arg^9-bradykinin (1 μM)]

	B_2 receptor systems						
	Human umbilical vein			Pig coronary artery		Rabbit jugular vein	
	Binding	Bioassay		Bioassay		Bioassay	
	pK_i	pEC_{50}	pA_2/*pK_B	pEC_{50}	pA_2/*pK_B	pEC_{50}	pA_2/*pK_B
Agonist							
Bradykinin	8.9[a]	8.5		8.7		8.6	
Antagonist							
HOE 140	9.8[a]		8.4[b]		*9.3[b]		9.2[b]
FR 173657	8.7[a]		8.2[b]		*9.2[b]		8.8[b]
FR 172357	8.6		8.6		*10.1		9.1

[a](Gessi et al., 1997).
[b](Rizzi et al., 1997b).

(i.e., 100 nM). This suggests that FR 172357 may act as a non-competitive antagonist in this preparation. This is supported by the Schild data (Fig. 3b) which yields a slope (0.74, $CL_{95\%}$ 0.12) significantly different from unity. Therefore, a pK_B value of 10.14 was determined according to Kenakin (1993).

On the rabbit jugular vein, bradykinin produces a concentration dependent contraction that reaches the maximum (about 3 g) at a concentration of 300 nM (Fig. 4a). The pEC_{50} value for bradykinin is 8.59 in accord with data published by Gaudreau et al. (1981). FR 172357 is effective in displacing to the right the concentration–response curve of bradykinin (Fig. 4a). The concentration–response curves measured in the presence of the antagonist (1, 10 and 100 nM) are quite parallel to the control concentration–response curve and reach the maximum. Schild regression derived from these data suggests that FR 172357 exerts an antagonism of competitive nature. The slope (0.91) of the Schild regression line although rather low, is not significantly different from unity, $CL_{95\%}$ 0.13 (Fig. 4b). The pA_2 value obtained by extrapolation from the Schild plot is 9.07.

Table 2
Specificity of FR 172357 action against various agents in human, rabbit, and pig preparations [human umbilical vein treated with Lys[Leu^8]-desArg^9-bradykinin (1 μM)]

Preparation	Agent	Control	FR 172357 (10 μM)
Human umbilical vein	Bradykinin (30 nM)	100±9	1±1*
	Noradrenaline (1000 nM)	100±8	81±15
	5-hydroxytyptamine (100 nM)	100±12	102±16
	Endothelin-1 (100 nM)	100±15	85±11
Rabbit jugular vein	Substance P (10 nM)	100±9	19±18*
	Angiotensin II (50 nM)	100±19	104±10
Pig coronary artery	Bradykinin (30 nM)	100±10	1±1*
	Adenosine (50 nM)	100±8	105±11
	Substance P (3 nM)	100±9	13±7*

* $p < 0.05$ vs. control according to Student's *t*-test for paired data.

The binding site labeled with [^{3}H]-bradykinin in human umbilical vein membranes has been characterized as a B_2 receptor in a previous study (Gessi et al., 1997). In this assay, FR 172357 competes with the binding of [^{3}H]-bradykinin, the displacement curve being parallel to that of bradykinin (data not shown). As shown in Table 1, a pK_i value of 8.6 has been obtained from these experiments ($n = 4$).

Moreover, the data obtained with FR 172357 in the present study are compared with data reported in literature for the B_2 receptor antagonists HOE 140 and FR 173657. As shown in Table 1, FR 172357 is as active as HOE 140 and FR 173657 as an antagonist of the B_2 receptor in man and rabbit, and is more potent in pig.

3.3. Specificity and selectivity of action of FR 172357

Specificity of the antagonism exerted by FR 172357 was established in the human umbilical vein by testing the new compound against several agents (see Table 2). Single concentrations of bradykinin (30 nM), noradrenaline (1000 nM), 5-hydroxytryptamine (100 nM), and endothelin-1 (100 nM) were tested in the absence and in the presence of FR 172357 (10 μM). The antagonist inhibits the contraction induced by bradykinin, without modifying the contractile effects of the other agents. Table 2 also shows data about the specificity of the antagonism exerted by FR 172357 in the rabbit jugular vein. Single concentrations of substance P (10 nM) and angiotensin II (50 nM) were tested in the absence and in presence of FR 172357 (10 μM). In this case, while the antagonist does not modify the contractile effects of angiotensin II, it significantly inhibits the contraction induced by substance P. Therefore, we performed complete concentration–response curve to substance P in the absence and in the presence of 1 and 10

μM FR 172357. This compound shifted to the right of the crc of substance P without modifying the maximal effect (data not shown). A pA_2 value of 6.46 ($CL_{95\%}$ 0.30, $n = 4$) and 6.04 ($CL_{95\%}$ 0.22, $n = 4$) was obtained from this series of experiments using 1 or 10 μM of FR 172357, respectively. Similar experiments performed on the pig coronary artery confirmed non-specificity of the antagonism exerted by FR 172357. In fact, when tested against substance P (NK_1 receptor) at various concentrations (0.1, 1.0 and 10 μM), FR 172357 showed antagonism with pA_2 values of 7.04, 6.53 and 6.62, respectively. On the contrary, at 10 μM FR 172357 was inactive against the relaxant effect of adenosine (pEC_{50} control = 5.08 ± 0.21; pEC_{50} treated = 5.15 ± 0.29).

In the rabbit aorta, human umbilical vein, and pig renal vein, FR 172357 was found to be inactive, up to 10 μM, on the contraction evoked by Lys-des-Arg^9-bradykinin. In the rabbit aorta, the pEC_{50} values for Lys-des-Arg^9-bradykinin as measured in the absence and in the presence of FR 172357 (10 μM) are 8.35 ± 0.31 and 8.02 ± 0.27, respectively. In the human umbilical vein pretreated with HOE 140 1 μM, the apparent affinity of Lys-des-Arg^9-bradykinin (control 8.09 ± 0.46) is not modified (7.95 ± 0.15) by the presence of FR 172357. In the pig renal vein the pEC_{50} values for Lys-des-Arg^9-bradykinin as measured in the absence and in the presence of FR 172357 (10 μM) are similar (7.82 ± 0.41 and 7.89 ± 0.06, respectively). This suggests that FR 172357 is selective for the bradykinin B_2 receptor.

4. Discussion

Chemical modifications of FR 173657 (as those made in FR 172357), directed to improve solubility and other pharmacokinetic features of the first non-peptide B_2 receptor antagonist (Asano et al., 1996; Inamura et al., 1997), appear to be well tolerated. In fact, FR 172357, the new compound investigated in the present study (a) acts as a pure antagonist of human, pig and rabbit B_2 receptor, similar to FR 173657 (Rizzi et al., 1997b), (b) shows high potency on the human receptor of the umbilical vein both in the binding and the functional assay, the pK_i (8.61) and pA_2 (8.65) values obtained with FR 172357 are very similar to those reported for FR 173657 (pK_i 8.71, Gessi et al., 1997; pA_2 8.22, Rizzi et al., 1997b), (c) both compounds act as competitive antagonists on human B_2 receptor, as indicated by the slope (not significantly different to unity) of the Schild plot obtained with FR 172357 in the present study and by the results reported for FR 173657 by Rizzi et al. (1997b), and (d) in other species, for instance, in the pig, FR 172357 behaves as a non-competitive antagonist. The apparent affinity of FR 172357 in this preparation evaluated in terms of pK_B is 10.14. This finding is similar to that reported before for FR 173657 (pK_B 9.2) (Rizzi et al., 1997b). High affinity values (pA_2 9.07) were obtained with FR 172357 also on the rabbit jugular vein, a preparation which has been extensively used in bradykinin B_2 receptor pharmacology (Regoli and Barabé, 1980; Gaudreau et al., 1981; Gobeil and Regoli, 1994; Gobeil et al., 1996). Schild plot slope estimated for FR 172357 in this tissue is 0.91, quite far (although not significantly different) from unity. Similarly high pA_2 values (see Table 1) were obtained by biological assay with FR 173657 (Rizzi et al., 1997b) in this preparation.

Differences of pA_2 values between species, as those described above, may not depend on the size or the chemical nature of the antagonist since they are similar to those reported for the peptide antagonist HOE 140 (see Table 1). They may, however, depend on the type and the duration of the antagonist interaction with the receptor because they are to be seen only with antagonists. As shown in Table 1, the pEC_{50} values of the agonist bradykinin are very similar in the three species. It is therefore proposed that compounds, such as HOE 140, possessing highly hydrophobic large residue (such as Tic and Oic), as well as non-peptide compounds containing large hydrophobic aromatic groups, may form strong slowly reversible binding with the bradykinin B_2 receptor and dissociate more slowly than bradykinin. The strength of the antagonist binding varies, however, from species to species and appears to be shorter in man than in the rabbit and even more in the pig. These features point again to differences in the receptor structures which are revealed by antagonists better than by the agonists (especially the naturally occurring agonists), as pointed out by Regoli et al. (1994) for the substance P/neurokinin-1 receptor system.

In contrast with FR 173657, FR 172357 does not show a full specificity as a B_2 kinin receptor antagonist since it interacts with the NK_1 receptor-system. Indeed, when applied at 1 μM in the rabbit jugular vein and even at 0.1 μM in the pig coronary artery, FR 172357 interferes with substance P induced contractions in the rabbit jugular vein (pA_2 6.04) and with the relaxant effect of substance P in the pig coronary artery (pA_2 7.04), two effects which are known to be mediated by the activation of NK_1 receptors (Rizzi, personal communication). The ratio of selectivity NK_1/B_2 is > 1000 in both tissues, thus reducing the possible impact of the interference of FR 172357 with the tachykinin system in physiological conditions.

It is concluded that FR 172357 is a potent, quite selective and specific bradykinin B_2 receptor antagonist with a pharmacological spectrum very similar to that of FR 173657 and may represent a good alternative to this compound for experimental and possibly clinical applications, because of same favorable pharmacocynetic properties.

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