ELSEVIER

European Journal of Pharmacology 388 (2000) 177–182

ejp

www.elsevier.nl/locate/ejphar

Characterization of bradykinin B_2 receptor antagonists in human and rat urinary bladder

Stefania Meini [a,*], Riccardo Patacchini [a], Sandro Giuliani [a], Massimo Lazzeri [b], Damiano Turini [b], Carlo Alberto Maggi [a], Alessandro Lecci [a]

[a] *Pharmacology Department, Menarini Ricerche, via Rismondo 12 A, 50135 Florence, Italy*
[b] *Urology Department, University of Ferrara, Ferrara, Italy*

Received 22 July 1999; received in revised form 2 December 1999; accepted 7 December 1999

Abstract

The effect of three selective bradykinin B_2 receptor antagonists, MEN11270 (*H*-DArg-Arg-Pro-Hyp-Gly-Thi-c(Dab-DTic-Oic-Arg)c(7γ–10α)), Icatibant (*H*-DArg-Arg-Pro-Hyp-Gly-Thi-Ser-DTic-Oic-Arg-OH), and FR173567 ((*E*)-3-(6-acetamido-3-pyridyl)-*N*-[*N*-[2,4-dichloro-3-[(2-methyl-8-quinolinyl) oxymethyl] phenyl]-*N*-methylaminocarbonylmethyl]acrylamide) was evaluated in the human and rat urinary bladder in vitro and in vivo in anaesthetized rats. Bradykinin evoked a concentration-dependent contraction of human ($pD_2 = 7.2$) and rat ($pD_2 = 7.7$) detrusor muscle strips. In human preparations, all the antagonists tested produced a rightward-shift in the concentration–response curve for bradykinin. Schild plot analysis yielded pK_B values of 8.4, 8.4 and 8.6 for MEN11270, Icatibant, and FR173567, respectively. In the rat preparations the three antagonists (at 100 nM concentration), produced a shift to the right which gave apparent pA_2 values of 8.2, 8.0 and 8.1 for MEN11270, Icatibant, and FR173567, respectively. In anaesthetized rats, both MEN11270 and Icatibant (1–10 nmol/kg i.v.) dose dependently reduced the bradykinin (100 nmol/kg i.v.)-induced urinary bladder contraction, their effect being prompt and long-lasting. In contrast, FR173567 (100 nmol/kg i.v.) produced a partial and short-lasting inhibition of bradykinin-induced bladder contractions. The present findings indicate that all the antagonists tested recognize with similar potencies the bradykinin B_2 receptors expressed in the detrusor muscle of both humans and rats. MEN11270 and Icatibant possess a higher potency and longer duration of action in vivo than FR173657, suggesting that the activity of this non-peptide antagonist in vivo is hampered by factors unrelated to its affinity for bradykinin B_2 receptors.

Keywords: Bradykinin B_2 receptor; Bradykinin receptor antagonist; Cystitis; MEN 11270; Urinary bladder, human; Urinary bladder, rat

1. Introduction

Kinins are small peptides (8–10 aminoacids) produced in either plasma or tissues during inflammatory processes by the proteolytic cleavage of larger precursors called kininogens (Bhoola et al., 1992). The biological effects of kinins are mediated by two different receptors, termed B_1 and B_2, which have both been cloned from various species, including humans, and shown to belong to the superfamily of G-protein-coupled receptors (Eggerickx et al., 1992; Hess et al., 1992; Menke et al., 1994).

The bradykinin B_2 receptor is constitutively expressed by various cell types, although both the level of expression and the functional consequences of its activation are modulated during inflammation (Lung et al., 1998; Schmidlin et al., 1998). On the other hand, the kinin B_1 receptor is expressed de novo after inflammatory stimuli or tissue injury (Marceau, 1998).

Kinins are believed to play an important role in urinary bladder inflammation and cystitis (Maggi, 1997). In fact, in addition to a local contractile effect on bladder smooth muscle (Maggi et al., 1989; Meini et al., 1998), kinins promote tissue extravasation of plasma proteins (Giuliani et al., 1993) and trigger reflex bladder contractions probably through a direct stimulation of bladder afferent nerves (Lecci et al., 1995). This triad of effects, which in the non-inflamed bladder are due to the activation of bradykinin B_2 receptors, basically reproduces the main symptoms of cystitis. The hypothesis that kinins generation in the bladder could be a pathophysiological mechanism for induction of the symptoms of cystitis (Maggi, 1997, for review) is

* Corresponding author. Tel.: +0039-55-5680-736; fax: +0039-55-5680-419.

0014-2999/00/$ - see front matter
PII: S0014-2999(99)00882-1

substantiated by the observation that Icatibant, a selective bradykinin B_2 receptor antagonist reduces both bladder hyperreflexia and plasma protein extravasation in models of chemically-induced cystitis (Giuliani et al., 1993; Maggi et al., 1993; Ahluwalia et al., 1994; Griesbacher, 1997; Jaggar et al., 1998). Moreover, high levels of kinins are found in the urine of patients with interstitial cystitis (Rosamilla et al., 1999) and the activity of the kinin-producing enzyme correlates with bladder pain symptoms and increase in voiding frequency during cystitis (Zuraw et al., 1994).

A few studies have investigated the contractile effect of bradykinin on the human isolated detrusor muscle (Andersson et al., 1992; Andersson, 1993, for review). No data have been presented until now regarding the affinity of any bradykinin B_2 receptor antagonist (Altamura et al., 1999, for recent review) in the human bladder smooth muscle, although this information could have great relevance for the planning of clinical studies aiming to explore the potential therapeutic role of these drugs in cystitis in humans.

Thus, in the present study we aimed at evaluating and comparing the effect of the novel peptide bradykinin B_2 receptor antagonist, MEN 11270 (*H*-DArg-Arg-Pro-Hyp-Gly-Thi-c(Dab-DTic-Oic-Arg)c(7γ–10α)) (Meini et al., 1999), with that of the parent compound, Icatibant (*H*-DArg-Arg-Pro-Hyp-Gly-Thi-Ser-DTic-Oic-Arg-OH) (Wirth et al., 1991), and of the non-peptide antagonist, FR173657 ((*E*)-3-(6-acetamido-3-pyridyl)-*N*-[*N*-[2,4-dichloro-3-[(2-methyl-8-quinolinyl) oxymethyl] phenyl]-*N*-methylaminocarbonylmethyl]acrylamide) (Asano et al., 1997), on bradykinin-induced responses in human and rat isolated urinary bladder. The potency and the duration of action of these antagonists were also investigated on bradykinin-induced contraction in urethane-anaesthetized rats.

2. Materials and methods

2.1. Organ bath studies

2.1.1. Human detrusor smooth muscle

Experiments, under authorization of the University of Ferrara Ethical Committee, were performed on mucosa-free muscle strips excised from the dome of the urinary bladder from 15 patients with a mean age of 57 (51–69) years, undergoing cystectomy because of carcinoma of the bladder base, as described previously (Maggi et al., 1988b). No patient had received radio- or chemotherapy before intervention. In all patients, preanesthetic medication was intramuscular atropine (1 mg) and diazepam (10 mg). Anesthesia was induced by sodium thiopental (500 mg i.v.) and maintained with N_2O/O_2 (1/2) and halothane (0.6–1%). The patients received pancuronium bromide (6 mg i.v.) during induction of anesthesia. All specimens appeared macroscopically normal without signs of tumor or inflammation. The tissues were placed in ice-cold Krebs' solution (composition mM: NaCl 119, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.5, NaH_2PO_4 1.2, $NaHCO_3$ 25 and glucose 11) within 2–3 min of surgical removal. The specimens were pinned flat on a Petri dish containing gassed (95% O_2, 5% CO_2) Krebs solution and the mucosa was carefully dissected out. Muscle strip preparations ($2 \times 2 \times 8$ mm) were transferred to organ baths (5 ml) and prepared for isotonic recording (load 10 mN) of mechanical activity (via Basile transducers) which was displayed on a Basile 7050 pen recorder.

After an equilibration period of 45 min, the preparations were repeatedly challenged with KCl (80 mM) to check their contractility until the responses were reproducible. The bath fluid was routinely changed every 15 min and replaced by fresh Krebs solution. Thereafter, a cumulative concentration–response curve for bradykinin (1 nM–10 μM) was obtained. At the end of each curve, a maximal contractile response was obtained by the addition of KCl (80 mM). Three cumulative concentration–response curves for bradykinin were reproducible, so that control and antagonist-treated responses were obtained from the same preparation.

An antagonist contact time of 15 min was used before commencing the concentration–response curve.

Peptidase inhibitors (thiorphan, bestatin and captopril, 1 μM each) were added 15 min prior to the determination of the agonist concentration–response curves.

2.1.2. Rat isolated urinary bladder

Experiments were performed with isolated urinary bladder from male albino rats of the Wistar strain (320–350 g). The animals were stunned and bled and the whole urinary bladder was removed and placed in gassed (95% O_2, 5% CO_2) Krebs' solution (composition as above). Four longitudinal strips of detrusor muscle were excised from each bladder. The strips were transferred to organ baths (5 ml) and prepared for isotonic recording (load 5 mN) of mechanical activity (as described above).

After an equilibration period of 45 min, the preparations were exposed to KCl (80 mM) to check their contractility, then after washout, a cumulative concentration–response curve for bradykinin (1 nM–10 μM) was made. At the end of the curve a maximal contractile response was obtained by the addition of KCl (80 mM). Bradykinin responses were evaluated in the absence or presence of bradykinin receptor antagonists on different strips from the same bladder, and studied in parallel.

An antagonist contact time of 15 min was used before commencing the agonist concentration–response curve.

Peptidase inhibitors (thiorphan, bestatin and captopril, 1 μM each) were added 15 min prior to the determination of the agonist concentration–response curves.

When selectivity studies with neurokinin A were performed, the same protocol was used, although concentration–response curves for the agonist in the absence and in

the presence of the antagonist were obtained from the same strip preparation (Maggi et al., 1988a).

2.2. In vivo experiments

Urethane (1.2 g/kg, s.c.)-anaesthetized Wistar male rats (350–400 g) were used for in vivo studies. The left jugular vein was cannulated for drug administration, a tracheal cannula was applied to facilitate respiration. After laparotomy, the ureters were tied, the pelvic ganglia were surgically ablated and a polyethylene catheter (PE 90, I.D. 0.86 mm, O.D. 1.27 mm) was inserted into and secured to the proximal urethra for the intravesical pressure recording as previously described (Lecci et al., 1995). Therefore, experiments were carried out under isovolumetric conditions in a decentralized urinary bladder, in order to avoid the triggering of reflex responses. The urinary bladder was filled with 0.5 ml of saline and the preparation was left to equilibrate for 1 h. Thereafter, bradykinin (100 nmol/kg i.v.) was administered 25 min before, and 5, 30, 60, 90, 120, 150 and 180 min after the antagonist or vehicle administration. MEN 11270 and Icatibant were dissolved in saline, FR173657 was dissolved in dimethylsulphoxide; all the antagonists or their corresponding vehicles were administered in a volume of 100 μl/kg. The effect of antagonists was evaluated with respect to their own time-matched vehicle group.

2.3. Analysis of data

Each value in the text is a mean ± S.E.M.

The agonist concentration producing 50% of the maximal response for that agonist was calculated as negative logarithm to base 10, and indicated as pD_2, and 95% confidence limits (C.L.) were calculated by non-linear regression of the concentration–response curves.

The nature of the interaction of antagonists with the kinin receptors in in vitro experiments was checked using Schild regression as follows: antagonist-induced parallel shifts of concentration–response curves for the agonist were calculated graphically for the half-maximal response as the ratio (concentration ratio, CR) of equieffective concentrations of agonist. Estimates of log [CR − 1] were plotted against log [antagonist concentration] (Arunlakshana and Schild, 1959). Antagonists yielding plots with linear regression lines and slopes not significantly different from unity were considered to act in a competitive manner. The affinity of competitive antagonists was expressed in terms of pK_B calculated from the equation: $pK_B = \log [CR - 1] - \log [\text{antagonist concentration}]$ (Kenakin, 1997).

One-way analysis of variance followed by Fisher's LSD test was used to compare concentration ratios or pK_B of antagonists.

Two-way analysis of variance followed by Fisher's least significant difference (LSD) test was used for the statistical evaluation of data from in vivo experiments; $P < 0.05$ was considered as significant.

Parallel control experiments, using only the vehicle, were carried out. For in vivo experiments the effect of test drugs was compared to changes observed in vehicle-treated animals. For in vitro experiments all drugs, at the concentrations tested, were dissolved in water which per se did not evoke any effect (data not shown).

2.4. Materials

Bradykinin and bestatin were obtained from Peninsula (Peninsula Laboratories Europe, Cheshire, UK). Thiorphan was from Bachem (Essex, UK), captopril from Sigma, (Dorset, UK). Neurokinin A was from Neosystem (Strasbourg, France). All salts used were purchased from Merck (Darmstadt, Germany). All bradykinin B_2 receptor antagonists used were synthesized at Menarini Ricerche (Florence, Italy). FR173657 was dissolved in dimethylsulfoxide up to 1 mM, whereas Icatibant and MEN 11270 were dissolved in distilled water at 10 mM. All compounds were stored at −25°C.

3. Results

3.1. In vitro experiments

In strips from the human detrusor muscle, bradykinin (1 nM–1 μM) produced a slowly developing concentration-dependent tonic contraction, yielding a pD_2 value of 7.2 (7.0–7.5, $n = 28$). The maximal effect averaged 66 ± 3% ($n = 28$) of that induced by KCl (80 mM).

The three antagonists tested, MEN 11270, Icatibant, and FR173657, were devoid of any agonist effect up to 300 nM concentration. On the other hand, MEN 11270, Icatibant, and FR173657 produced a concentration-dependent (30–300 nM) rightward shift of the concentration–response curve for bradykinin without inducing any depression of the maximal effect of the agonist (Fig. 1A, B, C). The slopes of the Schild plot were not different from unity for any of the compounds, resulting in −0.82 (−1.34; −0.30), −0.87 (−1.54; −0.20) and −0.99 (−1.49; −0.49) for MEN 11270, Icatibant, and FR173657, respectively (Fig. 1D, E, F). The pK_B values obtained from the Schild analysis were 8.4 ± 0.01 ($n = 18$), 8.4 ± 0.10 ($n = 16$) and 8.6 ± 0.08 ($n = 16$), for MEN 11270, Icatibant, and FR173657, respectively (Fig. 1D, E, F).

Bradykinin (1 nM–1 μM) produced a concentration-dependent contraction of detrusor strips from the rat urinary bladder, yielding a pD_2 of 7.4 (7.1–7.7, $n = 10$). The maximal contractile effect averaged 60 ± 3% ($n = 10$) of

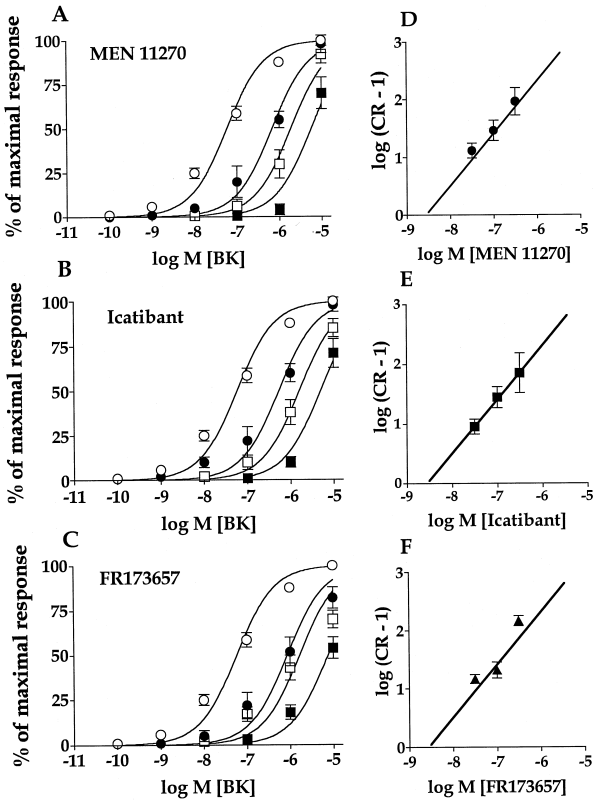

Fig. 1. Concentration–response curves for bradykinin in the human detrusor smooth muscle in the absence (○) and presence of 30 (●), 100 (□) and 300 nM (■) concentration of MEN 11270 (A), Icatibant (B) and FR173657 (C). Contact time of the antagonist was 15 min. (D,E,F) Schild plots of MEN 11270, Icatibant and FR173657, respectively, against bradykinin. Abscissa, log of the molar concentration of the antagonist. Ordinate, log of the concentration ratio − 1 (CR − 1) of the agonist. Values represent the means ± S.E.M. from four experiments.

the KCl (80 mM)-evoked contraction (Fig. 2). MEN 11270, Icatibant and FR173657 (all at 100 nM) induced a rightward shift of the concentration–response curve for bradykinin without depressing the maximal response which averaged 55 ± 4%, 64 ± 5% and 57 ± 4% of the KCl (80 mM)-induced response, in the presence of the stated concentration of each antagonist, respectively (Fig. 2).

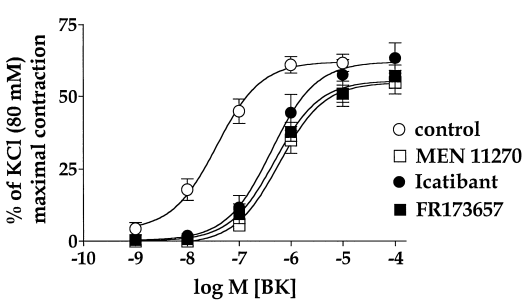

Fig. 2. Concentration–response curve for bradykinin in the rat isolated urinary bladder in the absence (○) or presence of MEN 11270 (□), Icatibant (●) and FR173657 (■). All antagonists were used at 100 nM concentration, and the contact time was 15 min. Values represent the means ± S.E.M. from five experiments.

From the rightward shifts of the concentration–response curves for bradykinin obtained in the presence of the three antagonists, concentration ratios of 16.1, 11.4 and 13.2 were calculated, for MEN 11270, Icatibant and FR173657, respectively. Assuming competitive antagonism, apparent pA_2 values of 8.2, 8.0 and 8.1 were calculated for MEN 11270, Icatibant, and FR173657, respectively.

The selectivity of MEN 11270, Icatibant and FR173657 (all at 100 nM) toward bradykinin B_2 receptors was tested against neurokinin A with rat urinary bladder. Neurokinin A (1 nM–1 μM) produced reproducible contractions of the rat detrusor muscle ($pD_2 = 8.3 \pm 0.08$, $n = 16$) through activation of tachykinin NK_2 receptors (Maggi et al., 1988a). Neither MEN 11270, nor Icatibant nor FR173657 (all at 100 nM) affected the curve for neurokinin A ($pD_2 = 8.0 \pm 0.1$; 8.1 ± 0.1 and 8.3 ± 0.1, respectively, $n = 4$ each), nor did they reduce the maximal effect.

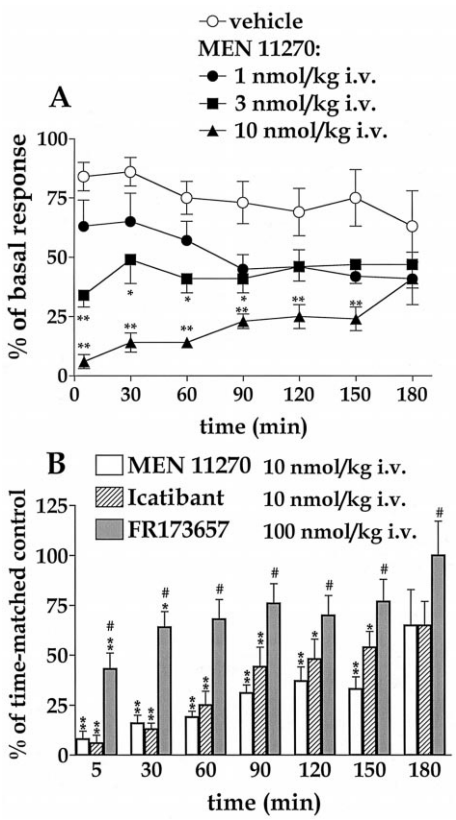

Fig. 3. Dose–response curve for MEN 11270 (1–10 nmol/kg i.v.) on bradykinin (100 nmol/kg i.v.)-induced bladder contractions (panel A). Comparison of the effects of MEN 11270 (10 nmol/kg i.v.), Icatibant (10 nmol/kg i.v.) and FR173657 (100 nmol/kg i.v.) on bradykinin (100 nmol/kg i.v.)-induced bladder contractions. Each value and bar represents the means ± S.E.M. from seven to eight experiments. Fisher's LSD test: $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. time-matched vehicle group; $\#P < 0.01$ vs. time-matched MEN11270 and Icatibant-treated group.

3.2. In vivo experiments

In animals with acute (1.5–2 h before) surgical ablation of the pelvic ganglia, bradykinin (100 nmol/kg i.v.) evoked a tonic-type bladder contraction having an amplitude of 8.5 ± 0.9 mmHg ($n = 22$). In vehicle-treated animals, the response to bradykinin remained relatively constant over a 180-min observation period (−32% vs. basal response at 180 min): time-matched and vehicle-treated controls were then used to evaluate the effect of bradykinin B_2 receptor antagonists on the response under study.

MEN 11270 (1–10 nmol/kg i.v.) dose dependently reduced the bradykinin-induced bladder contractions: statistically significant inhibitory effects lasting 60 min were observed at the dose of 3 nmol/kg; at the highest dose (10 nmol/kg) the inhibitory effect lasted up to 150 min from administration of MEN 11270 (Fig. 3A). The inhibitory effect of Icatibant (10 nmol/kg) against bradykinin-induced bladder contractions was comparable as to both intensity and time course of inhibition to that produced by an equimolar dose of MEN 11270 (10 nmol/kg) (Fig. 3B). At this dose level both MEN 11270 and Icatibant practically suppressed the contraction induced by bradykinin a short time (5 min) after antagonist administration (Fig. 3B). At this same dose level FR173657 was ineffective (data not shown); increasing the dose of the non-peptide antagonist 10-fold (100 nmol/kg) revealed a significant partial inhibitory effect (about 60% inhibition at 5 min from antagonist administration) which was short-lasting since no significant inhibition of the response to bradykinin was evident at 60 min from antagonist administration (Fig. 3B). As compared to the inhibitory effect produced by FR173657 (100 nmol/kg, Fig. 3B), MEN 11270, at a lower dose (3 nmol/kg, Fig. 3A) produced the same extent of inhibition at 5 min from its administration, whereas after 90 min an inhibitory effect could still be observed.

4. Discussion

The present results showed that the linear peptide, Icatibant, its cyclic derivative, MEN 11270, and the non-peptide FR173657 behave as competitive bradykinin B_2 receptor antagonists in the isolated human urinary bladder smooth muscle, and exhibit comparable affinities for the bradykinin B_2 receptors expressed in this preparation. These compounds have been shown to possess a high selectivity for bradykinin B_2 receptors in a number of preparations (Wirth et al., 1991; Asano et al., 1997; Meini et al., 1999, this study).

A major aim of this study was to determine the affinity of MEN 11270, Icatibant and FR173657 for bradykinin B_2 receptors expressed in the human detrusor smooth muscle to combine this information with data on their affinity and in vivo potency in animal models of cystitis: this type of information is essential in devising the dose levels of antagonists to be tested in humans in clinical studies for assessing a potential therapeutic effect of the drugs in cystitis.

In order to have a reference value for the apparent affinity for bradykinin B_2 receptors in the rat bladder, a few experiments were performed with this preparation: the results both indicate that the three compounds are equieffective as bradykinin B_2 receptor antagonists in this preparation and, assuming competitive antagonism, suggest that the affinity for bradykinin B_2 receptors in the rat urinary bladder is largely superimposable onto that measured in the human isolated detrusor muscle. Thus, although there is evidence for some species differences in the pharmacology of bradykinin B_2 receptor antagonists (Paquet et al., 1999), our data indicate that rat urinary bladder is a good model for predicting the potency of bradykinin B_2 receptor antagonists in the human urinary bladder smooth muscle.

Interestingly, when investigated in an in vivo setting, MEN 11270 and Icatibant were substantially superimposable for production of a potent and long-lasting blockade of bradykinin B_2 receptors in the rat urinary bladder. Notably, significant antagonism toward bradykinin-induced contraction was observed at doses of antagonists 10–30 fold lower than that of the agonist. The structural modifications introduced for the development of the linear peptide, Icatibant, produced a marked increase in the resistance of this compound to peptidases and these characteristics have been retained in MEN 11270. On the other hand, despite its non-peptide nature, and despite its good affinity for rat bradykinin B_2 receptors, FR173657 was decidedly less potent and long-lasting than MEN 11270 or Icatibant for blocking bradykinin B_2 receptors in the rat bladder in vivo. Much has been published regarding the in vivo pharmacology of this compound (Asano et al., 1997; Majima et al., 1997; Griesbacher et al., 1998; Hayashi and Majima, 1999; Watanabe et al., 1999): however the most of these data were obtained after oral administration of quite high doses of the antagonist (3–30 mg/kg in various models). To our knowledge no data have been presented until now with regard to intravenous administration of FR173657 and blocking bradykinin B_2 receptors in vivo. The reasons why FR173657 is, if compared to MEN 11270 and Icatibant, much less potent in vivo than expected on the basis of its affinity for bradykinin B_2 receptors in vitro cannot be ascertained at present. It is possible that differences in distribution and/or liver uptake and inactivation of this compound hampered its in vivo action.

In conclusion, the present data show that MEN 11270, Icatibant and FR173657 are potent bradykinin B_2 receptor antagonists in both rat and human bladder, but that only MEN 11270 and Icatibant retain favourable characteristics (duration and potency) in vivo. Therefore, the latter antagonists are likely candidates for exploring the role of kinins acting through bradykinin B_2 receptors in the pathophysiology of cystitis.

Acknowledgements

We wish to thank Ms. Carla Sezzatini for skillful technical assistance.

References

Ahluwalia, A., Maggi, C.A., Santicioli, P., Lecci, A., Giuliani, S., 1994. Characterization of the capsaicin-sensitive component of cyclophosphamide-induced inflammation in the rat urinary bladder. Br. J. Pharmacol. 111, 1017–1022.

Altamura, M., Meini, S., Quartara, L., Maggi, C.A., 1999. Nonpeptide antagonists for kinin receptors. Regul. Pept. 80, 13–26.

Andersson, K.-E., 1993. Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. Pharmacol. Rev. 45, 253–308.

Andersson, K.-E., Hedlund, H., Stahl, M., 1992. Contractions induced by angiotensin I, angiotensin II and bradykinin in isolated muscle from human detrusor. Acta Physiol. Scand. 145, 253–259.

Arunlakshana, O., Schild, H.O., 1959. Some quantitative uses of drug antagonists. Br. J. Pharmacol. Chemother. 14, 48–58.

Asano, M., Inamura, N., Hatori, C., Sawai, H., Fujiwara, T., Katayama, A., Kayakiri, H., Satoh, S., Abe, Y., Inoue, T., Sawada, Y., Nakahara, K., Oku, T., Okuhara, M., 1997. The identification of an orally active, nonpeptide bradykinin B2 receptor antagonist, FR173657. Br. J. Pharmacol. 120, 617–624.

Bhoola, K.D., Figueroa, C.D., Worthy, K., 1992. Bioregulation of kinins: kallikreins, kininogens, and kininases. Pharmacol. Rev. 44, 1–80.

Eggerickx, D., Raspe, E., Bertrand, D., Vassart, G., Parmentier, M., 1992. Molecular cloning, functional expression and pharmacological characterization of a human bradykinin B2 receptor gene. Biochem. Biophys. Res. Commun. 187, 1306–1313.

Giuliani, S., Santicioli, P., Lippe, I.Th., Lecci, A., Maggi, C.A., 1993. Effect of bradykinin and tachykinin receptor antagonist on xylene-induced cystitis in rats. J. Urol. 150, 1014–1017.

Griesbacher, T., 1997. Effects of the non-peptide bradykinin antagonist, FR173657, in experimental models of acute pancreatitis and cystitis in rats. Br. J. Pharmacol. 122, 352.

Griesbacher, T., Amann, R., Sametz, W., Diethart, S., Juan, H., 1998. The nonpeptide B_2 receptor antagonist FR173657: inhibition of effects of bradykinin related to its role in nociception. Br. J. Pharmacol. 124, 1328–1334.

Hayashi, I., Majima, M., 1999. Reduction of sodium deoxycholic acid-induced scratching behaviour by bradykinin B_2 receptor antagonists. Br. J. Pharmacol. 126, 197–204.

Hess, J.F., Borkowski, J.A., Young, G.S., Strader, C.D., Ransom, R.W., 1992. Cloning and pharmacological characterization of a human bradykinin (BK-2) receptor. Biochem. Biophys. Res. Commun. 184, 260–268.

Jaggar, S.I., Habib, S., Rice, A.S.C., 1998. The modulatory effects of bradykinin B_1 and B_2 receptor antagonists upon viscero-visceral hyper-reflexia in a rat model of visceral hyperalgesia. Pain 75, 169–176.

Kenakin, T.P., 1997. Competitive antagonism. In: In Pharmacologic Analysis of Drug–Receptor Interaction. 3rd edn. Lippincott-Raven Press Publishers, Philadelphia, PA, pp. 331–373.

Lecci, A., Giuliani, S., Meini, S., Maggi, C.A., 1995. Pharmacological analysis of the local and reflex responses to bradykinin on the rat urinary bladder motility in vivo. Br. J. Pharmacol. 114, 708–714.

Lung, C.-C., Jagels, M.A., Daffern, P.J., Tan, E.M., Zuraw, B.L., 1998. Induction of human B2 bradykinin receptor mRNA and membrane receptors by IFNγ. Immunopharmacology 39, 243–253.

Maggi, C.A., 1997. Bradykinin as an inflammatory mediator in the urinary tract. In: Farmer, S. (Ed.), The Kinin System. Academic Press, London, pp. 235–247.

Maggi, C.A., Parlani, M., Astolfi, M., Santicioli, P., Rovero, P., Abelli, L., Somma, V., Giuliani, S., Regoli, D., Patacchini, R., Meli, A., 1988a. Neurokinin receptors in the rat lower urinary tract. J. Pharmacol. Exp. Ther. 246, 308–315.

Maggi, C.A., Patacchini, R., Santicioli, P., Geppetti, P., Cecconi, R., Giuliani, S., Meli, A., 1989. Multiple mechanisms in the motor responses of the guinea-pig isolated urinary bladder. Br. J. Pharmacol. 98, 619–629.

Maggi, C.A., Santicioli, P., Del Bianco, E., Lecci, A., Giuliani, S., 1993. Evidence for the involvement of bradykinin in chemically-evoked cystitis in anaesthetized rats. Naunyn-Schmiedeberg's Arch. Pharmacol. 347, 432–437.

Maggi, C.A., Santicioli, P., Patacchini, R., Cellerini, M., Turini, D., Barbanti, G., Beneforti, D., Rovero, P., Meli, A., 1988b. Contractile response of the human isolated urinary bladder to neurokinins: involvement of NK2 receptors. Eur. J. Pharmacol. 145, 335–340.

Majima, M., Kawashima, N., Hiroshi, I., Katori, M., 1997. Effects of an orally active non-peptide bradykinin B2 receptor antagonist, FR173657, on plasma exudation in rat carrageenin-induced pleurisy. Br. J. Pharmacol. 121, 723–730.

Marceau, F., 1998. The B_1 receptors for kinins. Pharmacol. Rev. 50, 357–386.

Meini, S., Lecci, A., Cucchi, P., Catalioto, R.-M., Criscuoli, M., Maggi, C.A., 1998. Inflammation modifies the role of cyclooxygenases in the contractile responses of the rat detrusor smooth muscle to kinin agonists. J. Pharmacol. Exp. Ther. 287, 137–143.

Meini, S., Quartara, L., Rizzi, A., Patacchini, R., Cucchi, P., Giolitti, A., Calò, G., Regoli, D., Criscuoli, M., Maggi, C.A., 1999. MEN 11270, a novel selective constrained peptide antagonist with high affinity at the human B_2 kinin receptor. J. Pharmacol. Exp. Ther. 289, 1250–1256.

Menke, J.G., Borkowski, J.A., Bierilo, K.K., Macneil, T., Derrick, A.W., Schneck, K.A., Ransom, R.W., Strader, C.D., Linemeyer, D.L., Hess, J.F., 1994. Expression cloning of a human B1 bradykinin receptor. J. Biochem. Chem. 269, 21583–21586.

Paquet, J.-L., Luccarini, J.-M., Fouchet, C., Defrêne, E., Loillier, B., Robert, C., Bélichard, P., Cremers, B., Pruneau, D., 1999. Pharmacological characterization of the bradykinin B2 receptor: inter-species variability and dissociation between binding and functional responses. Br. J. Pharmacol. 126, 1083–1090.

Rosamilla, A., Clements, J.A., Dwyer, P.L., Kende, M., Campbell, D.J., 1999. Activation of the kallikrein kinin system in interstitial cystitis. J. Urol. 162, 129–134.

Schmidlin, F., Scherrer, D., Daeffler, L., Bertrand, C., Landry, Y., Gies, J.P., 1998. Interleukin-1β induces bradykinin B_2 receptor gene expression through a prostanoid cyclic AMP-dependent pathway in human bronchial smooth muscle cells. Mol. Phamacol. 53, 1009–1015.

Watanabe, M., Yoshihara, S., Abe, T., Oyama, M., Arisaka, O., 1999. Effects of the orally active non-peptide bradykinin B2 receptor antagonist, FR173657, on plasma extravasation in guinea pig airways. Eur. J. Pharmacol. 367, 373–378.

Wirth, K., Hock, F.J., Albus, U., Linz, W., Alpermann, H.G., Anagnastopulos, H., Henke, S., Breiphol, G., König, W., Knolle, J., Schölkens, B., 1991. Icatibant, a new potent and long-acting bradykinin antagonist: in vivo studies. Br. J. Pharmacol. 102, 774–777.

Zuraw, B.L., Sugimoto, S., Parsons, C.L., Hugli, T., Lotz, M., Koziol, J., 1994. Activation of urinary kallikrein in patients with interstitial cystitis. J. Urol. 152, 874–878.