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Effects of a nonpeptide bradykinin B_2 receptor antagonist, FR167344, on different *in vivo* animal models of inflammation

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1 The effects of a novel, potent and orally active nonpeptide bradykinin B_2 receptor antagonist, FR167344 (N-[N-[3-[(3-bromo-2-methylimidazo[1,2-a]pyridin-8-yl)oxymethyl]-2,4-dichlorophenyl]-N-methylaminocarbonylmethyl]-4-(dimethylaminocarbonyl) cinnamylamide hydrochloride) were tested in three different *in vivo* models of inflammation.

2 Oral administration of FR167344 inhibited carrageenin-induced paw oedema in rats (carrageenin: 1%, 0.1 ml per animal, intraplantar), with an ID_{50} of 2.7 mg kg^{-1} at 2 h after carrageenin injection ($n=10$ or 11).

3 Oral administration of the compound also inhibited kaolin-induced writhing (kaolin: 250 mg kg^{-1}, i.p.) in mice, with ID_{50} of 2.8 mg kg^{-1} in 10 min writhing and 4.2 mg kg^{-1} in 15 min writhing ($n=19$ or 20).

4 Additionally, oral administration of FR167344 inhibited caerulein-induced pancreatic oedema with an ID_{50} of 13.8 mg kg^{-1} as well as increases in amylase and lipase of blood samples with ID_{50} of 10.3 and 7.4 mg kg^{-1}, respectively, in rats ($n=10$).

5 These results show that FR167344 is an orally active, anti-inflammatory and anti-nociceptive agent in carrageenin-induced paw oedema, kaolin-induced writhing and caerulein-induced pancreatitis. FR167344 may have therapeutic potential against inflammatory diseases by oral administration and it may be a useful tool for studying the involvement of B_2 receptors in various *in vivo* models of inflammation.

Keywords: Bradykinin; antagonist; B_2 receptor; nonpeptide; orally active; FR167344; oedema; pain; pancreatitis

Introduction

Bradykinin, an endogenous nonapeptide produced by kallikrein, elicits various biological effects including oedema, pain, inflammation and hypotension (Burch *et al*., 1990; Bhoola *et al*., 1992). It thus seems that bradykinin could be involved in such inflammatory diseases as asthma, rhinitis, arthritis and pancreatitis (Bhoola *et al*., 1992; Hall, 1992). Two subtypes of bradykinin receptor, designated B_1 and B_2, have been identified by molecular cloning and pharmacological means (Regoli & Barabé, 1980; Hess *et al*., 1992; Menke *et al*., 1994). To investigate the pathophysiological role of bradykinin, many bradykinin receptor antagonists (mainly B_2 receptor antagonists) have been synthesized (Burch *et al*., 1990; Stewart, 1995). Recently, 'second-generation' B_2 receptor antagonists including Hoe 140 (D-Arg-[Hyp^3, Thi^5, D-Tic^7, Oic^8]bradykinin) and S 16118 (p-guanidobenzoyl-[Hyp^3, Thi^5, D-Tic^7, Oic^8]bradykinin) have been obtained. They are highly potent and long-acting against bradykinin-induced responses and can be used to inhibit inflammation *in vivo* (Hock *et al*., 1991; Wirth *et al*., 1991b; Cheronis *et al*., 1992; Félétou *et al*., 1995b). Hoe 140 and S 16118 showed inhibitory effects on various animal models, such as carrageenin-induced paw oedema, caerulein-induced pancreatitis and bronchial microvascular leakage (Wirth *et al*., 1991b; Griesbacher & Lembeck, 1992; Bertrand *et al*., 1993; Félétou *et al*., 1995a). These observations indicate the involvement of bradykinin in inflammatory reactions. However, these antagonists are all peptide analogues of limited therapeutic use owing to their poor oral bioavailability. Recently, a nonpeptide bradykinin B_2 receptor antagonists, WIN 64338 ([[4-[[2-[[bis(cyclohexylamino)methylene]amino]-3-(2-naphthyl)-1-oxopropyl]amino]phenyl]methyl]tributylphosphonium-chloride monohydrochloride), has been described (Sawutz *et al*., 1994; Hall *et al*., 1995), but this antagonist has not been shown to be orally active.

We have previously described a novel, potent, selective, orally active and long acting nonpeptide bradykinin B_2 receptor antagonist, FR167344 (N-[N-[3-[(3-bromo-2-methylimidazo[1,2-a]pyridin-8-yl)oxymethyl]-2,4-dichlorophenyl]-N-methylaminocarbonylmethyl]-4-(dimethylaminocarbonyl)cinnamylamide hydrochloride; Figure 1) (Aramori *et al*., 1997; Inamura *et al*., 1997). FR167344 antagonized [^{3}H]-bradykinin binding to B_2 receptors in guinea-pigs, rats and man with IC_{50} values of 6.6×10^{-10}, 1.2×10^{-9} and 1.3×10^{-8} M, respectively. However, it had no effect on [^{3}H]-[des-arg^{10}]-kallidin (a high-affinity bradykinin B_1 receptor ligand) binding to B_1 receptors even at 10^{-5} M (Inamura *et al*., 1997). Moreover this compound potently antagonized bradykinin-induced contractions with a pA_2 value of 9.3 in guinea-pig isolated ileum, but it did not inhibit [des-Arg^9]-bradykinin-induced rabbit aorta contractions (mediated by B_1 receptors) or acetylcholine or histamine-induced guinea-pig ileum contractions even at 10^{-6} M (Inamura *et al*., 1997). *In vivo*, oral administration of FR167344 inhibited bradykinin-induced bronchoconstriction in guinea-pigs and the bradykinin-induced hypotensive response in rats at a dose of 1 mg kg^{-1} (Inamura *et al*., 1997). Furthermore, FR167344 is highly B_2 selective not only *in vitro* but also *in vivo* and, unlike some peptide B_2-receptor antagonists, it is not converted into a B_1 antagonistic compound by peptidases such as carboxypeptidases which can convert peptidic B_2 receptor antagonists into B_1-receptor selective [des-Arg^9]-BK-forms (Drapeau *et al*., 1991; Wirth *et al*., 1991a).

The purpose of this study was to show that FR167344 is an orally active, anti-inflammatory and anti-nociceptive agent in carrageenin-induced paw oedema, kaolin-induced writhing and caerulein-induced pancreatitis, and to confirm the involvement of B_2 receptors in these models.

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Methods

Carrageenin-induced paw oedema

The carrageenin-induced paw oedema model was performed by the method previously described (Winter *et al*., 1962). Male Sprague-Dawley rats (8 weeks old, from Clea Japan, Inc.) were deprived of food overnight and treated orally with FR167344, 15 min before carrageenin was injected into the right hind paw intraplantar. Paw volume was measured by water plethysmometer before and 1, 2, 3 and 4 h after the injection of carrageenin. FR167344 was dissolved in 0.05 N HCl and administered orally at a volume of 5 ml kg^{-1}. Carrageenin was made up as 1% solution in saline. Each rat received 0.1 ml of the irritant. As saline-control, saline was administered in the same manner as carrageenin.

Kaolin-induced writhing

Male ICR mice (Slc:ICR, 5 weeks old, from Japan SLC, Inc.) were fasted overnight and used. Writhing responses were induced by an intraperitoneal injection of kaolin (250 mg kg^{-1}, 50 ml kg^{-1}). The responses were counted over a 10 or 15 min period by a trained observer. FR167344 dissolved in 0.05 N HCl or vehicle (10 ml kg^{-1}) was administered orally 30 min before the intraperitoneal injection of kaolin. As saline-control, saline was administered in the same manner as kaolin.

Caerulein-induced pancreatitis

Pancreatitis was induced according to the method previously described (Shimizu *et al*., 1993) with minor modifications. Female Sprague-Dawley rats (9–10 weeks old, from Clea Japan, Inc.) were used. After the rats has been deprived of food for 18 h, caerulein (20 μg kg^{-1}) was injected intraperitoneally four times at hourly intervals over a 3 h period. Saline-injected (i.p.) animals served as saline-control. FR167344 dissolved in 0.05 N HCl or vehicle (5 ml kg^{-1}) was administered orally 30 min before the first caerulein injection. Three hours after the last caerulein injection, a blood sample was taken from the abdominal artery with heparin under anaesthesia (diethyl-ether inhalation), and the animals were killed by exsanguination, the pancreas was taken and weighed and the plasma was removed by centrifugation. Amylase and lipase levels were determined by the modified 4-nitrophenylmaltoheptaoside method (Denka Seiken Co., Ltd., Tokyo, Japan) (Dupuy *et al*., 1987) and the monoglyceridelipase method (Nippon Shoji Co., Ltd., Osaka, Japan), respectively. Both enzyme assays were performed by use of an automatic analyser (model TBA-20R, Toshiba Co., Tokyo, Japan).

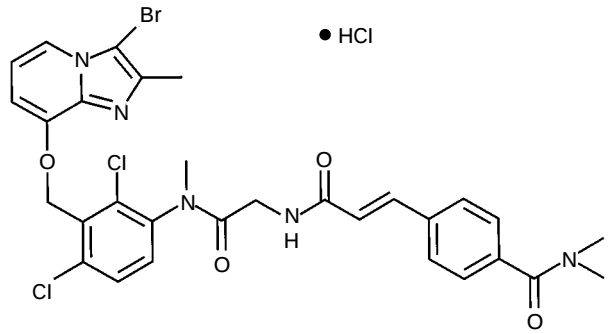

Figure 1 Structure of FR167344: N-[N-[3-[(3-bromo-2-methylimidazo[1,2-a]pyridin-8-yl)oxymethyl]-2,4-dichlorophenyl]-N-methylaminocarbonylmethyl]-4-(dimethylaminocarbonyl) cinnamylamide hydrochloride.

Materials

FR167344 was chemically synthesized in Fujisawa Pharmaceutical Co., Ltd. (Osaka, Japan). Carrageenin was purchased from Sigma Chemical Co. (St. Louis, U.S.A.). Kaolin was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Caerulein was purchased from Kyowa Hakko Kogyo Co., Ltd. (Tokyo, Japan).

Statistical analysis

The results are expressed as the mean ± s.e.mean and the statistical significance of differences between groups was analysed by one way analysis of variance (ANOVA) followed by Dunnett's multiple comparisons test. ID_{50} was obtained by using the non-linear curve fitting methods with an in-house computer programme.

Results

Carrageenin-induced paw oedema

An intraplantar injection of carrageenin (1%, 0.1 ml per animal) caused time-dependent paw oedema in the rat (Figure 2), although intraplantar injection of 0.1 ml saline caused almost no swelling (data not shown). In carrageenin-induced paw oedema in rats, oral administration of FR167344 inhibited paw swelling dose-dependently at 1, 2, 3 and 4 h after carrageenin injection (Figure 2). The ID_{50} of FR167344 was 2.7 mg kg^{-1} at the 2 h time point.

Kaolin-induced writhing

An intraperitoneal injection of kaolin (250 mg kg^{-1}, 50 ml kg^{-1}) caused time-dependent writhing in mice (Figure 3), although an intraperitoneal injection of saline (50 ml kg^{-1}) did not cause writhing (data not shown). Oral administration of FR167344 inhibited the kaolin-induced writhing response dose-dependently during 10 or 15 min after kaolin injection in mice (Figure 3). The ID_{50} values were 2.8 mg kg^{-1} in 10 min writhing and 4.2 mg kg^{-1} in 15 min writhing.

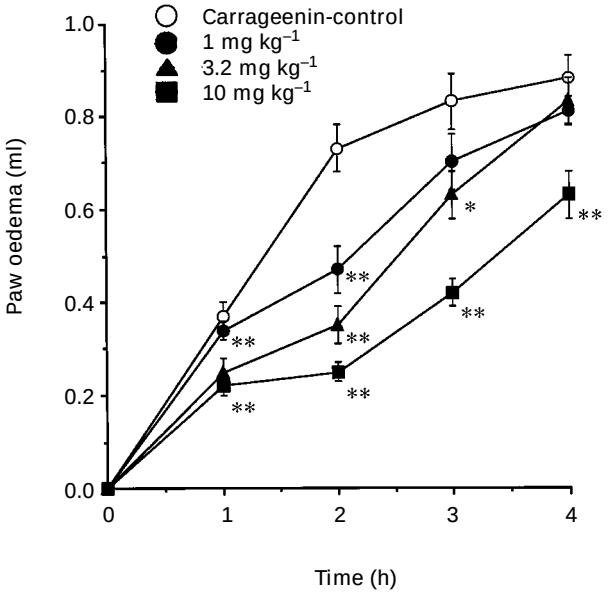

Figure 2 Inhibition of carrageenin-induced paw oedema by oral administration of FR167344 (1 mg kg^{-1}–10 mg kg^{-1}) in rats. Data are expressed as mean and vertical lines show s.e.mean ($n = 10$ or 11). $^*P < 0.05$, $^{**}P < 0.01$ vs control (Dunnett's test).

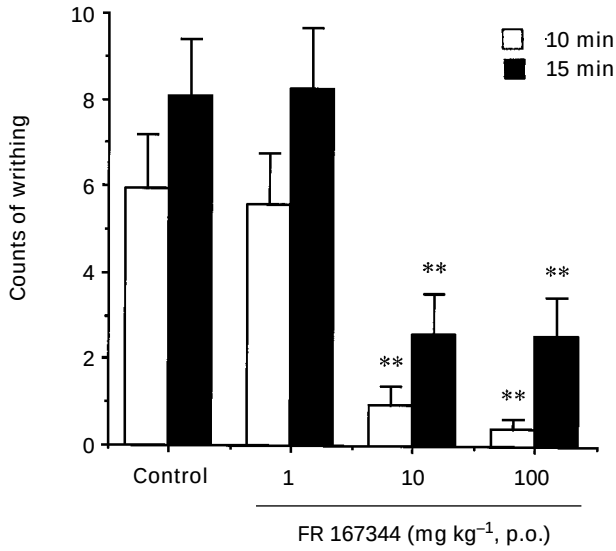

Figure 3 Inhibition of kaolin-induced writhing response by oral administration of FR167344 in mice. Data are expressed as mean and vertical lines show s.e.mean ($n=19$ or 20). Open columns and solid columns show counts of writhing in 10 min period and 15 min period after kaolin injection, respectively. $^{**}P<0.01$ vs control (Dunnett's test).

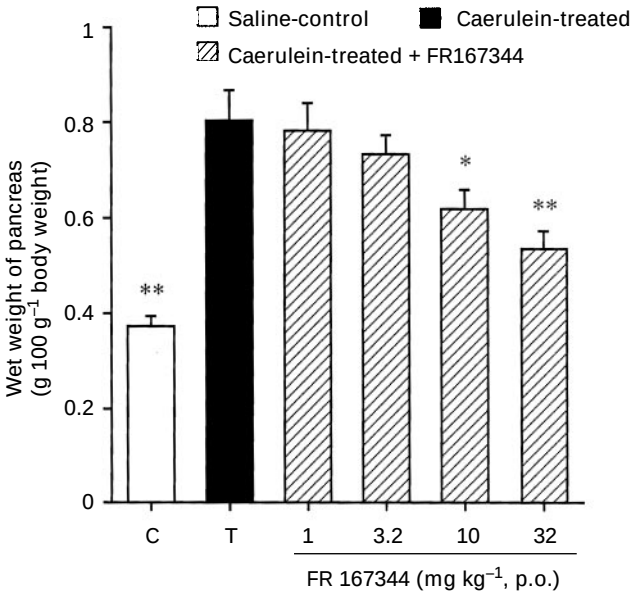

Figure 4 Inhibition of caerulein-induced pancreatic oedema by oral administration of FR167344 in rats. Data are expressed as mean and vertical lines show s.e.mean ($n=10$). $^{*}P<0.05$, $^{**}P<0.01$ vs caerulein-control (Dunnett's test).

Caerulein-induced pancreatitis

Oral administration of FR167344 inhibited caerulein-induced pancreatic oedema with an ID_{50} of 13.8 mg kg^{-1} (Figure 4). It also inhibited the increases in amylase and lipase of blood samples, and the ID_{50} estimates were 10.3 mg kg^{-1} and 7.4 mg kg^{-1}, respectively (Figure 5).

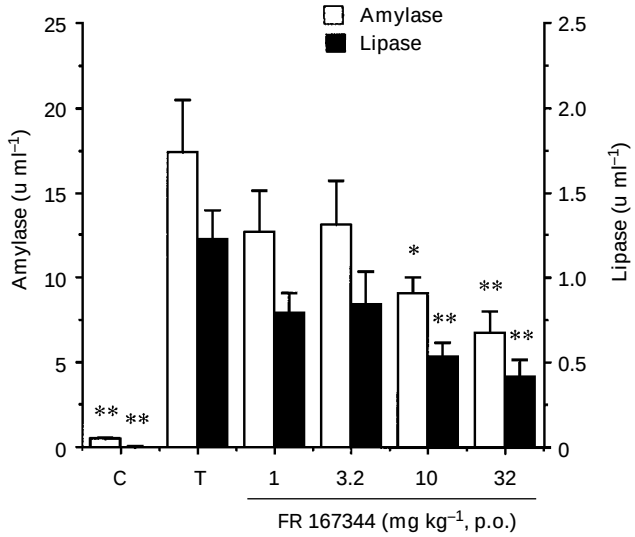

Figure 5 Inhibition of increase in amylase and lipase of blood samples by oral administration of FR167344 in caerulein-induced pancreatitis model. Data are expressed as mean and vertical lines shown s.e.mean ($n=10$). C and T show values in saline-control and caerulein-treated animals, respectively. $^{*}P<0.05$, $^{**}P<0.01$ vs caerulein-treated (Dunnett's test).

Discussion

In our investigation of the pathophysiological role of bradykinin and the development of drugs for inflammatory diseases, we have obtained the orally active nonpeptide bradykinin B_2 receptor antagonist, FR167344 (Inamura *et al*., 1997) and FR173657 (Asano *et al*., 1997) by optimization of a lead compound discovered by random screening. The present study demonstrates that oral administration of FR167344 inhibits carrageenin-induced paw oedema in rats, kaolin-induced writhing in mice, and caerulein-induced pancreatitis in rats. Our findings indicate that FR167344 may have therapeutic potential against inflammatory diseases by oral administration and that it may be a useful tool for studying the involvement of B_2 receptors in various *in vivo* models of inflammation.

Most biological actions of bradykinin are thought to be mediated by B_2 receptors (Burch *et al*., 1990; Bhoola *et al*., 1992). However, the active carboxypeptidase metabolites of bradykinin and kallidin, [des-Arg^9]bradykinin and [des-Arg^{10}]kallidin, preferentially stimulate B_1 receptors, which are generally absent in normal tissues, but inducible and functionally expressed in response to interleukin-1β (deBlois *et al*., 1991), bacterial lipopolysaccharides (Regoli *et al*., 1981), *in vitro* tissue incubation (Regoli & Barabé, 1980; Regoli *et al*., 1981) and *in vivo* arterial trauma (Pruneau *et al*., 1994). Although the importance of B_1 receptors remains to be fully established, B_1 receptors are clearly involved in persistent inflammatory hyperalgesia (Perkins *et al*., 1993; Perkins & Kelly, 1993) and other pathological conditions such as arthritis (Cruwys *et al*., 1994), septic shock and hypotension (Hall, 1992). FR 167344 is highly B_2 selective *in vitro* (Inamura *et al*., 1997), and it is not converted into a B_1 antagonistic compound by peptidases *in vivo*.

Previously, it has been shown that intravenous injection of B_2 receptor antagonists (Hoe 140, S 16118 and NPC 567 (D-Arg-[Hyp^3, D-Phe^7]bradykinin)) reduces carrageenin-induced paw oedema (Costello & Hargreaves, 1989; Wirth *et al*., 1991b; Félétou *et al*., 1995a). Inhibition of carrageenin-induced inflammation has been shown to be highly predictive of anti-inflammatory drug activity in human inflammatory diseases (Wirth *et al*., 1991b). Therefore, these B_2 receptor antagonists may have therapeutic potential against inflammatory diseases. Our data suggest that FR167344 may also have therapeutic potential against inflammatory diseases by oral administration. In the case of a chronic disease such as rheumatoid arthritis or asthma, oral activity of FR167344 would be of considerable merit in regard to patient's compliance with therapy. Our data also confirm that B_2 receptors (not B_1 re-

ceptors) play an important role in carrageenin-induced paw oedema. However, it has recently been shown that B_1 receptors are involved in intra-articular plasma extravasation in chronic antigen-induced arthritis (Cruwys *et al*., 1994), which suggests that B_1 receptor antagonists may also reduce joint swelling in inflammatory arthritis.

Oral administration of FR167344 inhibited kaolin-induced writhing response in mice. Kaolin activates the kallikrein system (Fujiyoshi *et al*., 1989) and induces the release of kinins (Fujiyoshi *et al*., 1990). Subcutaneous administration of a potent peptidic B_2 antagonist, Hoe 140 (Hock *et al*., 1991), also inhibits kaolin-induced writhing (Heapy *et al*., 1993). Our results and these findings confirm the involvement of bradykinin in kaolin-induced writhing and suggest that FR167344 may be an effective drug for treatment of inflammatory pain by oral administration. Although FR167344 produced an almost complete inhibition in 10 min writhing, it produced only partial inhibition in 15 min writhing, and a similar result was obtained with Hoe 140 (Heapy *et al*., 1993). These results indicate that bradykinin is a major mediator in the early phase of kaolin-induced writhing, but other mediators contribute to the late phase response. Compared with B_2 receptors, B_1 receptors do not seen to be involved in pain and hyperalgesia (Whalley *et al*., 1987; Mizumura *et al*., 1990), but it has recently been shown that the B_1 receptors are involved in chronic inflammatory hyperalgesia (Perkins *et al*., 1993; Perkins & Kelly, 1993). Potent B_1 receptor antagonists may therefore be useful for the relief of chronic pain.

Additionally, FR167344 inhibited caerulein-induced pancreatic oedema and the increases in amylase and lipase of blood samples in rats. Hyperstimulation of exocrine function of the pancreas by the cholecystokinin analogue, caerulein, causes pancreatic oedema and increases in serum amylase and lipase (Steer & Meldolesi, 1987; Griesbacher & Lembeck, 1992; Félétou *et al*., 1995a). This method is widely used for inducing morphological and biochemical changes in the pancreas similar to those observed in human oedematous pancreatitis (Willemer *et al*., 1990; Griesbacher & Lembeck, 1992). In this model, other B_2 receptor antagonists (Hoe, 140 and S 16118) also prevented pancreatic oedema (Griesbacher & Lembeck, 1992; Félétou *et al*., 1995a). Our results confirm that B_2 receptors are involved in the caerulein-induced pancreatic oedema. FR167344 also inhibited the caerulein-induced increases in amylase and lipase in blood. However, Hoe 140 augmented those in blood (Griesbacher & Lembeck, 1992) and inhibited those in the pancreas (Griesbacher *et al*., 1993). The cause of this discrepancy may be differences in the experimental conditions. Further investigations are required to elucidate the exact inhibitory mechanism of B_2 antagonists in the pancreatitis model.

In conclusion, this study shows that a nonpeptide B_2 receptor antagonist, FR167344, has inhibitory effects on some animal models of inflammation by oral administration. This compound would be not only a good tool for studying the pathophysiological role of B_2 receptors but also a useful oral treatment for inflammatory diseases.

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