ELSEVIER

European Journal of Pharmacology 298 (1996) 149–154

ejp

Role of bradykinin B_2 receptors and mast cells in the bradykinin-induced skin response in the rat

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Received 13 November 1995; accepted 17 November 1995

Abstract

We investigated the role of activation of bradykinin receptors and mast cells in the microvascular leakage of the vessels of the skin induced by the intracutaneous (i.c.) injection of bradykinin in the rat. We evaluated the effects of HOE140 (D-Arg-[Hyp^3,Thi^5,D-Tic^7,Oic^8]bradykinin), a bradykinin B_2 receptor antagonist, and ketotifen (4-(1-methyl-4-piperidylidene)4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10(9*H*)-one hydrogen fumarate), a histamine H_1 receptor antagonist with mast cell stabilizing properties, on the skin response. Evans blue dye extravasation served as an index of the increase in vascular permeability. Bradykinin (2–100 nmol/site i.c.) induced the extravasation of Evans blue dye in a dose-dependent manner. Ketotifen (20 mg/kg i.p.) significantly inhibited the leakage of dye induced by bradykinin (10 nmol/site i.c.) by 66.2%, while HOE140 (1 mg/kg i.v.) had no effect. The concomitant injection of HOE140 (0.2, 2 nmol/site) and bradykinin (10 nmol/site i.c.), also did not significantly reduce the extravasation of dye. We conclude that the extravasation of plasma induced by the i.c. injection of bradykinin is mediated mainly by stimulation of the skin mast cells, but not by bradykinin B_2 receptors.

Keywords: Bradykinin; HOE140; Ketotifen; Bradykinin receptor; Mast cell; Vascular permeability

1. Introduction

Such mammalian kinins as bradykinin and kallidin are potent vasoactive mediators. They are formed as cleavage products from the action of kallikrein-like enzymes on high and low molecular weight kininogens (Regoli and Barabé, 1980; Proud and Kaplan, 1988). The kinins induce wheal-and-flare responses when injected intracutaneously into humans (Crossman and Fuller, 1988; Wallengren and Håkanson, 1992; Polosa et al., 1993). The skin flare that follows allergen challenge may involve the activation of the kallikrein-kinin system (Warren et al., 1988). The kinins also increase vascular permeability in the skin of experimental animals (Becker et al., 1968; Whalley, 1987). The mechanism underlying these effects is not completely understood.

The effects of bradykinin may be mediated through the activation of at least two types of receptors, the bradykinin B_1 and B_2 receptors (Regoli and Barabé, 1980; Regoli et al., 1990). Bradykinin B_2 receptor antagonists block microvascular leakage in several organs of the rat including the trachea, duodenum and bladder, as well as the hypotensive responses induced by bradykinin administration (Griesbacher et al., 1989; Lembeck et al., 1991; Wirth et al., 1991). Thus, bradykinin appears to produce plasma extravasation and vasodilation leading to edema in the rat predominantly via the bradykinin B_2 receptors. However, there is no evidence for the role of bradykinin B_2 receptors in the vascular permeability of rat skin induced by bradykinin (Whalley et al., 1987). We have now evaluated the role of the bradykinin B_2 receptors in rat skin using a new selective bradykinin B_2 receptor antagonist, HOE140 (D-Arg-[Hyp^3,Thi^5,D-Tic^7,Oic^8]bradykinin) (Hock et al., 1991; Wirth et al., 1991).

Studies of isolated rat peritoneal mast cells (Johnson and Erdös, 1973; Lee and Pearce, 1990) have led to the idea that bradykinin induces the degranulation of mast cells in the skin of rats. Becker et al. (1968) showed that histamine H_1 antagonists such as mepyramine and chlorpheniramine can partially inhibit the local increase in vascular permeability induced by an intracutaneous injec-

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SSDI 0014-2999(95)00793-8

tion of bradykinin in the rat. However, there are some conflicting results on the inhibitory effect of histamine H_1 receptor antagonists (Janoff, 1966; Whalley, 1987). Accordingly, the involvement of mast cell stimulation in the skin response is presently unclear. In the present study, we also evaluated the effect of ketotifen (4-(1-methyl-4-piperidylidene)4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10(9*H*)-one hydrogen fumarate), a potent histamine H_1 receptor antagonist that stabilizes the mast cell (Martin and Römer, 1978), on the response induced by bradykinin in the skin of the rat.

2. Materials and methods

2.1. Animal preparation

Male, specific pathogen-free Wistar rats (250–300 g) that were purchased from Japan SLC (Hamamatsu, Japan) were used. They were anesthetized with pentobarbital (40 mg/kg i.p.) on the day after their dorsal skin was shaved. An adequate level of anesthesia, which was indicated by the disappearance of the corneal reflex and the withdrawal response to pinching the paw, was maintained by an additional injection of pentobarbital (30 mg/kg i.p.). The external jugular vein was cannulated with a polyethylene catheter filled with 0.9% saline for administration of intravenous drugs and solutions. Each animal was placed on a heated blanket (KN-474, Natsume, Tokyo, Japan) that maintained the rectal temperature at about 36.5°C.

2.2. Measurement of plasma extravasation

Vascular permeability in the skin was measured by quantifying the extravasation of Evans blue dye bound to plasma protein. Evans blue dye (20 mg/kg) was infused intravenously for a period of 1 min, and was immediately followed by the intracutaneous (i.c.) injection of bradykinin and its diluent. Thirty minutes later, animals were killed by exsanguination, and the dorsal skin was removed. Areas of skin that contained the entire blue area around the sites of injection were punched out as disks of approximately 20 mm in diameter. Evans blue dye was extracted in 5 ml of formamide at 40°C for 72 h. The amount of dye in the supernatants was measured by spectrophotometry (Model 450, BioRad Laboratories, Hercules, CA, USA) at a wavelength of 620 nm. The tissue content of Evans blue dye was calculated by interpolation on a standard curve of dye concentrations in the range of 0.3–100 μg/ml.

2.3. Protocol

2.3.1. Effect of different doses of bradykinin

The effect of different doses (2, 5, 10, 20, 50, 100 nmol/site) of i.c. bradykinin on microvascular leakage in the skin was evaluated in five animals. Immediately after the injection of Evans blue dye (20 mg/kg i.v.), each dose of bradykinin and its vehicle (0.9% saline) were administered i.c. in 100 μl volumes into seven areas marked on the shaved back skin of the animal in random order. The animals were killed 30 min later and the skin samples were collected as described.

2.3.2. Effect of HOE140 against bradykinin-induced skin response

2.3.2.1. Effect of intravenous HOE140. Animals were divided into two groups to study the effect of i.v. injection of HOE140 on the extravasation of plasma into the skin induced by the i.c. injection of bradykinin. A single dose (1 mg/kg) of HOE140 ($n = 6$) or its vehicle (0.9% saline, 0.5 ml/kg, $n = 5$) was injected i.v., followed in 15 min by an infusion of Evans blue dye (20 mg/kg i.v.). The i.c. injections of 100 μl of bradykinin (5, 10 nmol/site) and the diluent (0.9% saline) were allocated at random to three sites marked on the back of the animal. Animals were killed 30 min later to measure the extravasation of Evans blue dye as described.

We selected the dose of 1 mg/kg i.v. of HOE140 according to previous results (Wirth et al., 1991), in which doses ranging from 0.01 to 1 mg/kg i.v. inhibited the paw edema produced by carrageenan in rats. Preliminary study showed that this dose of HOE140 given alone did not significantly alter the mean systemic arterial blood pressure in the rat (data not shown).

2.3.2.2. Effect of i.c. HOE140. We have evaluated the effect of administering HOE140 concomitantly together with bradykinin on the microvascular leakage induced by bradykinin. Seven anesthetized animals were administered Evans blue dye (20 mg/kg i.v.) and then received a dose of 100 μl of 0.9% saline that contained bradykinin (10 nmol) and HOE140 (0.2, 2 nmol). The same volume of bradykinin solution (10 nmol) and its vehicle (0.9% saline) were injected i.c. into four marked sites on the back skin in random order. These areas of the skin were removed after 30 min of extravasation. Dye leakage was measured as described.

The two doses of i.c. HOE140 used in this study were chosen according to results of a preliminary test done to determine whether the i.c. injection of HOE140 alone would increase the vascular permeability of rat skin. The two doses (0.2, 2 nmol/site i.c.) of HOE140 had no significant effect on the extravasation of Evans blue dye in the skin (0.2 nmol/site: 12.7 ± 3.3 μg/site, $n = 6$; 2 nmol/site: 17.1 ± 4.1 μg/site, $n = 6$) as compared with sham control (9.3 ± 2.3 μg/site, $n = 6$). A dose of 20 nmol/site of HOE140 significantly induced the leakage of dye into the skin (26.7 ± 7.3 μg/site, $n = 6$; Williams' test).

2.3.3. Effect of ketotifen against bradykinin-induced skin response

The effect of ketotifen on the vascular permeability on the skin induced by the i.c. bradykinin was investigated in three groups of animals. The effect of ketotifen combined with HOE140 was also examined. Animals were pretreated with ketotifen at a dose of 5 mg/kg ($n = 6$) or 20 mg/kg ($n = 5$), or the vehicle (0.9% saline, 4 ml/kg i.p., $n = 7$), followed in 15 min by an injection of Evans blue dye (20 mg/kg i.v.). Immediately thereafter, 100 μl of bradykinin (10 nmol), its diluent (0.9% saline), and 0.9% saline containing bradykinin (10 nmol) and HOE140 (0.2, 2 nmol) were injected i.c. into four sites marked symmetrically on the right and left of the median line on the back. Animals were killed 30 min later, and the extravasation of dye into the skin was measured as described above.

2.4. Drugs

HOE140 was donated by Hoechst (Frankfurt, Germany), while ketotifen was donated by Sandoz Pharmaceuticals (Basle, Switzerland). Bradykinin and Evans blue dye were purchased from the Sigma Chemical Co. (St. Louis, MO, USA); formamide and sodium chloride from Katayama Chemical Industries (Osaka, Japan), and pentobarbital sodium from Abbott Laboratories (North Chicago, IL, USA). Small aliquots of bradykinin dissolved in 0.9% saline (1 mM) were stored at −80°C until used. Each aliquot was diluted in 0.9% saline to the specified concentration before use. Evans blue dye was dissolved in 0.9% saline and passed through a 5-μm filter (Millipore Products Division, Bedford, MA, USA).

2.5. Statistics

Values are expressed as the mean ± S.E.M. To evaluate the significance of the difference between two independent groups with equal variance, which was assessed with the F-test, we used the unpaired Student's t-test (two-tailed). When variance was unequal, we used the Mann-Whitney U-test (two-tailed). Williams' test was applied for multiple comparisons with control. A level of $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Effect of different doses of bradykinin

The i.c. injection of bradykinin produced a dose-dependent extravasation of Evans blue dye in rat skin (Fig. 1). Bradykinin injected i.c. at doses of 10 nmol or higher per site induced significant dye leakage. A dose of bradykinin of 50 nmol/site produced a maximal increase in the skin response, whereas a dose of bradykinin of 10 nmol/site submaximally increased the leakage of dye. We therefore used the latter dose of bradykinin in subsequent studies.

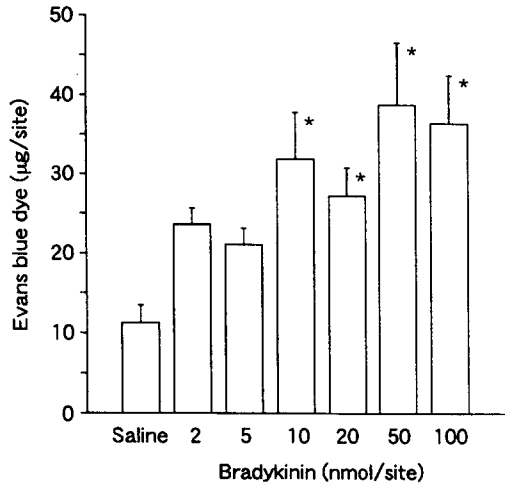

Fig. 1. Effect of different doses of bradykinin and its vehicle (0.9% saline) injected intracutaneously into the dorsal skin of rats on vascular permeability ($n = 5$). Extravasation of Evans blue dye was measured as an index of skin microvascular leakage. Results are expressed as means ± S.E.M. Statistical significance: * $P < 0.05$ compared with 0.9% saline-stimulated group (Williams' test).

3.2. Effect of HOE140 on bradykinin-induced skin response

Intravenous HOE140 had no effect on the leakage of Evans blue dye induced by two i.c. doses of bradykinin (5 or 10 nmol/site) (Fig. 2). The i.c. administration of HOE140 (0.2, 2 nmol/site) together with bradykinin (10 nmol/site) did not significantly inhibit the skin response induced by the single dose of bradykinin (Fig. 3).

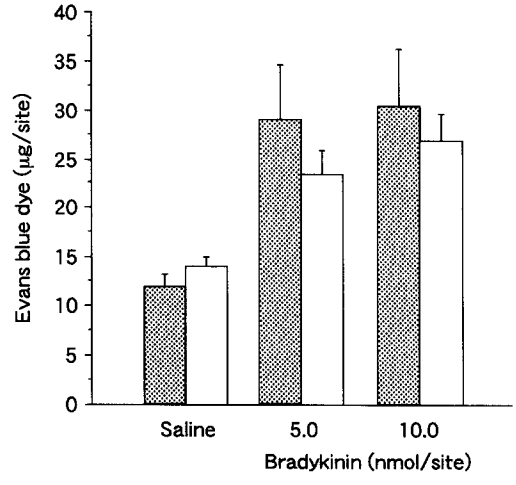

Fig. 2. Effect of i.v. HOE140 (1 mg/kg) on Evans blue dye extravasation into the rat skin induced by bradykinin (5, 10 nmol/site i.c.). HOE140 ($n = 6$, open columns) or its vehicle (0.9% saline, $n = 5$, shaded columns) was given intravenously 15 min before i.c. administration of bradykinin. 0.9% saline (100 μl/site i.c.) was given as sham stimulation. Results are expressed as means ± S.E.M. There was no significant difference in extravasation of Evans blue dye between the two groups pretreated with HOE140 or 0.9% saline (unpaired Student's t-test).

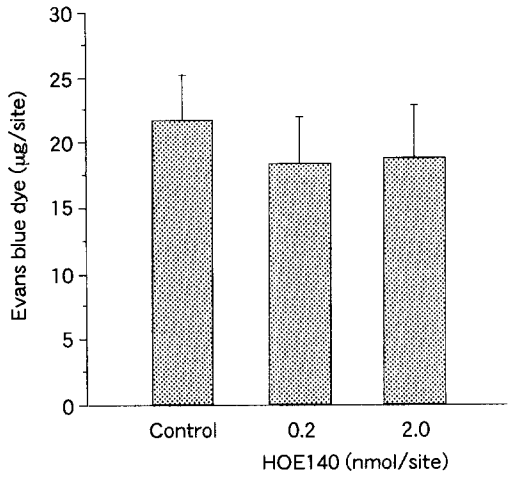

Fig. 3. Effect of two doses (0.2, 2 nmol/site) of HOE140, when injected intracutaneously with bradykinin, on skin microvascular leakage induced by bradykinin (10 nmol/site i.c.) in the rat ($n = 7$). Extravasation of Evans blue dye was measured as an index of skin microvascular leakage. The leakage of dye induced by i.c. bradykinin alone was used as control. Results are expressed as means ± S.E.M. HOE140 had no effect on the skin response at any dose used (Williams' test).

3.3. Effect of ketotifen on bradykinin-induced skin response

The doses of ketotifen of 5 and 20 mg/kg i.p. significantly suppressed the extravasation of Evans blue dye into the skin induced by the i.c. injection of 0.9% saline (5 mg/kg: 3.7 ± 1.0 μg/site; 20 mg/kg: 3.0 ± 1.0 μg/site vs. 9.3 ± 6.0 μg/site in control). The doses of ketotifen also inhibited the extravasation of dye induced by i.c. bradykinin (10 nmol/site) dose-dependently (Fig. 4). The higher dose of ketotifen significantly reduced the extravasation by 66.2%. The combined administration of ketotifen and HOE140 had no additive effect on the leakage of dye induced by bradykinin (Table 1).

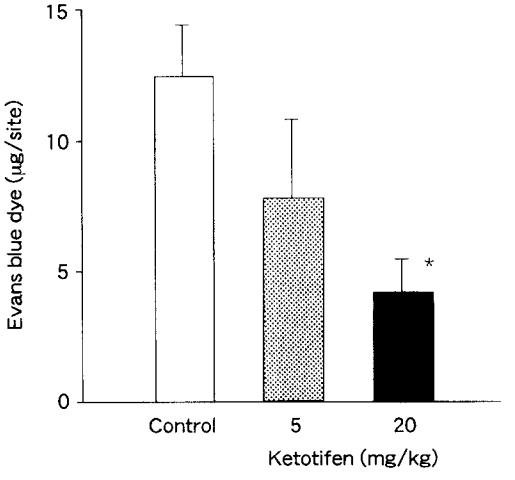

Fig. 4. Effect of ketotifen on the leakage of Evans blue dye induced by bradykinin (10 nmol/site i.c.) in the rat skin. Ketotifen at a dose of 5 mg/kg ($n = 6$) or 20 mg/kg ($n = 5$), or its vehicle (0.9% saline, 4 ml/kg, $n = 7$) were injected intraperitoneally 30 min before i.c. administration of bradykinin (10 nmol/site) and 0.9% saline (100 μl/site). All values have been corrected by subtracting the amount of dye leakage obtained following the i.c. injection of 0.9% saline alone. Results are expressed as means ± S.E.M. Statistical significance: * $P < 0.05$ compared with control group (Williams' test).

Table 1
Effect of the combined administration of HOE140 and ketotifen on extravasation of Evans blue dye induced by bradykinin (10 nmol/site i.c.) in rat skin

Ketotifen (mg/kg i.p.)	HOE140 (nmol/site i.c.)	n	Amount of Evans blue dye (mg/site)
5	0	6	7.7 ± 3.1
	0.2	6	6.7 ± 2.9
	2.0	6	6.3 ± 3.8
20	0	5	4.2 ± 1.3
	0.2	5	5.6 ± 2.1
	2.0	5	3.5 ± 1.0

Values have been corrected by subtracting the amount of dye leakage obtained following the i.c. injection of 0.9% saline alone. Values are means ± S.E.M. Pretreatment with a combination of HOE140 and ketotifen had no additive effect.

4. Discussion

We observed that the intracutaneous injection of bradykinin produced a dose-dependent increase in vascular permeability of rat skin. Ketotifen, which is a histamine H_1 receptor antagonist with a stabilizing effect on mast cells, significantly inhibited this response, whereas HOE140, a bradykinin B_2 receptor antagonist, had no effect. Thus, bradykinin increased the extravasation of plasma into the skin mainly via degranulation of the mast cells in skin, not by activating the bradykinin B_2 receptors.

The higher dose of ketotifen (20 mg/kg i.p.) inhibited the effect of i.c. bradykinin by 66.2%. Ketotifen, at doses above 20 mg/kg i.p. (e.g., 32 mg/kg i.p.), reportedly had no effect on the microvascular leakage into skin induced by i.c. platelet-activating factor in the rat (Achterrath-Tuckermann et al., 1988). Protein extravasation may depend in part on the blood flow in the skin (Brain and Williams, 1989). However, such a difference in the effect of ketotifen suggests that its inhibition of the action of bradykinin may not be based on a decrease in blood flow in the skin. In a preliminary study, ketotifen, 20 mg/kg i.p., given alone did not alter the blood pressure in rats. Our results agree with those of a previous study (Becker et al., 1968) which showed that the histamine H_1 receptor antagonists, mepyramine and chlorpheniramine, inhibit the extravasation of plasma in rat skin induced by bradykinin. However, Whalley (1987) showed that this response was not reduced by mepyramine at doses that abolish the histamine-induced increase in vascular permeability in rat skin. Disodium cromoglycate also had no effect on the

bradykinin-induced skin response (Bennett and West, 1980). Ketotifen is much more potent as an antianaphylactic agent than mepyramine or disodium cromoglycate (Martin and Römer, 1978; Martin and Baggiolini, 1981). This evidence helps to explain the discrepancy regarding the action of bradykinin on mast cells in the skin.

Previous studies with HOE140 (Wirth et al., 1991; Damas and Remacle-Volon, 1992) showed that doses of 0.01–1 mg/kg i.v. block the rat paw edema induced by carrageenan including the exudation of plasma, which indicates that bradykinin B_2 receptor mediation is involved in the plasma leakage from skin microvasculature caused by release of endogenous bradykinin. However, our results failed to find the action of bradykinin B_2 receptors on the vascular permeability of the skin induced by i.c. bradykinin in the rat. We did not evaluate the effect of higher doses of HOE140 to resolve the discrepancy, because weak agonist activity has been observed at doses of HOE140 above 1 mg/kg (e.g. 2.0 mg/kg) (Lembeck et al., 1991; our unpublished preliminary data).

In the present study, we evaluated the effect of HOE140 injected i.c. concomitantly with bradykinin to clarify the discrepancy between the effects of i.v. HOE140 on the responses of rat skin to exogenous and endogenous bradykinin. Higher concentrations of HOE140 may be achieved at the site of action of bradykinin by the concomitant i.c. injection with bradykinin rather than using the i.v. route. Unexpectedly, the i.c. HOE140 had no effect. A previous study (Whalley et al., 1987) showed that the administration of various bradykinin B_2 receptor antagonists administered i.c. in combination with bradykinin had no effect on the exudation of plasma induced by i.c. bradykinin in rats whereas those agents inhibited the skin response in rabbits, consistent with our findings. Doses of HOE140 above 20 nmol/site, administered i.c., significantly increased the vascular permeability of the skin as effectively as bradykinin B_2 receptor antagonists previously evaluated (Whalley, 1987). We therefore did not evaluate the effect of higher doses of the concomitant injection of HOE140 with bradykinin. As we did not investigate the role of bradykinin B_1 receptors in the bradykinin response, a minor contribution of bradykinin receptors cannot be excluded. The bradykinin B_1 receptor agonist, des-Arg^9-bradykinin, was previously shown to be relatively ineffective in increasing vascular permeability in rat skin (Whalley, 1987). In addition, the bradykinin B_1 receptor-antagonist, des-Arg^9-Leu^8-bradykinin, had no effect on the plasma extravasation induced in rat skin by bradykinin (Whalley, 1987). Thus, it is unlikely that bradykinin B_1 receptors play a key role in the response to bradykinin in rat skin.

Results of studies on isolated rat peritoneal mast cells (Johnson and Erdös, 1973; Devillier et al., 1989; Lee and Pearce, 1990) suggest that bradykinin may induce mast cell degranulation without binding to a specific bradykinin receptor. Our data indicate that bradykinin increases the vascular permeability of the skin mainly by a degranulation of the mast cells in skin. HOE140 had no effect on the bradykinin-induced exudation of plasma into skin, suggesting that the mast cells in the skin may be degranulated by bradykinin without involving the bradykinin B_2 receptors, as postulated previously.

Ketotifen did not completely abolish the vascular permeability induced by bradykinin in the skin, which suggests that other mechanisms that increase the skin response remain to be defined. Bradykinin has been shown to induce microvascular leakage in the airways, in part, via the release of tachykinins from sensory nerves (Lundberg and Saria, 1983; Qian et al., 1993). Tachykinins, including substance P and neurokinin A, induce vascular permeability in the rat skin (Couture and Kérouac, 1987). These observations suggest the possible involvement of sensory C-fibers in the vascular effect of bradykinin in the rat skin, as demonstrated in the mouse paw (Shibata et al., 1986). However, further investigation on this point is needed.

In conclusion, the i.c. injection of bradykinin increased the vascular permeability in rat skin, mainly by releasing vasoactive mediators such as histamine from the mast cells. Bradykinin B_2 receptors are unlikely to play an important role in the skin response.

Acknowledgements

We are grateful to Professor Kazuyoshi Watanabe of the Department of Pediatrics, Nagoya University School of Medicine (Nagoya, Japan) for his kind support. We thank Hoechst A.G. (Frankfurt, Germany) and Sandoz Pharmaceutical Ltd. (Basle, Switzerland) for their gifts of HOE140 and ketotifen, respectively.

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