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Participation of histamine H_1 and H_2 receptors in passive cutaneous anaphylaxis-induced scratching behavior in ICR mice

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Abstract

Scratching behavior associated with passive cutaneous anaphylaxis was examined and compared to that induced by compound 48/80 or histamine in ICR mice. Elicitation of passive cutaneous anaphylaxis, and intradermal injections of compound 48/80, histamine or serotonin induced both scratching behavior and vascular permeability increase in ICR mice. In mast cell-deficient WBB6F1-W/W^v mice, although histamine induced scratching behavior and vascular permeability increase, passive cutaneous anaphylaxis was not observed. Cetirizine and terfenadine significantly inhibited the scratching behavior and vascular permeability increase caused by passive cutaneous anaphylaxis, compound 48/80 and histamine. The histamine H_1 receptor antagonists inhibited the vascular permeability increase almost completely, whereas they failed to abolish the scratching behavior. Famotidine and ranitidine significantly inhibited the scratching behavior caused by histamine. The histamine H_2 receptor antagonists did not affect the vascular permeability increase caused by histamine. The combination of cetirizine and ranitidine abolished the histamine-induced scratching behavior. The combination, however, failed to potentiate the inhibition of passive cutaneous anaphylaxis-induced scratching behavior significantly. The results indicated that histamine induces scratching behavior in ICR mice through both histamine H_1 and H_2 receptors, and that histamine plays a major role in passive cutaneous anaphylaxis-induced scratching behavior. Histamine might also play an important role in compound 48/80-induced scratching behavior.

Keywords: Scratching behavior; Passive cutaneous anaphylaxis; Compound 48/80; Histamine; Histamine H_1 receptor; Histamine H_2 receptor; Cetirizine; Terfenadine; Famotidine; Ranitidine

1. Introduction

Itching is a sensation which causes a strong desire to scratch, and is one of the most important symptoms of inflammatory skin diseases including allergic dermatitis. Despite being an important symptom of skin diseases, however, it is poorly understood because of the difficulty of its quantitative evaluation. Therefore, no suitable animal model has been available, and no specific anti-itch drug has been developed (Bernhard, 1987; Greaves, 1992, 1993).

In 1995, Kuraishi et al. reported that scratching behavior in ddY mice caused by a rostral back injection with pruritogenic agents, compound 48/80 or substance P might be due to itch, but not to pain. They also indicated that histamine and algesiogenic agents, capsaicin and formalin do not cause significant scratching (Kuraishi et al., 1995). In agreement with their report, we observed scratching behavior associated with immunoglobulin E (IgE)-dependent, hapten-induced allergic cutaneous reaction in BALB/c mice, and confirmed that the IgE-mediated allergic cutaneous reaction actually induces scratching behavior in mice (Musoh et al., 1997). Prednisolone and naloxone inhibit the scratching behavior, but histamine H_1 receptor antagonists do not.

On the other hand, passive cutaneous anaphylaxis, another allergic cutaneous reaction, described by Ovary (1958a,b) is one of the most frequently used models for evaluating antiallergic drugs (Cox, 1967; Azuma et al., 1976; Church and Miller, 1978). In the immediate phase of passive cutaneous anaphylaxis, passively sensitized skin mast cells are activated by intravenously administered

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specific antigen, and release vasoactive mediators such as histamine, which cause a vascular permeability increase in the sensitized skin site.

In the present study, to study itching associated with allergic cutaneous reaction, attempts were made to observe and characterize the scratching behavior associated with passive cutaneous anaphylaxis in mice.

2. Materials and methods

2.1. Animals

Female ICR and WBB6F1-W/W^{v} mice, 8–10 weeks of age, obtained from Japan SLC (Hamamatsu, Japan) were used. Experiments were undertaken following the guidelines for the care and use of experimental animals from the Japanese Association for Laboratory Animal Science (1987).

2.2. Monoclonal IgE

Mouse monoclonal IgE against dinitrophenyl residue was prepared by culturing a cell line, EC1, as reported previously (Sakurai et al., 1994). The culture supernatant of EC1 was stored at −80°C and used as a source of IgE. The IgE content of the preparation, as estimated by enzyme-linked immunosorbent assay, was 1.5 μg/ml.

2.3. Antigen

Dinitrophenylated bovine serum albumin was prepared according to the method described by Eisen et al. (1953)

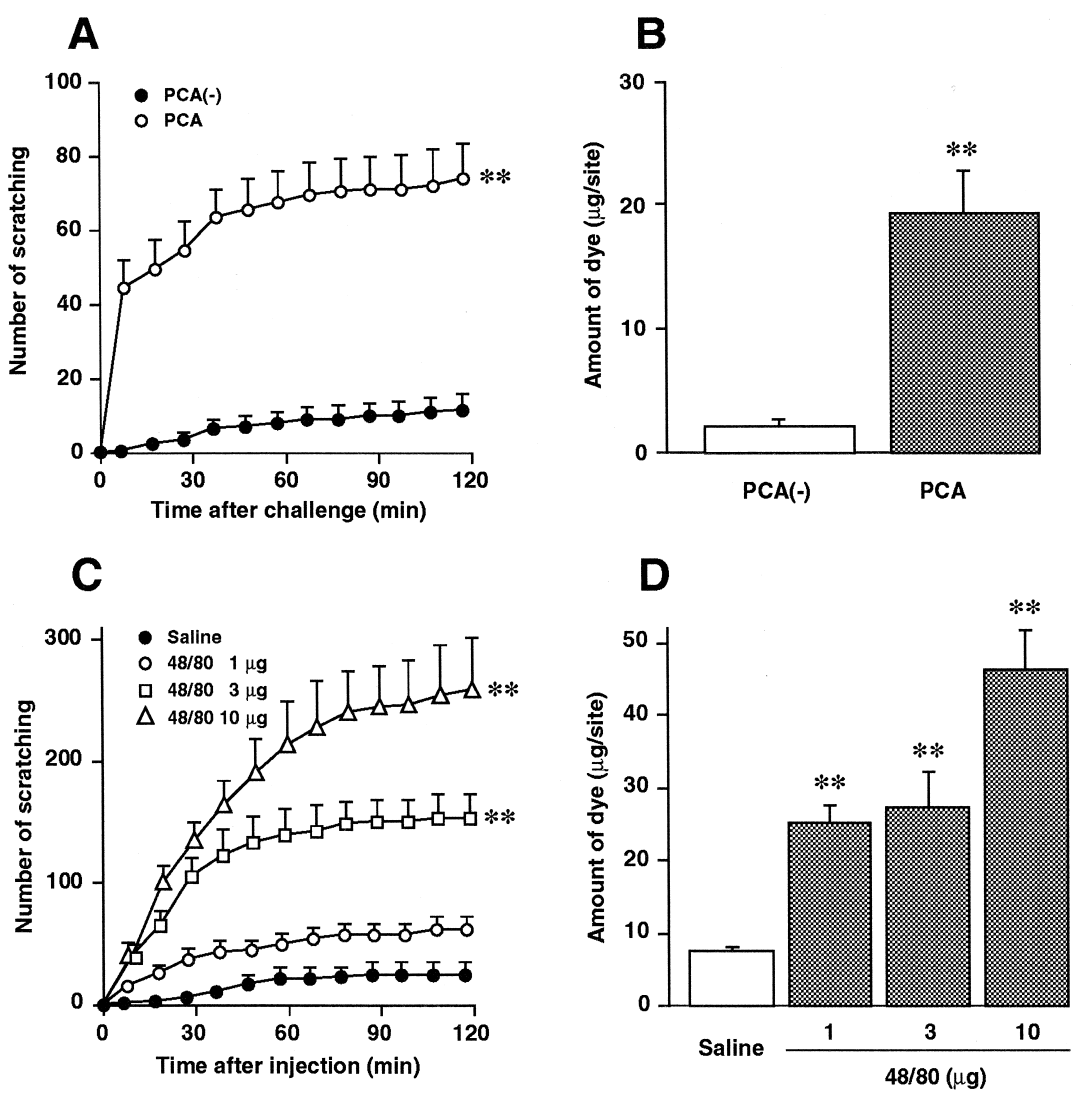

Fig. 1. Scratching behavior and vascular permeability increase associated with passive cutaneous anaphylaxis and compound 48/80 injection in ICR mice. (A) and (B): IgE was injected intradermally, and antigen was injected intravenously 24 h later. (C) and (D): compound 48/80 in doses of 1, 3 and 10 μg was injected intradermally. Each value represents the mean ± S.E.M. for 4–8 mice. Number of scratchings is indicated cumulatively and was statistically evaluated based on the total number for 120 min. PCA: passive cutaneous anaphylaxis, 48/80: compound 48/80, $^{**}P < 0.01$.

and used as an antigen. The average number of dinitrophenyl residues introduced to a bovine serum albumin molecule was 8.7.

2.4. Agents and reagents

Cetirizine (Hokuriku Seiyaku, Fukui, Japan), terfenadine (Sigma, St. Louis, MO, USA), famotidine (Yamanouchi Pharmaceutical, Tokyo, Japan) and ranitidine (hydrochloride, Sigma) were used. These agents were dissolved in saline and administered to mice intraperitoneally.

Compound 48/80 (Sigma), histamine (dihydrochloride, Nacarai Tesque, Kyoto, Japan) and serotonin (serotonin-creatinin sulfate, Merck, NJ, USA) were dissolved in saline and used for inducing cutaneous reactions.

2.5. Passive cutaneous anaphylaxis

The rostral part of the back skin of mice was clipped, and 20 μl of five-fold diluted IgE preparation was injected intradermally. Twenty-four hours after sensitization, passive cutaneous anaphylaxis was elicited by injecting 0.25 ml of saline containing 0.25 mg (protein) of dinitrophenylated bovine serum albumin intravenously. Immediately after the antigen challenge, mice were placed in a chamber to observe their behavior. When the vascular permeability increase was to be examined, 1.25 mg of Evans blue dye was injected simultaneously with the antigen. The vascular

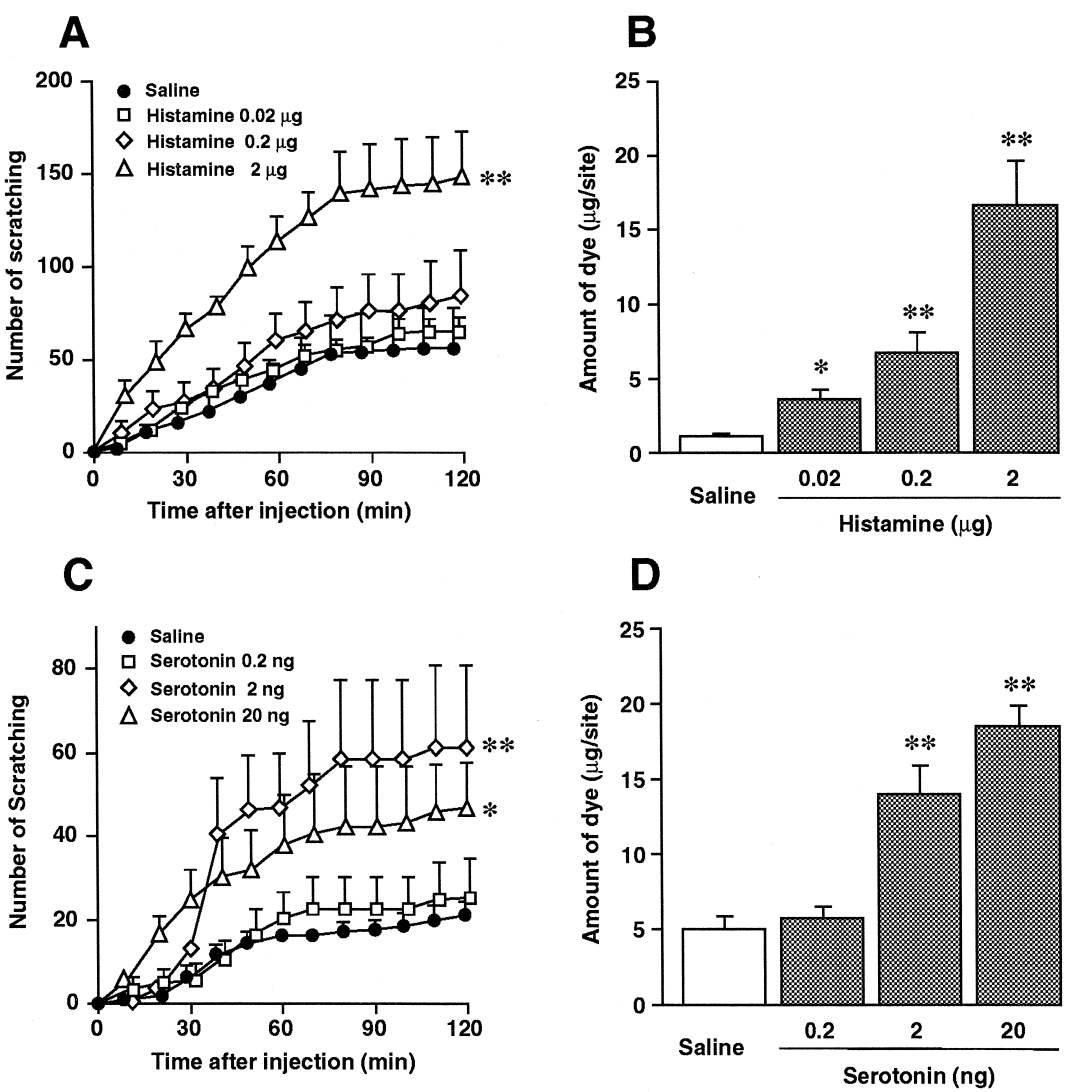

Fig. 2. Scratching behavior and vascular permeability increase associated with histamine and serotonin injection in ICR mice. (A) and (B): histamine in doses of 0.02, 0.2 and 2 μg was injected intradermally. (C) and (D): serotonin in doses of 0.2, 2 and 20 ng was injected intradermally. Each value represents the mean ± S.E.M. for 4 or 6 mice. Number of scratchings is indicated cumulatively and was statistically evaluated based on the total number for 120 min. $^{*}P < 0.05$, $^{**}P < 0.01$.

permeability increase was assessed by measuring the amount of extravasated dye 30 min after the antigen challenge. Control mice received the antigen challenge without sensitization with IgE, and the results are indicated as passive cutaneous anaphylaxis (-).

2.6. Compound 48 / 80-, histamine- and serotonin-induced cutaneous reactions

The rostral part of the back skin of mice was clipped, and 20 μl of compound 48/80, histamine or serotonin solution was injected intradermally. Control mice received a saline injection instead. Immediately after the injection, the mice were placed in a chamber to observe their behavior. When the vascular permeability increase was to be evaluated, 1.25 mg of Evans blue dye was injected intravenously at the same time. The amount of dye extravasated for 30 min after the injection was examined.

2.7. Observation of scratching behavior

Scratching behavior was observed according to the method described by Kuraishi et al. (1995) and Musoh et al. (1997). In brief, immediately after elicitation of the cutaneous reactions, mice were placed in an observation chamber. The behavior was recorded in the absence of an observer using a video camera for 120 min. Scratching of the reaction site with the hindpaws was counted at 10-min intervals. Mice generally scratched several times for about one second and a series of scratchings was counted as one incidence. The number of scratchings is indicated cumulatively.

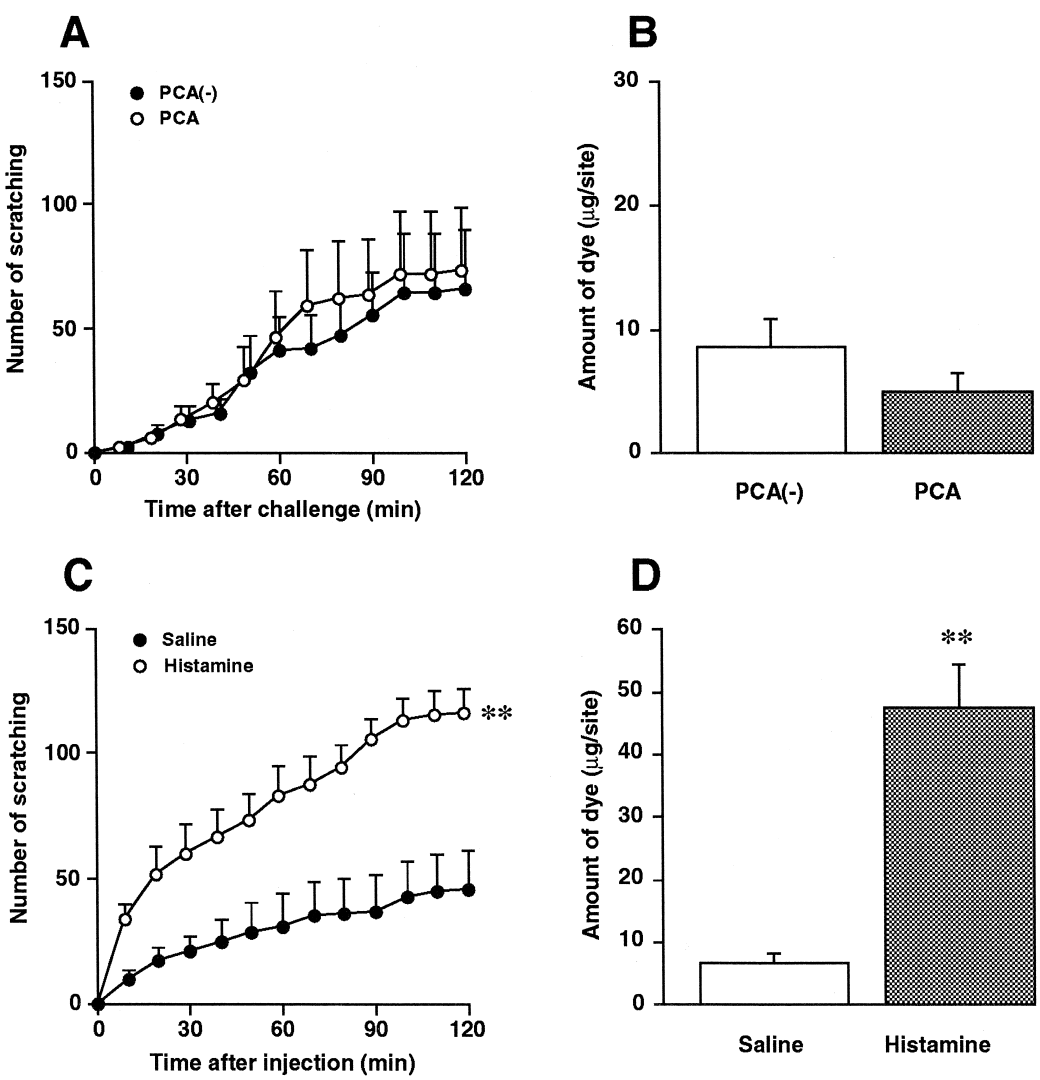

Fig. 3. Scratching behavior and vascular permeability increase associated with passive cutaneous anaphylaxis, and histamine injection in WBB6F1-W/W^{v} mice. (A) and (B): IgE was injected intradermally, and antigen was injected intravenously 24 h later. (C) and (D): histamine in a dose of 2 μg was injected intradermally. Each value represents the mean ± S.E.M. for four mice. Number of scratchings is indicated cumulatively and was statistically evaluated based on the total number for 120 min. PCA: passive cutaneous anaphylaxis, $^{**}P < 0.01$.

2.8. Measurement of vascular permeability increase

The increase in vascular permeability was assessed as reported previously (Inagaki et al., 1986a,b). In brief, the mice were killed 30 min after elicitation of the cutaneous reactions, and the reaction site was excised. The skin specimen was dissolved in 0.7 ml of 1 N KOH solution, and 9.3 ml of a mixture of 0.6 N H_3PO_4 solution and acetone (5:13) was added. After vigorous shaking, the precipitates were filtered off and the amount of dye extracted was measured colorimetrically at 620 nm.

2.9. Statistics

The data were expressed as the mean values with standard error. In experiments containing two experimental groups, either Student's or Aspin–Welch's *t*-test was employed to evaluate the statistical significance of differences after the variances of the data were evaluated with the *F*-test ($P < 0.05$). For data including three or more experimental groups, either a parametric or a non-parametric Tukey's multiple range test was used after Bartlett's analysis ($P < 0.05$). When the P value was smaller than 0.05, the difference was considered to be significant.

3. Results

3.1. Scratching behavior and vascular permeability increase caused by passive cutaneous anaphylaxis, compound 48 / 80, histamine and serotonin in ICR mice

The scratching behavior and vascular permeability increase associated with the induction of passive cutaneous

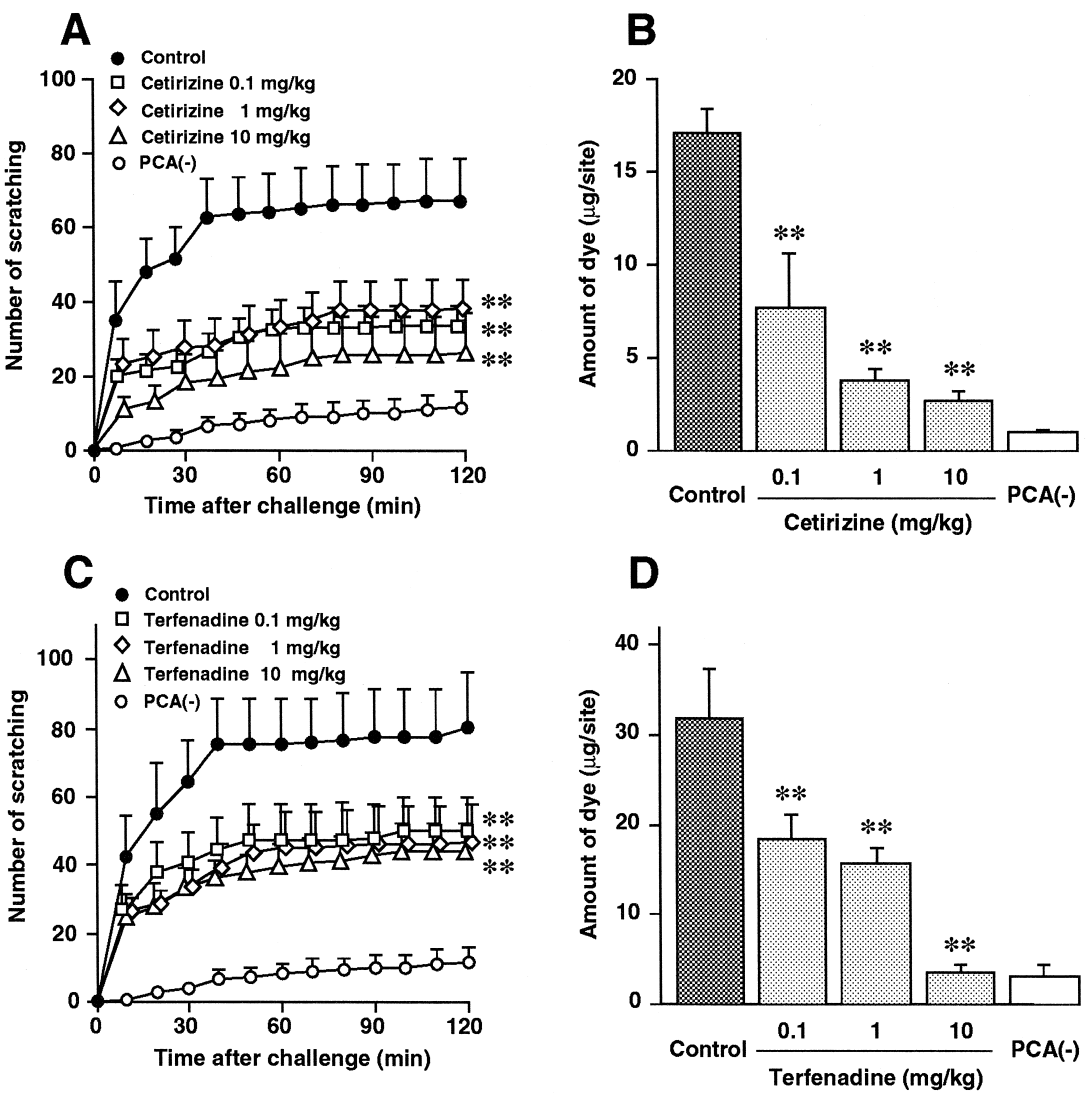

Fig. 4. Effects of cetirizine and terfenadine on the scratching behavior and vascular permeability increase caused by passive cutaneous anaphylaxis in ICR mice. Mice were sensitized with IgE and subsequently challenged with antigen to induce passive cutaneous anaphylaxis. Cetirizine (A and B) and terfenadine (C and D) in doses of 0.1, 1 and 10 mg/kg were administered 1 h before antigenic challenge. Each value represents the mean ± S.E.M. for 4 or 6 mice. Number of scratchings is indicated cumulatively and was statistically evaluated based on the total number for 120 min. PCA: passive cutaneous anaphylaxis, $^{**}P < 0.01$.

anaphylaxis, and with intradermal injections of compound 48/80, histamine and serotonin were compared in ICR mice.

As shown in Fig. 1A and B, the elicitation of passive cutaneous anaphylaxis in ICR mice caused both scratching behavior and dye leakage. The scratching behavior was observed soon after the antigenic challenge. The incidence of scratching peaked at the first 10 min, and decreased thereafter. Intradermal injection of 1–10 μg of compound 48/80 caused both scratching behavior and dye leakage dose dependently (Fig. 1C and D). The scratching behavior and dye leakage caused by 3 μg of compound 48/80 were almost comparable to those induced by passive cutaneous anaphylaxis. The intradermal injection of 0.02–2 μg histamine also caused scratching behavior and dye leakage (Fig. 2A and B). The scratching behavior and dye leakage induced by 2 μg of histamine were almost comparable to those induced by passive cutaneous anaphylaxis. Although 0.2–20 ng of serotonin induced dye leakage dose dependently, it failed to induce dose-dependent scratching behavior in ICR mice (Fig. 2C and D). The potency of serotonin to induced dye leakage was 100–1000 times greater than that of histamine.

3.2. Scratching behavior and vascular permeability increase caused by passive cutaneous anaphylaxis and histamine in WBB6F1-W/W^{v} mice

Scratching behavior and vascular permeability increase associated with the induction of passive cutaneous anaphylaxis and with intradermal injection of histamine were observed in mast cell-deficient WBB6F1-W/W^{v} mice.

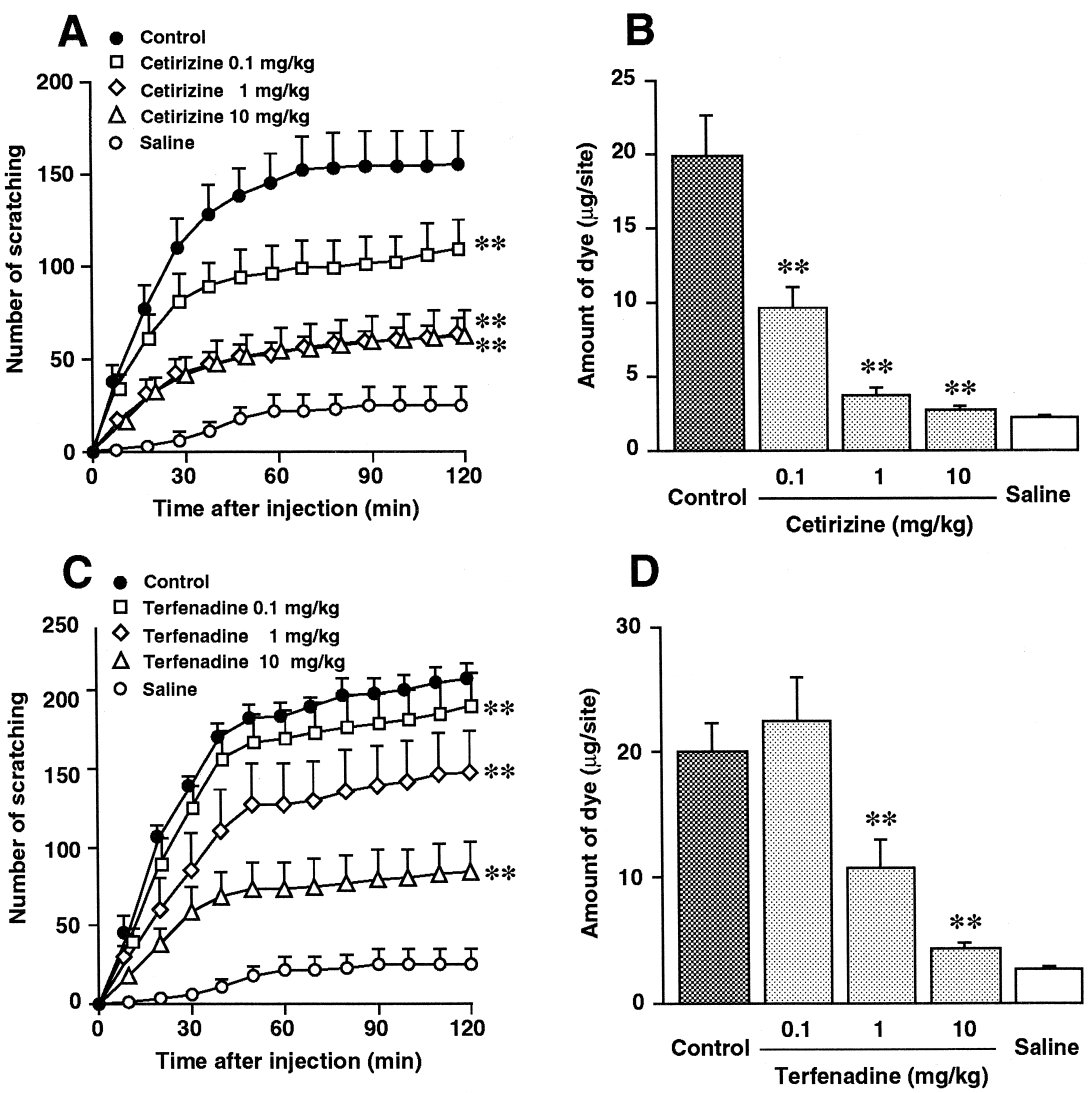

Fig. 5. Effects of cetirizine and terfenadine on the scratching behavior and vascular permeability increase caused by compound 48/80 injection in ICR mice. Scratching behavior and vascular permeability increase were induced by an intradermal injection of 3 μg of compound 48/80. Cetirizine (A and B) and terfenadine (C and D) in doses of 0.1, 1 and 10 mg/kg were administered 1 h before compound 48/80 injection. Each value represents the mean ± S.E.M. for six mice. Number of scratchings is indicated cumulatively and was statistically evaluated based on the total number for 120 min. $^{**}P < 0.01$.

As shown in Fig. 3A and B, sensitization with IgE and subsequent challenge with antigen failed to induce scratching behavior and dye leakage, although the control values were slightly increased. In contrast, intradermal injection of 2 μg of histamine induced both scratching behavior and dye leakage (Fig. 3C and D). The vascular permeability increase in WBB6F1-W/W^{v} mice appeared greater than that in ICR mice (Fig. 2B).

3.3. Effects of histamine H_1 receptor antagonists on the scratching behavior and vascular permeability increase caused by passive cutaneous anaphylaxis, compound 48/80 and histamine in ICR mice

Effects of cetirizine and terfenadine on the scratching behavior and vascular permeability increase caused by passive cutaneous anaphylaxis, compound 48/80 or histamine in ICR mice were examined. Drugs were administered to mice intraperitoneally 1 h prior to the elicitation of reaction.

The results for passive cutaneous anaphylaxis are shown in Fig. 4. Both cetirizine and terfenadine at doses of 0.1–10 mg/kg inhibited the scratching behavior and dye leakage significantly. The inhibition by 10 mg/kg of these drugs of scratching behavior was 74.1% and 52.5%, respectively, which was weaker than the values for dye leakage, 89.3% and 98.3%, respectively.

As shown in Fig. 5, cetirizine and terfenadine at doses of 0.1–10 mg/kg also inhibited significantly the scratching behavior and dye leakage caused by compound 48/80. Similar to the case of passive cutaneous anaphylaxis, these drugs at 10 mg/kg inhibited the scratching behavior by

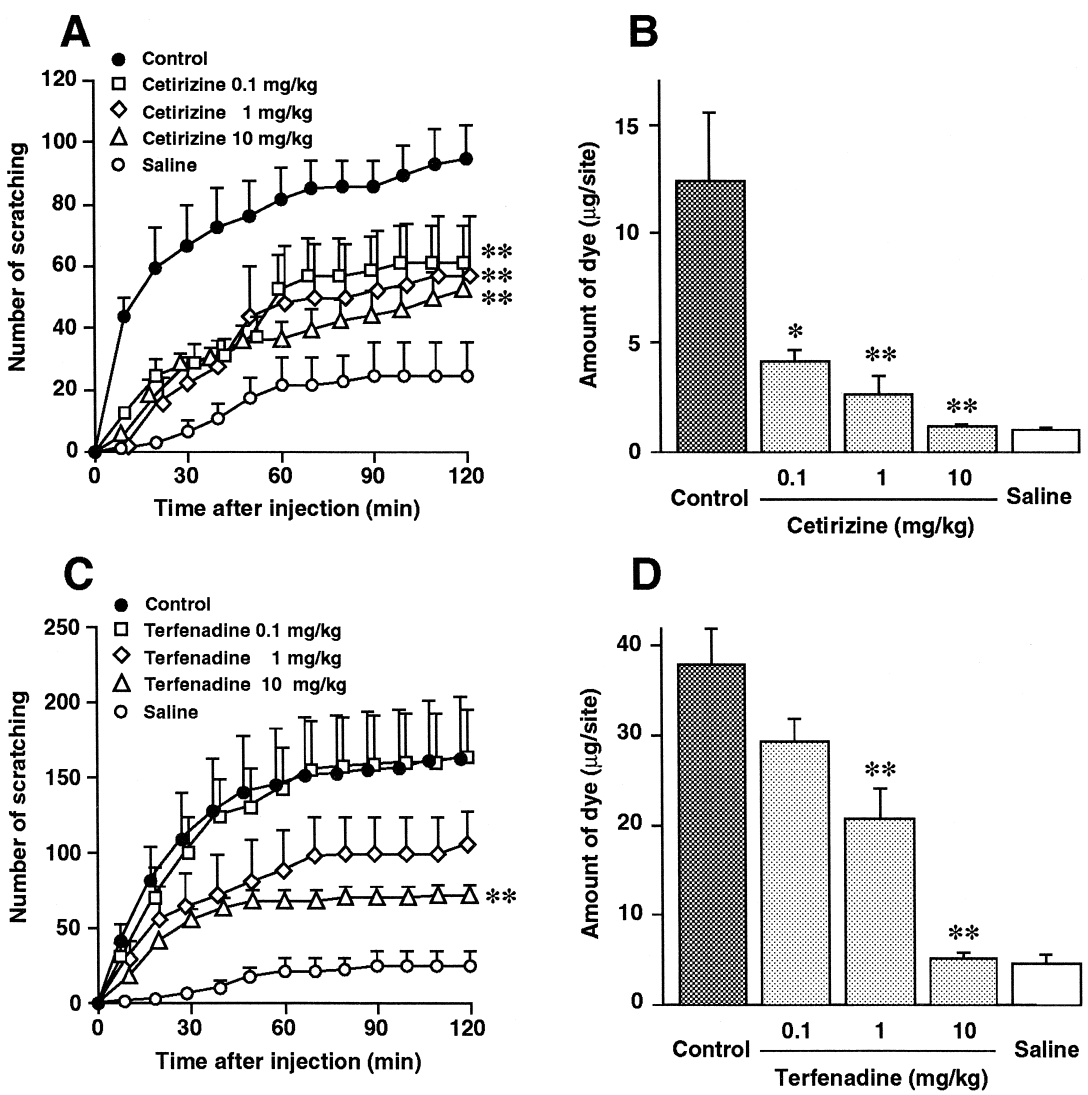

Fig. 6. Effects of cetirizine and terfenadine on the scratching behavior and vascular permeability increase caused by histamine injection in ICR mice. Scratching behavior and vascular permeability increase were induced by an intradermal injection of 2 μg of histamine. Cetirizine (A and B) and terfenadine (C and D) in doses of 0.1, 1 and 10 mg/kg were administered 1 h before histamine injection. Each value represents the mean ± S.E.M. for 4 or 6 mice. Number of scratchings is indicated cumulatively and was statistically evaluated based on the total number for 120 min. $^{*}P < 0.05$, $^{**}P < 0.01$.

71.6% and 67.8%, respectively, and dye leakage by 96.0% and 90.4%, respectively.

The results for histamine-induced scratching behavior and dye leakage are shown in Fig. 6. Cetirizine and terfenadine inhibited the histamine-induced dye leakage dose dependently (Fig. 6B and D). The inhibition caused by 10 mg/kg of these drugs was almost complete, 98.7% and 98.3%, respectively. Both drugs also inhibited the scratching behavior significantly, but the inhibition was only 60.0% and 66.1%, respectively (Fig. 6A and C).

3.4. Effects of histamine H_2 receptor antagonists on the scratching behavior and vascular permeability increase caused by histamine in ICR mice

The effects of famotidine and ranitidine on the scratching behavior and vascular permeability increase caused by histamine in ICR mice were examined. Drugs at doses of 1 and 10 mg/kg were administered to mice intraperitoneally 1 h prior to the injection of histamine.

As shown in Fig. 7, famotidine and ranitidine inhibited the scratching behavior induced by 2 μg of histamine in a dose-dependent manner (Fig. 7A and C). The inhibition caused by 10 mg/kg of these drugs was 80.3% and 54.5%, respectively. These drugs, however, did not affect dye leakage at all (Fig. 7B and D).

3.5. Effects of combination of histamine H_1 and H_2 receptor antagonists on the scratching behavior caused by histamine and passive cutaneous anaphylaxis in ICR mice

The effects of the combination of cetirizine and ranitidine on the scratching behavior caused by histamine and

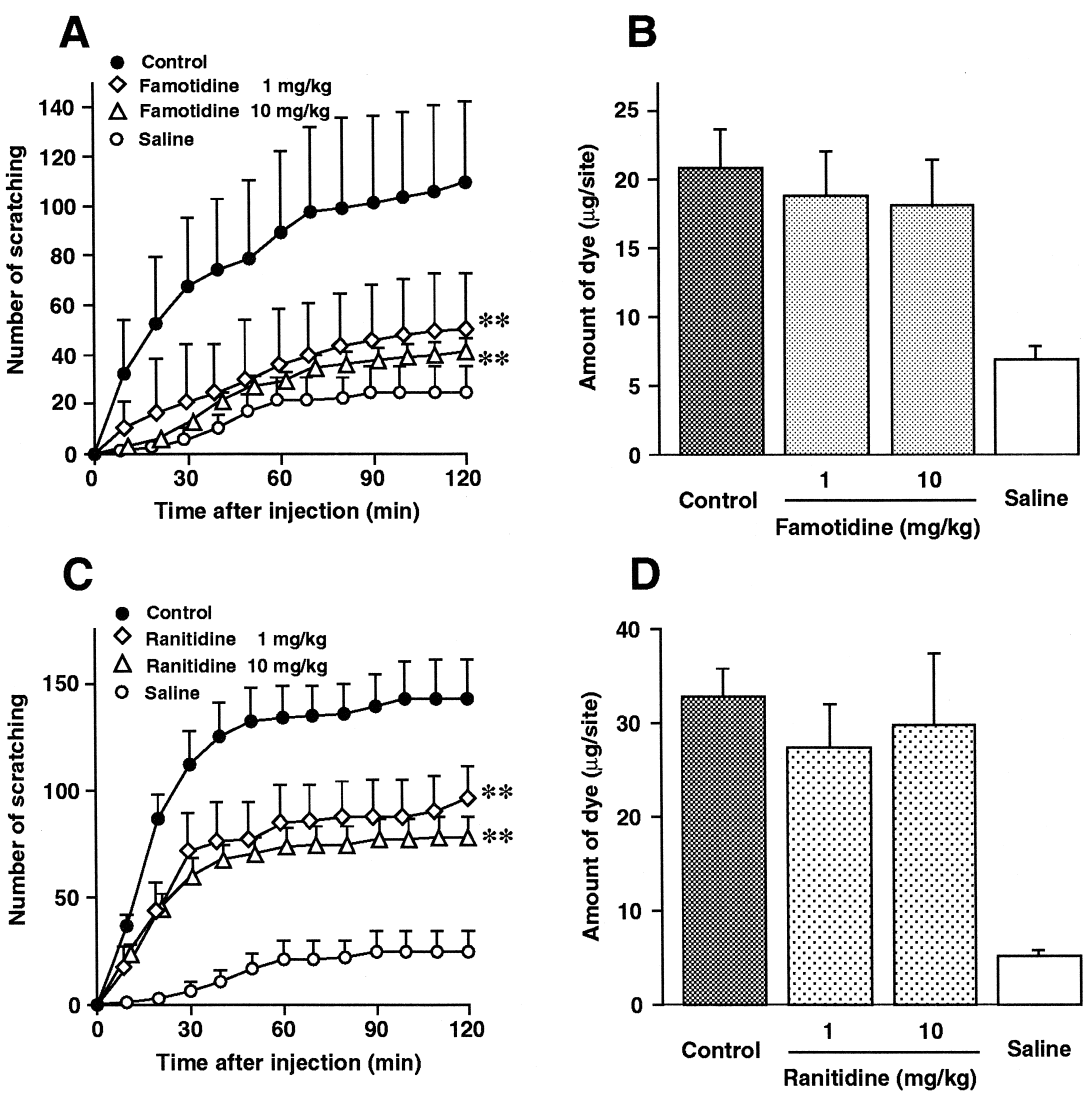

Fig. 7. Effects of famotidine and ranitidine on the scratching behavior and vascular permeability increase caused by histamine injection in ICR mice. Scratching behavior and vascular permeability increase were induced by an intradermal injection of 2 μg of histamine. Famotidine (A and B) and ranitidine (C and D) in doses of 1 and 10 mg/kg were administered 1 h before histamine injection. Each value represents the mean ± S.E.M. for 4–6 mice. Number of scratchings is indicated cumulatively and was statistically evaluated based on the total number for 120 min. $^{**}P < 0.01$.

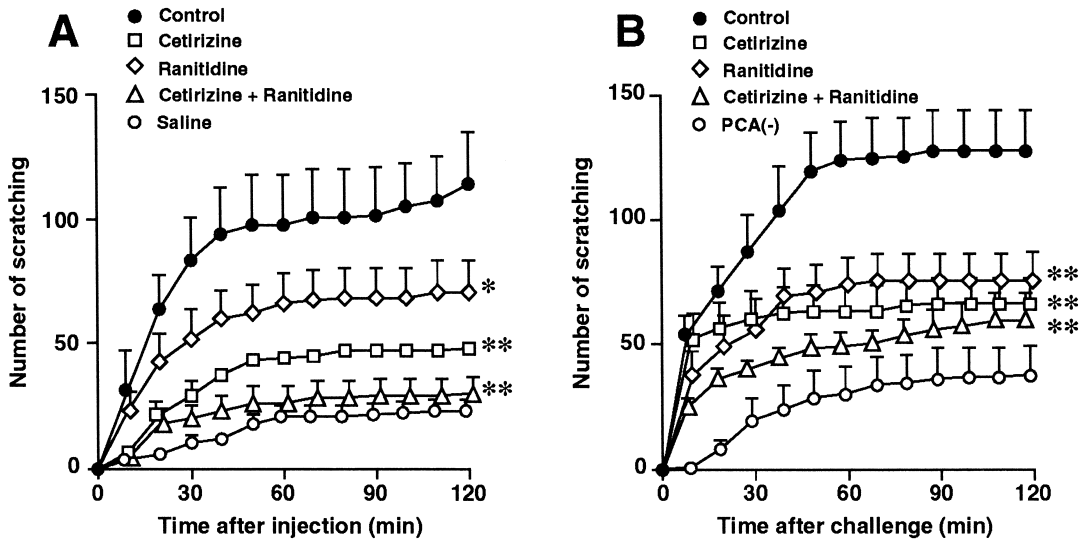

Fig. 8. Effects of cetirizine and ranitidine on the scratching behavior caused by histamine injection and passive cutaneous anaphylaxis in ICR mice. Scratching behavior was induced by 2 μg of histamine (A) and passive cutaneous anaphylaxis (B). Cetirizine and ranitidine in a dose of 10 mg/kg were administered separately or simultaneously 1 h before. Each value represents the mean ± S.E.M. for six mice. Number of scratchings is indicated cumulatively and was statistically evaluated based on the total number for 120 min. PCA: passive cutaneous anaphylaxis, $^{*}P < 0.05$, $^{**}P < 0.01$.

passive cutaneous anaphylaxis in ICR mice were examined.

As shown in Fig. 8A, the histamine-induced scratching behavior was significantly inhibited by 10 mg/kg of cetirizine and ranitidine. The inhibition was 73.0% and 48.1%, respectively. When mice were treated with both drugs simultaneously, the inhibition was significantly potentiated (cetirizine:combination, $P < 0.05$; ranitidine:combination, $P < 0.01$) and reached to 92.8%.

The results for passive cutaneous anaphylaxis are shown in Fig. 8B. Cetirizine and ranitidine inhibited the passive cutaneous anaphylaxis-induced scratching behavior by 68.3% and 58.0%, respectively. Contrary to the histamine-induced scratching behavior, in this case the inhibition was not significantly potentiated by combination of the two drugs. The inhibition increased only slightly and reached to 75.6%.

4. Discussion

In the present study, we demonstrated that IgE-mediated passive cutaneous anaphylaxis induces scratching behavior in ICR mice, and that histamine plays an important role in the induction of passive cutaneous anaphylaxis-associated scratching behavior. The ICR mouse is a good responder for inducing passive cutaneous anaphylaxis, and exhibits a potent vascular permeability increase (Inagaki et al., 1986b). In contrast, the vascular permeability increase associated with passive cutaneous anaphylaxis was not observed in WBB6F1-W/W^{v} mice, demonstrating that mast cell-derived mediators are solely responsible for causing the reaction (Inagaki et al., 1986b). In the present study, we confirmed that not only vascular permeability increase but also scratching behavior was not induced in WBB6F1-W/W^{v} mice in association with passive cutaneous anaphylaxis, although histamine apparently induced both scratching behavior and vascular permeability increase. It is obvious, therefore, that mast cell-derived mediators are also responsible for causing passive cutaneous anaphylaxis-associated scratching behavior. On the other hand, in ddY mice, histamine does not induce scratching behavior (Kuraishi et al., 1995), although it causes a substantial vascular permeability increase (Inagaki et al., 1986a). Furthermore, in the case of the IgE-dependent, hapten-induced allergic cutaneous reaction in BALB/c mice, histamine H_1 receptor antagonists do not affect scratching behavior in spite of their apparent inhibition of edema formation (Musoh et al., 1997). These results indicate that there is a strain difference in the responsiveness to histamine for causing scratching behavior, and that this responsiveness to histamine for causing scratching behavior does not parallel the vascular permeability increase. ICR and WBB6F1-W/W^{v} mice may be higher responders for scratching behavior, but ddY and BALB/c mice may be lower responders. Although the higher responsiveness to histamine to cause scratch observed in ICR and WBB6F1-W/W^{v} mice is interesting, the mechanism involved has yet to be elucidated.

The histamine H_1 receptor antagonists, cetirizine and terfenadine, apparently inhibited the scratching behavior and vascular permeability increase caused by passive cutaneous anaphylaxis in ICR mice. The inhibition of the vascular permeability increase, which was almost complete at the highest dose employed, 10 mg/kg, was always more potent than that of scratching behavior. Similar results were obtained when scratching behavior and vascular permeability increase were induced by compound 48/80.

These results indicate that passive cutaneous anaphylaxis and compound 48/80 injection cause mast cell activation and histamine release, and that histamine is a dominant mediator which causes a vascular permeability increase through histamine H_1 receptors. On the contrary, the histamine H_1 receptor antagonists failed to inhibit the scratching behavior caused by passive cutaneous anaphylaxis completely at the highest dose, indicating that different mediators or different histamine receptors are also involved in the induction of scratching behavior.

Histamine-induced scratching behavior and vascular permeability increase were also inhibited by the histamine H_1 receptor antagonists. The vascular permeability increase was abolished by the treatment with the histamine H_1 receptor antagonists, whereas the inhibition of scratching behavior was not complete. These results demonstrate that histamine increases vascular permeability predominantly through histamine H_1 receptors, but that scratching behavior is induced not only through histamine H_1 receptors but also through other types of histamine receptors. We could confirm that famotidine and ranitidine, histamine H_2 receptor antagonists, partially inhibited the histamine-induced scratching behavior without affecting the vascular permeability increase. Furthermore, the histamine-induced scratching behavior was abolished by the simultaneous treatment with cetirizine and ranitidine. These results clearly demonstrate that histamine induces scratching behavior in ICR mice through both histamine H_1 and H_2 receptors. The participation of histamine H_2 receptors in increasing vascular permeability is considered to be minimal.

Ranitidine also inhibited the scratching behavior induced by passive cutaneous anaphylaxis, however, the simultaneous treatment with cetirizine and ranitidine failed to abolish the scratching behavior. These results indicate that different mediators also participate in passive cutaneous anaphylaxis, although the extent of the participation is slight. It is well known that rodent mast cells contain serotonin and release it simultaneously with histamine upon stimulation (Schwartz and Austen, 1982; Weitzman et al., 1985). Serotonin potently increases vascular permeability with an activity about 100 times greater than that of histamine on a weight basis in ddY mice (Inagaki et al., 1986a). In the present study, we confirmed that serotonin potently induced a vascular permeability increase in ICR mice, although the activity for causing scratching behavior was relatively small. Serotonin may be a candidate as the second mediator involved in passive cutaneous anaphylaxis-induced scratching behavior and vascular permeability increase, but its precise role should be further investigated.

Histamine is the most usual mediator causing itch in humans, and histamine H_1 receptor antagonists are widely used for the treatment of itch (Bernstein and Bernstein, 1986; Simons et al., 1986; Juhlin and Arendt, 1988). On the other hand, many attempts have been made to find an additional benefit of simultaneous treatment with histamine H_1 and H_2 receptor antagonists for the treatment of itch (Davies et al., 1979; Hagermark et al., 1979; Davies and Greaves, 1980; Diller and Orfanos, 1983; Sahai et al., 1989; Runge et al., 1992; Sharpe and Shuster, 1993; Greaves, 1995; Charlesworth, 1996). Although most of the attempts to demonstrate any benefit failed, Davies et al. (1979) indicated that the combination of chlorpheniramine and cimetidine was more effective than chlorpheniramine or cimetidine alone for the treatment of experimentally induced pruritus. Furthermore, Diller and Orfanos (1983) indicated that the combined administration of chlorpheniramine and cimetidine is beneficial for some patients who respond poorly to chlorpheniramine. These reports suggest that, not only histamine H_1 receptors, but also histamine H_2 receptors are involved in the mediation of pruritus in humans. However, the role of histamine H_2 receptors in the mediation of itching in humans has not yet been established.

5. Conclusion

In conclusion, we demonstrated that IgE-mediated passive cutaneous anaphylaxis induces scratching behavior in ICR mice, and that histamine plays an important role in the induction of passive cutaneous anaphylaxis-associated scratching behavior through both histamine H_1 and H_2 receptors. Histamine might also play an important role in compound 48/80-induced scratching behavior in ICR mice. We suggest, therefore, that histamine H_2 receptors play some role in the mediation of pruritus in humans.

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