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Biphasic response of cutaneous blood flow induced by passive cutaneous anaphylaxis in rats

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Abstract

In the immediate phase of passive cutaneous anaphylaxis, sensitized skin mast cells release various mediators when activated by antigen. The present study investigated the effects of the mediators on cutaneous blood flow at the antigen–antibody reaction site. Induction of passive cutaneous anaphylaxis produced a biphasic response consisting of an initial decrease, followed by a sustained increase, in the cutaneous blood flow. The initial phase was almost eliminated by the 5-hydroxytryptamine receptor antagonist methysergide, whereas the second phase was sensitive to the histamine H_2 receptor antagonist ranitidine. The histamine H_1 receptor antagonist chlorpheniramine, the denervation of sensory nerves with capsaicin, the cyclooxygenase inhibitor indomethacin, or the bradykinin B_2 receptor antagonist D-arginyl-L-arginyl-L-prolyl-trans-4-hydroxy-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-D-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-(2α,3β,7aβ)-octahydro-1*H*-indole-2-carbonyl-L-arginine (HOE140) did not affect the blood-flow changes caused by the anaphylaxis. These results suggest that 5-hydroxytryptamine and histamine H_2 receptors mediate the initial decrease and the subsequent increase in cutaneous blood flow, respectively, induced by passive cutaneous anaphylaxis in rats.

Keywords: Cutaneous blood flow; Passive cutaneous anaphylaxis; 5-Hydroxytryptamine receptor; Histamine H_2 receptor; (Rat)

1. Introduction

Rat 48 h homologous passive cutaneous anaphylaxis is one of the most frequently used models for evaluating antiallergic drugs. In the immediate phase of passive cutaneous anaphylaxis, passively sensitized cutaneous mast cells are known to be activated by intravenously administered specific antigen, and to release mediators such as histamine and serotonin, which increase vascular permeability in the sensitized skin site (Mielens et al., 1974). However, little information is available regarding the change in regional skin blood flow induced by passive cutaneous anaphylaxis.

Allergens have been shown to induce a continuous increase in local cutaneous blood flow after a prick test in allergic subjects (Hammarlund et al., 1990). This report also indicated that the increase in cutaneous blood flow is partially inhibited by the histamine H_1 receptor antagonist loratadine, suggesting the involvement of histamine H_1 receptors in the increased blood flow (Hammarlund et al., 1990). However, since the participation of the other mediators was not investigated, a detailed mechanism for the blood-flow changes during allergic skin reaction remains to be elucidated.

In the present study, we investigated whether passive cutaneous anaphylaxis induces changes in cutaneous blood flow and, if so, which inflammatory mediators produce the blood-flow changes in rats.

2. Materials and methods

2.1. Preparation of antiserum

Brown–Norway rats weighing 179–185 g (Charles River Japan, Kanagawa, Japan) received a total of 1 ml (four 0.25 ml portions) of saline containing 1 mg of ovalbumin (grade III; Sigma, St. Louis, MO, USA), 100 mg of $Al(OH)_3$, and 8×10^9 killed *Bordetella pertussis* (inactive bacterial suspension; Wako, Osaka, Japan) into four foot-

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pads. Two weeks later, the blood was obtained by heart puncture, and the serum was then pooled and stored at −20 °C. The 48 h passive cutaneous anaphylaxis titer of antiserum was 1:800, which was estimated in the rat back skin.

2.2. Passive cutaneous anaphylaxis

The back skin of male Wistar rats weighing 220–330 g (SLC, Shizuoka, Japan) was clipped, and 50 μl of 100-fold diluted antiserum was injected intracutaneously. At 48 h after the sensitization, the rats were surgically operated on, as described below. Then, passive cutaneous anaphylaxis was elicited by intravenously injecting 0.5 ml of saline containing 5 mg Evans blue (Wako) and 2 mg ovalbumin.

2.3. Measurement of vascular permeability

The vascular permeability was assessed as reported previously (Hayashi et al., 2001a,b). In brief, the rat was sacrificed 30 min after induction of the cutaneous reaction, and the skin at the reaction site was excised. The skin specimen was dissolved in 1 ml of 1 mol/l KOH solution. Nine milliliters of a mixture of 0.6 mol/l H_3PO_4 solution and acetone (5:13) was added, and the sample was centrifuged at 1200 × *g* for 10 min. The absorbance of dye extracted in the supernatant was measured at 620 nm with a spectrophotometer (U-2000; Hitachi, Tokyo, Japan). The leaked dye amount was calculated by subtracting the dye content of the untreated site from that of the antiserum-injected site.

2.4. Measurement of blood pressure, heart rate, and blood flow

The sensitized rats were anesthetized with pentobarbital sodium (50 mg/kg, i.p.). Cannulas were inserted into the trachea, the left femoral vein, and the left carotid artery for spontaneous ventilation, drug or antigen administration, and measurement of arterial blood pressure via a pressure transducer (TDN-R; Gould, Oxnard, CA, USA), respectively. The mean arterial pressure and heart rate were recorded on a Macintosh computer with an AD converter (Lab Stack; Keisoku Giken, Tokyo, Japan). The skin blood flow was measured with a laser Doppler flow meter (CDF-2000; OAS, Tokyo, Japan), and recorded on a Windows computer with the software CDFoneP (OAS). The laser Doppler flow probe was placed at the skin surface of the antiserum-injected site. After the surgical operation, the additional administration of pentobarbital sodium (6 mg/kg, i.v.) was performed. The experiment was started after allowing the parameters to stabilize. The rectal temperature was maintained at 37 °C with a heating pad.

2.5. Capsaicin treatment

On the second day of life, neonatal Wistar rats received a single subcutaneous dose of 50 mg/kg of capsaicin (Sigma) according to the methods of Jancsó et al. (1977). Capsaicin was prepared in saline containing 10% Tween 80 and 10% ethanol. Control rats were treated only with the solvent. The effectiveness of the neonatal capsaicin treatment was tested before each experiment by employing the eye-wiping response to topical application of capsaicin (0.1% in ethanol) to the cornea according to the method of Eglezos et al. (1992).

2.6. Drugs

(±)-Chlorpheniramine maleate, a histamine H_1 receptor antagonist; D-arginyl-L-arginyl-L-prolyl-trans-4-hydroxy-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-D-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-(2α,3β,7aβ)-octahydro-1*H*-indole-2-carbonyl-L-arginine (HOE140), a bradykinin

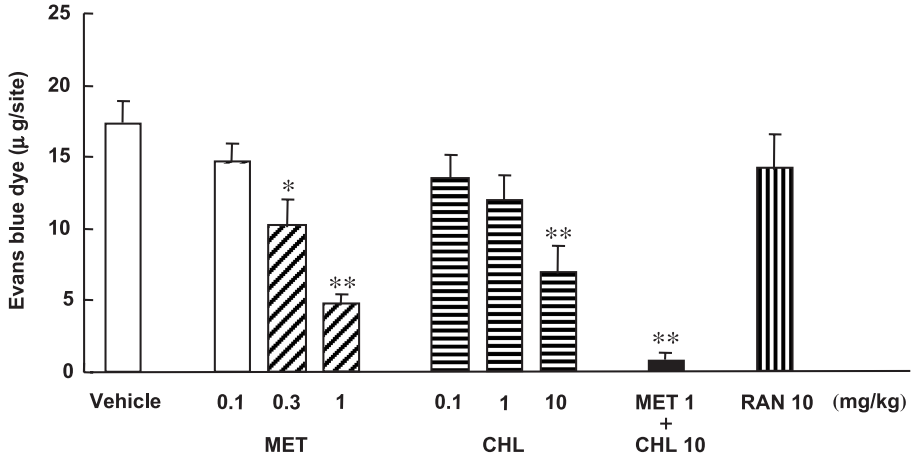

Fig. 1. Effects of methysergide (MET), chlorpheniramine (CHL), and ranitidine (RAN) on the plasma extravasation induced by passive cutaneous anaphylaxis in rat skin. Methysergide (0.1, 0.3, and 1 mg/kg), chlorpheniramine (0.1, 1, and 10 mg/kg), ranitidine (10 mg/kg), or a combination of methysergide (1 mg/kg) and chlorpheniramine (10 mg/kg) was administered intravenously 5 min before the intravenous injection of ovalbumin. Each value represents the mean ± S.E.M. of 4–6 animals. *$P<0.05$, **$P<0.01$ compared with the value in the vehicle group.

Table 1
Effects of capsaicin, indomethacin, and HOE140 on the plasma extravasation induced by passive cutaneous anaphylaxis in rat skin

Treatment	*n*	Evans blue dye (μg/site)
Vehicle	3	19.2 ± 5.5
HOE140 (100 nmol/kg)	3	18.7 ± 5.4
Vehicle	3	12.0 ± 3.9
Indomethacin (10 mg/kg)	3	14.5 ± 2.1
Vehicle	4	22.1 ± 3.4
Capsaicin treatment	5	17.3 ± 1.8

Each value represents the mean ± S.E.M.

B_2 receptor antagonist; indomethacin, a cyclooxygenase inhibitor; and methysergide maleate, a 5-hydroxytryptamine (5-HT) receptor antagonist were obtained from Sigma. Ranitidine hydrochloride, a histamine H_2 receptor antagonist, was obtained from Wako. Indomethacin was dissolved in 0.1 mol/l $NaHCO_3$, and others were dissolved in saline. All drugs were intravenously administered at a volume of 1 ml/kg via a cannula inserted into the left femoral vein. Methysergide, chlorpheniramine or ranitidine was administered 5 min before the induction of passive cutaneous anaphylaxis. Indomethacin or HOE140 was administered 10 or 15 min, respectively, before induction of the cutaneous reaction.

2.7. Data analyses

All data are shown as mean ± S.E.M. The statistical significance was evaluated by the Student's *t*-test, the Aspin–Welch test, or one-way analysis of variance (ANOVA) followed by the Dunnett test. *P* values less than 0.05 were considered significant.

3. Results

3.1. Plasma extravasation

The intravenous administration of antigen caused a marked increase in the leaked dye amount, i.e., plasma extravasation. The 5-HT receptor antagonist methysergide at 0.3 and 1 mg/kg and the histamine H_1 receptor antagonist chlorpheniramine at 10 mg/kg significantly inhibited the plasma extravasation (Fig. 1). In contrast, the histamine H_2 receptor antagonist ranitidine (10 mg/kg, i.v.) did not (Fig. 1). A combination of 1 mg/kg methysergide and 10 mg/kg chlorpheniramine nearly abolished the plasma extravasation (Fig. 1). The treatment of newborn rats with capsaicin (50 mg/kg, s.c.), which induces degeneration of the primary sensory nerves, did not affect the plasma extravasation (Table 1). Moreover, neither the cyclooxygenase inhibitor indomethacin (10 mg/kg, i.v.) nor the bradykinin B_2 receptor antagonist HOE140 (100 nmol/kg, i.v.) had any effect on the plasma extravasation (Table 1). The doses of ranitidine (10 mg/kg, i.v.; Law et al., 1989), indomethacin (10 mg/kg, i.v.; Boucher et al., 1986), and HOE140 (100 nmol/kg, i.v.; Holzer et al., 1995) used in the present study have previously been reported to be effective.

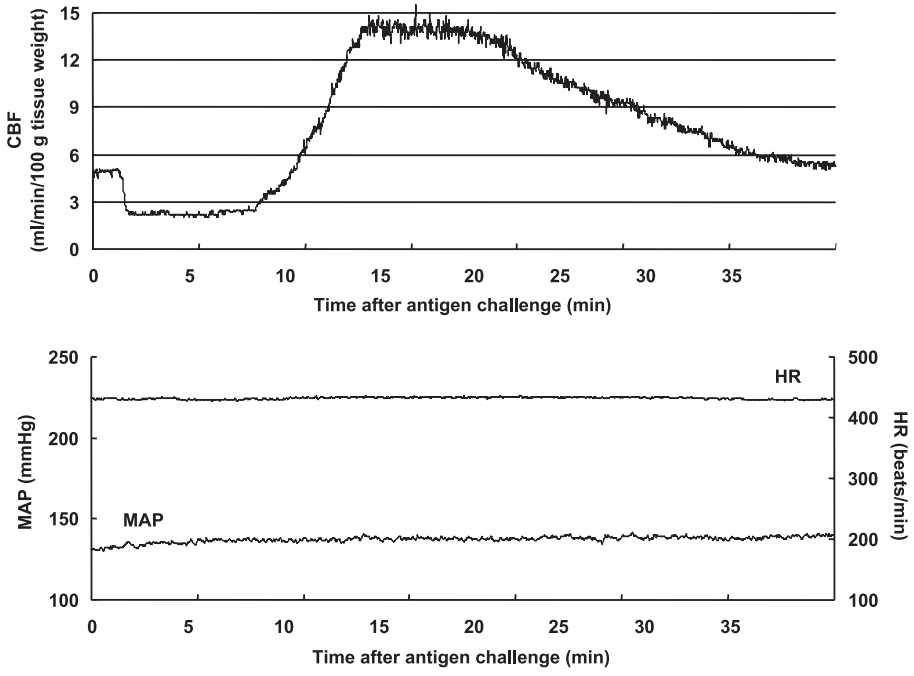

Fig. 2. Representative traces of cutaneous blood flow (CBF; upper), mean arterial pressure (MAP), and heart rate (HR; lower) following antigen challenge in passively sensitized rats.

3.2. Changes in cutaneous blood flow

The induction of passive cutaneous anaphylaxis produced a biphasic response consisting of an initial decrease followed by a sustained increase in the cutaneous blood flow. The decrease in the blood flow reached a peak (60.1 ± 4.1%, $n = 6$), 2.0 ± 0.5 min ($n = 6$) after the beginning of induction, and lasted for 4–8 min. The blood flow was then increased, reaching a maximum (142.9 ± 10.8%, $n = 6$) after 14.1 ± 1.0 min ($n = 6$). After that, the blood flow was gradually decreased and recovered to the basal level after approximately 30 min (Fig. 2). The apparent changes in the mean arterial pressure and heart rate were not caused by induction of the passive anaphylaxis (Fig. 2). In nonsensitized rats, the antigen challenge did not affect the cutaneous blood flow, mean arterial pressure, and heart rate (data not shown).

3.3. Pharmacological analyses of the anaphylaxis-induced changes in cutaneous blood flow

First, the effects of drugs on the initial decrease in cutaneous blood flow induced by the passive cutaneous anaphylaxis were examined. Methysergide (0.1, 0.3 and 1 mg/kg, i.v.) significantly inhibited the blood-flow reduction (Fig. 3A) and shortened the time to the peak (Fig. 3B). In

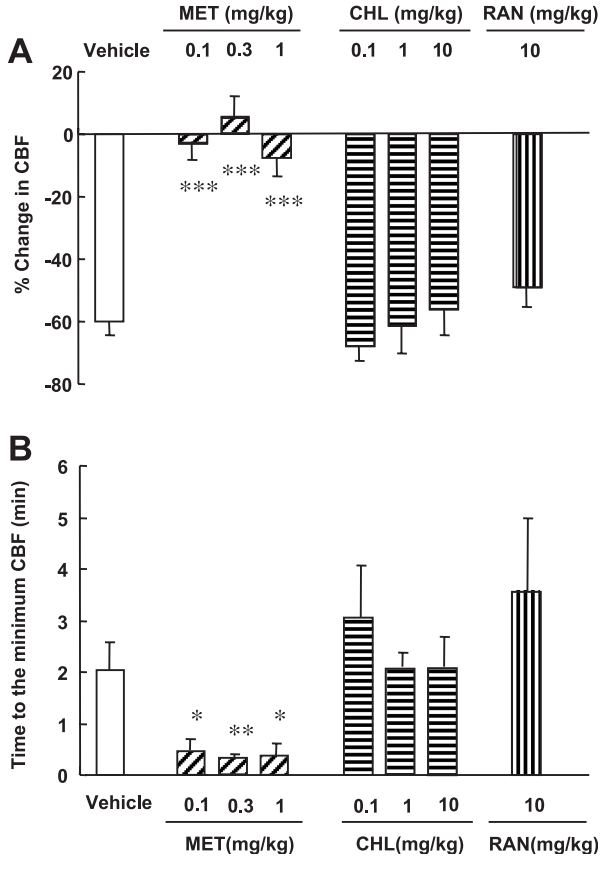

Fig. 3. Effects of methysergide (MET), chlorpheniramine (CHL), and ranitidine (RAN) on the decrease in cutaneous blood flow (CBF; A) and the time to its peak (B) after antigen challenge in passively sensitized rats. Changes in CBF are expressed as a percentage of CBF just before antigen challenge. Each value represents the mean ± S.E.M. of 4–6 animals. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with the value in the vehicle group.

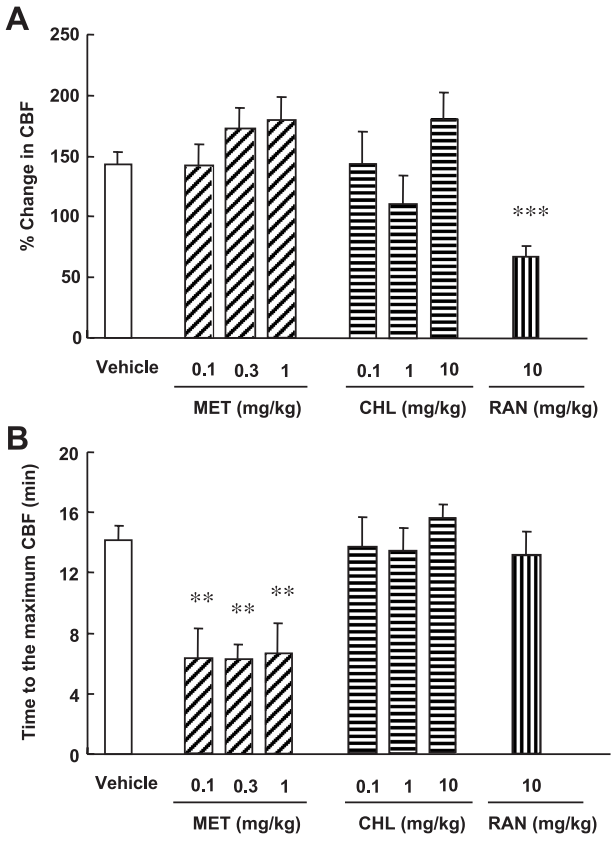

Fig. 4. Effects of methysergide (MET), chlorpheniramine (CHL), and ranitidine (RAN) on the increase in cutaneous blood flow (CBF; A) and the time to its peak (B) after antigen challenge in passively sensitized rats. Changes in CBF are expressed as a percentage of the CBF just before antigen challenge. Each value represents the mean ± S.E.M. of 4–6 animals. **$P < 0.01$, ***$P < 0.001$ compared with the value in the vehicle group.

Table 2
Effects of capsaicin, indomethacin, and HOE140 on biphasic changes in cutaneous blood flow (CBF) induced by passive cutaneous anaphylaxis in rats

Treatment	n	1st phase minimum CBF	2nd phase maximum CBF
Vehicle	3	−59.7 ± 5.0 (2.3 ± 0.8 min)	150.8 ± 20.8 (13.8 ± 2.2 min)
HOE140 (100 nmol/kg)	3	−63.9 ± 7.9 (2.2 ± 0.8 min)	127.3 ± 24.4 (13.9 ± 1.7 min)
Vehicle	3	−73.7 ± 7.5 (2.6 ± 0.5 min)	85.2 ± 12.0 (11.0 ± 1.5 min)
Indomethacin (10 mg/kg)	3	−81.1 ± 2.5 (1.8 ± 0.3 min)	105.9 ± 28.2 (13.4 ± 1.1 min)
Vehicle	4	−60.2 ± 7.2 (1.7 ± 0.8 min)	131.7 ± 5.6 (13.3 ± 3.0 min)
Capsaicin treatment	5	−56.8 ± 6.8 (1.6 ± 0.7 min)	134.1 ± 15.5 (10.9 ± 1.0 min)

Values show percentage changes in CBF, which are expressed as a percentage of the CBF just before antigen challenge. Values in parentheses show the time to the peak after antigen challenge.
Each value represents the mean ± S.E.M.

Table 3
Effects of various drugs on basal levels of cutaneous blood flow (CBF), mean arterial pressure (MAP), and heart rate (HR) in rats

Treatment	Dose (mg/kg)	CBF (ml/min/100 g tissue)		MAP (mm Hg)		HR (beats/min)	
		Before	After	Before	After	Before	After
Vehicle	–	5.7 ± 0.5	5.7 ± 0.5	131 ± 9	126 ± 8	418 ± 12	420 ± 13
Methysergide	0.1	6.3 ± 0.4	6.6 ± 0.5	134 ± 2	136 ± 7	430 ± 5	438 ± 6
	0.3	6.3 ± 0.7	7.0 ± 1.0	124 ± 5	130 ± 3	409 ± 7	417 ± 8
	1	5.8 ± 0.6	5.8 ± 0.7	110 ± 8	109 ± 11	400 ± 10	400 ± 16
Chlorpheniramine	0.1	5.3 ± 0.3	5.5 ± 0.4	124 ± 8	127 ± 9	425 ± 16	426 ± 22
	1	4.9 ± 0.7	5.0 ± 0.7	135 ± 8	131 ± 7	441 ± 15	463 ± 11
Ranitidine	10	5.5 ± 0.6	5.4 ± 0.5	130 ± 10	126 ± 7	442 ± 10	425 ± 6
Vehicle	–	5.8 ± 0.2	5.7 ± 0.4	134 ± 6	129 ± 3	423 ± 16	432 ± 9
HOE140	100[a]	6.2 ± 0.7	6.4 ± 1.0	124 ± 8	120 ± 11	405 ± 20	407 ± 30
Vehicle	–	8.5 ± 3.0	8.0 ± 2.3	108 ± 10	101 ± 11	373 ± 17	373 ± 25
Indomethacin	10	6.3 ± 1.3	6.3 ± 1.0	125 ± 12	118 ± 8	400 ± 34	409 ± 36
Vehicle	–	–	6.3 ± 0.6	–	125 ± 14	–	397 ± 21
Capsaicin treatment	–	–	5.9 ± 0.4	–	115 ± 4	–	377 ± 18

Each value represents the mean ± S.E.M. of 3–6 animals.
[a] The unit of the dose of HOE140 is nmol/kg.

contrast, neither chlorpheniramine (0.1, 1 and 10 mg/kg, i.v.) nor ranitidine (10 mg/kg, i.v.) affected the blood-flow decrease (Fig. 3A and B).

Second, the effects of drugs on the second increase in cutaneous blood flow induced by the passive cutaneous anaphylaxis were examined. Methysergide (0.1, 0.3 and 1 mg/kg, i.v.) did not affect the amplitude of the blood-flow increase, although it significantly shortened the time to the maximum response (Fig. 4A and B). Chlorpheniramine (0.1, 1 and 10 mg/kg, i.v.) affected neither the blood-flow increase nor the time to its peak (Fig. 4A and B). In contrast, ranitidine (10 mg/kg, i.v.) significantly suppressed the blood-flow increase, although it did not affect the time to the maximum response (Fig. 4A and B).

Neither HOE140 (100 nmol/kg, i.v.), indomethacin (10 mg/kg, i.v.), nor the capsaicin treatment affected the anaphylaxis-induced changes in blood flow (Table 2).

Neither methysergide (0.1, 0.3, and 1 mg/kg, i.v.), chlorpheniramine (0.1, 1, and 10 mg/kg, i.v.), ranitidine (10 mg/kg, i.v.), HOE140 (100 nmol/kg, i.v.), nor indomethacin (10 mg/kg, i.v.) significantly affected the basal levels of the cutaneous blood flow, mean arterial pressure, and heart rate (Table 3). There was no significant difference in the cutaneous blood flow, mean arterial pressure, and heart rate between capsaicin (50 mg/kg, s.c.)- and vehicle-treated rats (Table 3).

4. Discussion

In the present study, we found that passive cutaneous anaphylaxis induces not only plasma extravasation but also changes in cutaneous blood flow, with no alteration of the systemic blood pressure and heart rate in rats. Moreover, the blood-flow changes were shown to be a biphasic response consisting of an initial decrease and a subsequent increase. These results suggest that both vasoconstricting and vasodilating mediators are involved in the microvascular reactions induced by passive cutaneous anaphylaxis.

Histamine and serotonin are known to be involved in the plasma extravasation induced by passive cutaneous anaphylaxis in rats (Mielens et al., 1974). The present study also showed that the histamine H_1 receptor antagonist chlorpheniramine and the 5-HT receptor antagonist methysergide inhibit the plasma extravasation. In contrast, it has previously been reported that the selective histamine H_2 receptor agonist impromidine fails to enhance vascular permeability in rat skin (Owen et al., 1984). We also found that the histamine H_2 receptor antagonist ranitidine has no effect on the plasma extravasation. Taken together, these results suggest that histamine H_1 and 5-HT receptors, but not histamine H_2 receptors, are involved in the plasma extravasation induced by passive cutaneous anaphylaxis in rats.

In the present study, the involvement of sensory nerves, prostanoids, and bradykinin in the plasma extravasation caused by passive cutaneous anaphylaxis was also investigated. The treatment of newborn rats with capsaicin results in selective and permanent degeneration of the primary sensory nerves and a significant decrease in substance P content (Jancsó et al., 1980). We found that capsaicin treatment does not affect the plasma extravasation, suggesting no contribution of sensory nerve-derived mediators such as substance P and calcitonin gene-related peptide (CGRP) to the response. In addition, neither the cyclooxygenase inhibitor indomethacin nor the bradykinin B_2 receptor antagonist HOE140 was shown to affect the plasma extravasation. Thus, neither prostanoids nor bradykinin are likely to contribute to the plasma extravasation.

It has been shown that histamine causes vasodilatation of microvessels through both histamine H_1 and H_2 receptors in rats (Owen and Woodward, 1980). In contrast, serotonin has been shown to constrict the microvessels in the human

skin (Hechtman and Jageneau, 1985) and rat hindquarters (Calama et al., 2002) through 5-HT_2 receptors. In the present study, the initial decrease in the cutaneous blood flow was abolished by the 5-HT receptor antagonist methysergide, whereas the subsequent increase was partially inhibited by the H_2 receptor antagonist ranitidine. These results suggest the involvement of 5-HT and histamine H_2 receptors in the cutaneous microvascular constriction and dilatation, respectively, induced by cutaneous passive anaphylaxis. In addition, we found that methysergide shortens the time to the peak of the increase in blood flow, which implies that the serotonin-induced first vasoconstriction may counteract the earlier development of the second vasodilator response.

It remains possible that some mechanism other than the activation of H_2 receptors is involved in the second vasodilator response, since ranitidine inhibited the increase in the blood flow by only 53%. Histamine H_1 receptors are unlikely to mediate the responses since the histamine H_1 receptor antagonist chlorpheniramine had no effects. Moreover, the vasodilator response was not affected by HOE140, indomethacin, or the capsaisin treatment, suggesting that bradykinin, vasodilator prostanoids such as prostaglandin I_2, and sensory nerve-derived mediators such as substance P and CGRP are not involved. Further experiments will be required to identify the other substance mediating the second vasodilator response.

Vasodilatation with an increase in blood flow is an essential part of any inflammatory response (Ryan, 1973), resulting in erythema in the skin (Shanley, 1988). The erythema induced during an immediate allergic reaction is likely to be mediated by a rapid release of inflammatory mediators targeting the blood vessels (Olsson et al., 1988). It has been suggested that both histamine H_1 and H_2 receptors mediate the histamine-induced increase in cutaneous blood flow in the human skin (Chipman and Glover, 1976; Knigge et al., 1988). Furthermore, the erythematous reaction to the injection of histamine has been shown to be sensitive to both histamine H_1 and H_2 receptor antagonists in human skin (Marks and Greaves, 1977). In the present study, however, histamine H_2 receptors, but not H_1 receptors, were shown to mediate the cutaneous vasodilatation caused by passive cutaneous anaphylaxis in rats. Therefore, the role of histamine H_1 receptors in the regulation of cutaneous microcirculation may differ between rats and humans.

In summary, the present study has demonstrated that passive cutaneous anaphylaxis induces biphasic changes in cutaneous blood flow in rats. The initial decrease and the subsequent increase in blood flow appear to be mediated by 5-HT and histamine H_2 receptors, respectively. In contrast, bradykinin, vasodilator prostanoids such as prostaglandin I_2, and sensory nerve-derived mediators such as substance P and CGRP are unlikely to be involved in the blood-flow changes. The blood-flow response induced by passive cutaneous anaphylaxis would be a useful model for investigating the pathophysiology of allergic dermatitis and to examine the effects of drugs on this disease.

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