

The control effect of histamine on body temperature and respiratory function in IgE-dependent systemic anaphylaxis

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Background: The systemic anaphylaxis reaction comprises various symptoms, including hypotension, changes in respiration pattern, and hypothermia.

Objective: To elucidate the role of histamine in each of these symptoms, we induced the passive systemic anaphylaxis reaction in histidine decarboxylase gene knockout (HDC [−/−]) mice, which lack histamine.

Methods: HDC(−/−) mice were generated by knocking out the HDC gene, which codes for the unique histamine-synthesizing enzyme. Twenty-four hours after the injection of IgE, HDC(+/+) and HDC(−/−) mice were injected with allergen and body temperature, blood pressure, and respiratory function were monitored in each mouse.

Results: Blood pressure dropped in both the HDC(−/−) mice and the HDC(+/+) mice. In contrast, respiratory frequency dropped and the expiratory respiration time was elongated only in the HDC(+/+) mice. Body temperature was decreased in the HDC(+/+) mice and was practically unchanged in the HDC(−/−) mice. Histamine receptor antagonists blocked the body temperature drop in the HDC(+/+) mice. Intravenous histamine induced similar patterns of body temperature decrease in the HDC(+/+) mice and the HDC(−/−) mice. Mast cell-deficient *W/W^v* mice did not show the decrease in body temperature; this suggests that the histamine that contributed to the decrease in body temperature was derived from mast cells.

Conclusion: According to the results of this investigation, in the passive systemic anaphylaxis reaction, respiratory frequency, expiratory time, and body temperature are shown to be controlled by the activity of histamine, but its contribution to blood pressure is negligible. (*J Allergy Clin Immunol* 2002; 110:298-303.)

Key words: Anaphylaxis, mast cells, allergy, knockout, histamine, histidine decarboxylase, body temperature, respiration, blood pressure, bronchial asthma

The anaphylactic reaction is an IgE-dependent, immediate-type allergic reaction observed in many clinical situations, including bronchial asthma, urticaria, allergic rhinitis, and systemic anaphylaxis.¹ Systemic anaphylaxis is a systemically manifested anaphylactic reaction that includes hypotension, airway obstruction, and hypothermia.^{2,3} The Fcε receptor is found especially on the plasma membrane of mast cells and basophils and is bound to IgE antibody.⁴⁻⁹ Once an antigen makes a cross-bridge of the IgE molecules, those cells secrete the intragranular content into the environmental fluid, leading to the symptoms observed in systemic anaphylaxis.⁴⁻⁹ The reaction starts from a few minutes to 30 minutes after the allergen challenge, and it leads to an increase in vascular permeability, contraction of smooth muscle, and an increase in mucin secretion; the final results are (1) circulatory collapse, which is observed as hypotension, (2) an increase in heart rate, and (3) a decrease in peripheral blood resistance, sometimes leading to death.

It is believed that the mast cells play a chief role in the anaphylactic reaction.¹⁰⁻¹² Recently, after studies of genetically mast cell-deficient mice—namely, *WBB6F1-W/W^v*, *WCBF1-SI/SId* mice—it was reported that mast cells play a critical role in the development of the cardiopulmonary changes and mortality associated with anti-IgE-induced anaphylaxis.^{3,13} It has therefore been suggested that the intragranular mediators from mast cells are involved in these changes. Many kinds of mediators are released from the mast cells in the anaphylactic reaction, including amines (histamine, serotonin), interleukins, leukotrienes, tryptase, chymase, peroxides, heparin, and proteoglycan. Therefore, the effect of each mediator must be clarified for a complete understanding of the molecular basis of the systemic anaphylaxis reaction. Research to dissect the symptoms according to the effect of each mediator on the mediator-related symptoms requires us to use knockout animals, because the pharmacologic evidence with receptor antagonists and/or synthesis blockers could reflect unknown side effects.

In this report, we used mice (lately generated by us) in which the histidine decarboxylase (HDC) gene has been knocked out, because they have no histamine-producing

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Abbreviations used

HDC: Histidine decarboxylase
OVA: Ovalbumin
PAF: Platelet-activating factor
TNP: Trinitrophenyl

activity and therefore lack histamine in their bodies.¹⁴ We induced the systemic anaphylaxis reaction by passive immunization of the mice with anti-trinitrophenyl [TNP]-specific IgE and then triggered an allergic reaction by TNP antigen. We assessed the anaphylactic reaction by monitoring body temperature, respiration pattern, and blood pressure.

MATERIALS AND METHODS

Animals

HDC gene knockout mice were generated through use of a gene-targeting method, as described previously.¹⁴ Mast cell-deficient WBB6F1-*W/W^v* (*W/W^v*) mice and mast cell-sufficient control WBB6F1 *+/+* mice, purchased from Japan SLC, Inc (Shizuoka, Japan), were kept in our animal facility for at least 2 weeks before use. The experiments were performed on the following animals: 8- to 12-week-old male inbred 129/Sv strain HDC gene knockout mice and their wild-type controls or 8- to 9-week-old *W/W^v* mice and their *+/+* controls.

Antibodies

Mouse anti-TNP IgE (IGELa2; American Type Culture Collection) was purified from the ascites of hybridomas by ion exchange chromatography on DEAE-cellulose (Merck, Whitehouse Station, NJ)¹⁵ and by affinity isolation with a protein G column¹⁶; this was followed by removal of aggregated materials by means of ultracentrifugation at 130,000g for 90 minutes at 20°C.

Induction of passive systemic anaphylaxis

Mouse IgE anti-TNP mAbs were administered intravenously through the tail vein in volumes of 200 μ L per mouse. Twenty-four hours after the injection of IgE, mice were injected intravenously with 1.0 mg TNP₄-ovalbumin (OVA) in PBS. Control mice received OVA in PBS instead. After the introduction of antigen into the mice, changes in rectal temperature, blood pressure, and respiration pattern were monitored after the systemic anaphylaxis reaction.

Monitoring of body temperature

Changes in core temperature associated with systemic anaphylaxis were monitored through measurement of changes in the rectal temperature by means of a rectal probe coupled to a digital thermometer (Shibaura Electronics, Saitama, Japan), as described previously.¹⁷⁻¹⁹

Monitoring of blood pressure

Mice were anesthetized with sodium pentobarbital (50 mg/kg, injected intraperitoneally), and a 30-gauge polyethylene catheter connected to a liquid-filled pressure transducer system (model TP 300-T; Nihon Kohden, Tokyo, Japan) was inserted and tied into the right carotid artery. The system was flushed intermittently with heparinized saline solution. Arterial blood pressure tracings were continuously recorded until 40 minutes after the injection of TNP₄-OVA.

Whole-body plethysmography

Ventilatory function was assessed with whole-body plethysmography²⁰⁻²² under unanesthetized and unrestrained conditions, as

previously described (with a slight modification).²³ Each animal was permitted to acclimate to the chamber for at least 15 minutes before the ventilation measurements. Compressed air was humidified (90% relative humidity) and directed through the chamber at a flow rate of approximately 300 mL/min. After the animal became quiescent, the chamber was sealed while breathing was recorded on a strip chart recorder (Grass Polygraph, model 7D; Grass Instruments Co, Quincy, Mass). Pressure changes in the chamber due to inspiratory and expiratory temperature changes were measured through use of a differential pressure transducer (model 8510B-2; Endevco, San Juan Capistrano, Calif).

Plasma histamine assay

Blood was collected (by puncturing the hearts of the sacrificed mice) into microcentrifuge tubes containing EDTA on ice just after the antigen challenge; the blood was centrifuged for the plasma separation. The amounts of histamine in the plasma samples were measured through use of ELISA plates (Immunotech, Marseille, France) according to the manufacturer's instructions.

Histamine administration

To observe the direct effect of histamine on body temperature, we administered 10 μ mol, 1 μ mol, and 0.1 μ mol of histamine dichloride (Sigma, St Louis, Mo) in 200 μ L PBS by injection into the tail vein. After the administration of the histamine, body temperature was monitored as described above.

Histamine receptor antagonist experiments

We used histamine receptor antagonists to clarify what kinds of histamine receptor subtypes contribute to the decrease in body temperature and to confirm the effect of histamine as a mediator of body temperature. We administered the histamine receptor antagonists 30 minutes before the injection of the TNP antigen and monitored body temperature. The histamine receptor antagonists used were pyrilamine (Sigma) as the H₁ receptor antagonist and cimetidine (Sigma) as the H₂ receptor antagonist. We administered 2.5 mg/kg of pyrilamine and 15 mg/kg of cimetidine in 100 μ L PBS intravenously, as described in a previous report.³

Statistical analysis

Statistical analysis of all data was performed through use of the unpaired Student *t* test. *P* values for significance were set at .05 or .01. The value for each measurement is expressed as the mean $\pm$ SEM.

RESULTS

Body temperature after the passive systemic anaphylaxis reaction

Twenty-four hours after the administration of anti-TNP antibody, we challenged with TNP antigen to produce the passive systemic anaphylaxis reaction; we then monitored body temperature. The change in body temperature after the administration of the antigen in HDC(+/+) mice was completely different from that in HDC(-/-) mice (Fig 1). We observed an immediate and significant decline in body temperature in the HDC(+/+) mice; it dropped by $2.3^{\circ} \pm 0.3^{\circ}$ at 20 minutes after injection. This decrease in temperature was temporary, the lowest temperature being observed 20 minutes after administration. The temperature returned gradually to the baseline level and reached almost the initial level 60 minutes after the administration of antigen. In contrast,

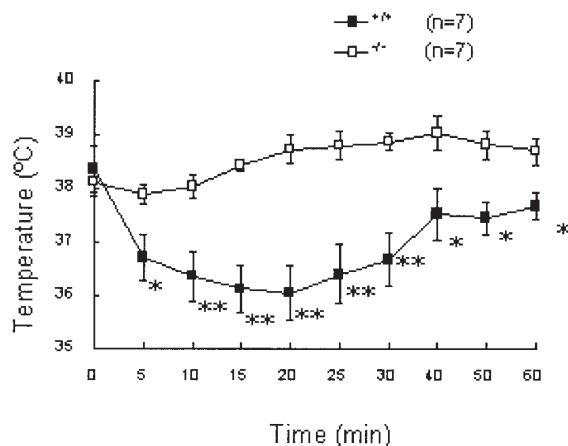


FIG 1. Change in body temperature in HDC(-/-) and HDC(+/+) mice after the passive systemic anaphylaxis reaction. Body temperature was monitored after intravenous injection of TNP₄-OVA. **P* < .05 in comparison with HDC(-/-) mice. ***P* < .01 in comparison with HDC(-/-) mice.

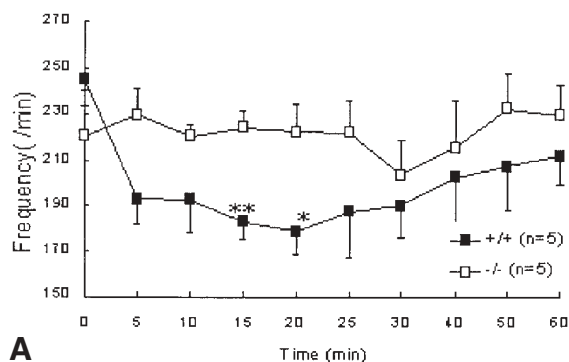
there was no significant temperature decrease in the HDC(-/-) mice. There was no significant difference in basal body temperature between the 2 mouse genotypes.

Changes in respiratory parameters after the passive systemic anaphylaxis reaction

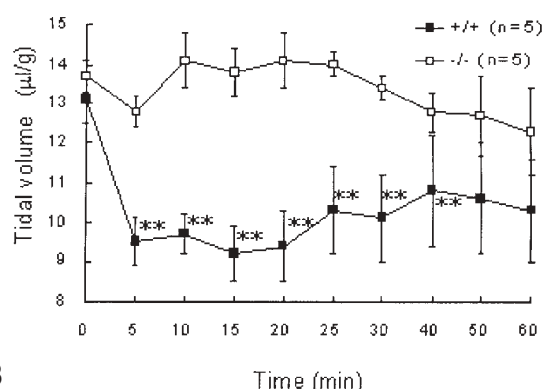
Changes in respiratory parameters were monitored through use of a body box. We measured respiratory frequency, duty cycle, tidal volume, inspiratory time, expiratory time, and ventilation. There was a significant decrease in respiratory frequency in the HDC(+/+) mice in comparison with what was seen in the HDC(-/-) mice (Fig 2, A). The frequency started to decrease within 5 minutes after the antigen challenge in the HDC(+/+) mice, continued to remain at a low level until 30 minutes, and increased gradually. On the other hand, the HDC(-/-) mice showed a fairly constant frequency. There was a significant decrease in tidal volume in the HDC(+/+) mice within 5 minutes (Fig 2, B). The tidal volume remained decreased for a longer time and did not return to the initial value even at 60 minutes after the antigen challenge. In contrast, tidal volume remained at a fairly constant level in the HDC(-/-) mice challenged with antigen. Consequently, the minute ventilation—that is, the product of the tidal volume and the frequency—started to decrease within 5 minutes, and this decrease continued for 60 minutes in the HDC(+/+) mice (Fig 2, C). The expiratory time was significantly longer in the HDC(+/+) mice than in the HDC(-/-) mice at 15 and 20 minutes after the challenge (data not shown). The inspiratory time increased in both HDC(+/+) mice and HDC(-/-) mice (data not shown).

Change in blood pressure in the passive systemic anaphylaxis reaction

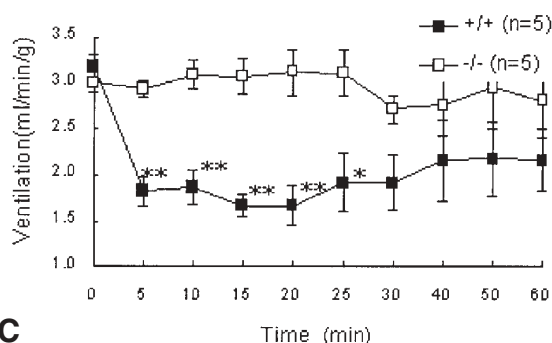
The blood pressure was monitored after passive systemic anaphylaxis. The transduced arterial pressure signal was electronically damped to provide the mean sys-



A



B



C

FIG 2. Changes in respiratory functions. **A**, Respiratory frequency. **B**, Tidal volume. **C**, Minute ventilation was followed after the challenge. **P* < .05 in comparison with HDC(-/-) mice. ***P* < .01 in comparison with HDC(-/-) mice.

temic arterial pressure. The pressure decreased in both the HDC(+/+) mice and the HDC(-/-) mice, though there was large interindividual variation. The pressure decreased to 19.0% in the HDC(+/+) mice and to 18.7% in the HDC(-/-) mice. However, the decrease from baseline was not statistically significant in either group or when the groups were combined. In addition, the difference between the 2 groups was not statistically significant at any time (data not shown).

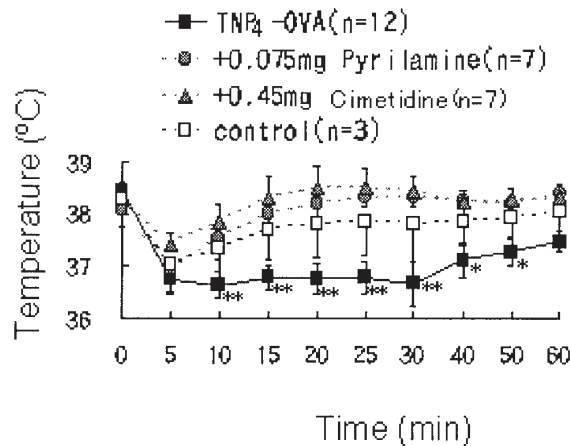


FIG 3. Effect of histamine receptor antagonists on body temperature. Two kinds of histamine receptor antagonists were injected into the tail vein along with the antigen challenge. * $P < .05$ in comparison with any of the other groups. ** $P < .01$, in comparison with any of the other groups.

Change in plasma histamine concentration after systemic anaphylaxis

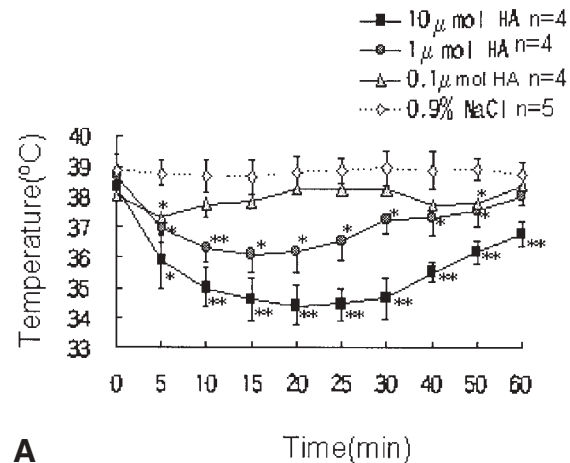
The concentration of plasma histamine was measured before and 5 minutes after the antigen challenge. It rose from $0.41 \pm 0.02 \mu\text{mol/L}$ ($n = 3$) to $4.1 \pm 0.7 \mu\text{mol/L}$ ($n = 3$) after the challenge in the HDC(+/+) mice but remained at a very low level (from $23 \pm 6 \text{ nmol/L}$ before challenge to $30 \pm 6 \text{ nmol/L}$ after the challenge [$n = 3$]) in the HDC(−/−) mice. The concentration of histamine in the HDC(+/+) mice was significantly higher than that in the HDC(−/−) mice after the challenge ($P < .01$; data not shown).

Effect of H_1 and H_2 receptor antagonists on change in body temperature

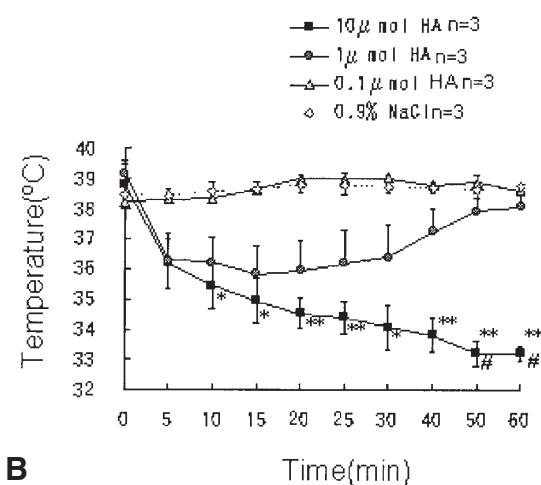
We next performed experiments using H_1 and H_2 antagonists to confirm the contribution of the histamine receptors to the changes in body temperature in the systemic anaphylaxis reaction. The difference in the change in body temperature was a clear phenotype seen exclusively in the HDC(+/+) mice. We therefore checked the effects of histamine antagonists on body temperature. The decrease in body temperature was inhibited after the treatment of either H_1 or H_2 antagonist, and the inhibition was dose-dependent (Fig 3; some data not shown).

Direct effect of histamine on body temperature

We injected various doses of histamine intravenously in HDC(−/−) mice and HDC(+/+) mice and monitored body temperature (Fig 4, A and B). The decrease in the temperature was dependent on the dose of histamine. The effect of the histamine was already obvious at 5 minutes after the injection, and the lowest temperature was induced at approximately 20 minutes. After 20 minutes the temperature gradually increased and recovered near-



A



B

FIG 4. Direct effect of histamine on body temperature. Histamine was injected into the tail vein of HDC(+/+) mice (A) and HDC(−/−) mice (B) at 3 different doses (0.1, 1, and $10 \mu\text{mol/L}$). * $P < .05$ in comparison with control. ** $P < .01$ in comparison with control. # $P < .01$ in comparison with HDC(+/+) mice.

ly to the baseline level, except in the HDC(−/−) mice receiving the highest concentration of histamine, which retained the drop in body temperature for a longer time.

Body temperature after the passive systemic anaphylaxis reaction in mast cell-deficient W/W^v mice

The sources of histamine in the body include neurons, mast cells, basophils, and gastric enterochromaffin-like cells. Accordingly, it is important to clarify the source of the histamine in the reduced body temperature reaction in the passive anaphylaxis reaction. The temperature decreased approximately 2.5°C in control mice after the systemic anaphylaxis reaction, whereas there were no decreases in the W/W^v mice (Fig 5); this suggests that in the passive anaphylaxis reaction, the major source of the histamine responsible for the decline in the body temperature is mast cells.

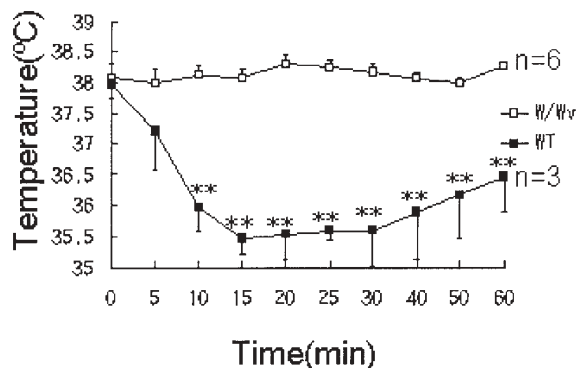


FIG 5. Body temperature in *W/W^v* and congenic control mice after the passive systemic anaphylaxis reaction. Body temperature was monitored after intravenous injection of TNP₄-OVA. ***P* < .01 in comparison with *W/W^v* mice.

DISCUSSION

The systemic anaphylaxis reaction is often lethal, and it is therefore an important clinical subject of investigation.²⁴ Various symptoms emerge during systemic anaphylaxis, but the role of each mediator in the anaphylactic reaction has not been elucidated well. Our results clarified that the decrease in body temperature is controlled with histamine and that some of the respiratory parameters are controlled with histamine. In contrast, because there were no differences in change in blood pressure between HDC(−/−) mice and HDC(+ / +) mice, the contribution of histamine to blood pressure control appeared to be minor; presumably, it is controlled by other mediators released from cells other than mast cells, as also suggested by a previous report.³ We further studied body temperature because its changing pattern showed the dramatic differences between HDC(−/−) animals and HDC(+ / +) animals. Two types of histamine receptor antagonists (H_1 and H_2) administered to HDC(+ / +) mice inhibited the change in body temperature. The histamine antagonists administered after the intracerebroventricular injection of histamine into the mice indicated that both H_1 and H_2 receptors work in the control of body temperature.²⁵ Intravenous injection of the histamine produced a pattern in body temperature that was similar to that observed in systemic anaphylaxis, suggesting that the release of the histamine occurs transiently in the systemic anaphylaxis reaction. Because we observed that mast cells from HDC(−/−) mice are abnormal, with reductions in the amounts of various proteases,¹⁴ we needed to confirm that the phenotype seen in HDC(−/−) mice was under the effect of histamine by using histamine antagonists and histamine moiety itself. We also counted IgE Fcε receptors by fluorescence-activated cell sorting analysis; it proved that the number was similar in the 2 kinds of bone marrow-derived mast cells derived from HDC(−/−) and HDC(+ / +) mice (data not shown). The response of bone marrow-derived mast cells to IgE-dependent stimuli was similar in HDC(−/−) and HDC(+ / +) mice.²⁶ The blood pressure response of the HDC(−/−) mice to the highest dose (10

μmol) of histamine was accelerated and long-lasting in comparison with that of the HDC(+ / +) mice to the same dose of histamine, suggesting the existence of a feedback system in the response to histamine. Because a very small dose (1 μg) of histamine injected into the ventricle causes a dramatic decrease in the rectal temperature,²⁵ the released histamine in the systemic anaphylaxis reaction appears to act in the brain, presumably via binding to histamine receptors in the hypothalamus.²⁷ The concentration of plasma histamine reached approximately 4 μmol/L in the HDC(+ / +) mice after the passive systemic anaphylaxis reaction. This level was still much lower than the concentration calculated from the injected histamine to reduce the body temperature. This discrepancy in the histamine concentration probably indicates that the site of the histamine release was in the brain, the histamine presumably being released by mast cells, and that the histamine acted on receptors in the hypothalamus. The injected histamine was probably degraded by the activity of histamine methyltransferase in the plasma,²⁸ excreted in urine,²⁹ and/or transferred to the extravascular space and intraperitoneum, only a very small amount reaching the receptors in the hypothalamus.

We monitored 3 kinds of parameters during systemic anaphylaxis: body temperature, respiratory function, and blood pressure. Decreases in the first two of these parameters were controlled with histamine. With regard to respiratory function, the HDC(+ / +) mice showed reduced respiratory frequency; however, this was not seen in the HDC(−/−) mice. The expiratory time was elongated in the HDC(+ / +) mice but not in the HDC(−/−) mice. The elongation of the expiratory time seen in the HDC(+ / +) mice resembles the pattern of asthmatic changes.³⁰ Taken together, these findings indicate that in the asthmatic attack the elongation of the expiratory time might be related to the action of histamine. The lung resistance after the active anaphylaxis reaction increased transiently, and the peak resistance was seen at 1 minute after the challenge, which was not seen in HDC(−/−) mice (our unpublished data). According to these results, histamine appeared to contribute to the respiratory change in the anaphylactic reaction in mice.

The decrease in blood pressure was observed in the HDC(−/−) mice to the same extent as in the HDC(+ / +) mice, indicating that one or more mediator other than histamine controlled the decrease in blood pressure. Histamine is not required to produce the hypotension in passive systemic anaphylaxis. Previously, in a study using mast cell-deficient *W/W^v* or *Sl/Sl^d* mice, it was reported that mast cells are not important in changes in blood pressure in active anaphylaxis in mice.³ The mice lacking a platelet-activating factor (PAF) receptor did not show the severe hypotension, though it was observed in the wild-type mice after active systemic anaphylaxis by OVA treatment.³¹ The source of PAF is not limited to hematopoietic cells but comes from many other tissues.^{32–35} Therefore, at least some part of the hypotension might have been caused by the effect of PAF in our study. In contrast to what was

seen with blood pressure, the *W/W^v* mice showed complete abolishment of the decline in body temperature, suggesting that the hypothermia accompanying the passive systemic anaphylaxis reaction was completely controlled by the histamine coming from the mast cells in the body. It might be important in the clinical situation to subclassify the symptoms according to the activities of each mediator and to treat them separately. To develop such symptom-specific treatments, the use of mediator-deficient mice generated by gene targeting might be indispensable.

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