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Anaphylactic responses to histamine in mice utilize both histamine receptors 1 and 2

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Abstract

Background—Anaphylaxis is a severe, potentially life-threatening reaction that can occur in response to common triggers, including food allergens (e.g., peanut), insect stings, and several medications. Activation of mast cells and basophils to release preformed mediators, such as histamine, is thought to be an important process that underlies reactions. Histamine can exert effects through four different receptors, termed H1R–H4R. Despite clinical use of both H1R and H2R blockers in the therapy for acute allergic reactions, there is little mechanistic evidence to support the necessity for blocking H2R, a receptor best characterized for its role in stomach acid production.

Methods—Here, we sought to define the necessity for histamine receptors in the pathology of anaphylaxis using H1R and H2R knockout (KO) mice, as well as a H1R/H2R double KO strain.

Results—In response to IgE-mediated systemic anaphylaxis, the symptoms and decreases in core body temperature observed in wild-type mice were reduced but not ablated in either H1R or H2R KO. In contrast, H1R/H2R KO were significantly protected and were indistinguishable from histamine-deficient mice. Intravenous injection of histamine was sufficient to elicit these responses, and similar to IgE-mediated anaphylaxis, loss of both H1R and H2R was necessary for complete protection.

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Author contributions

JBW, HAS, AJB, KBC, and PJB designed and performed the experiments. PJB wrote the manuscript. JBW, HAS, and AJB edited the manuscript.

Conflict of interests

The authors declare that they have no conflict of interest.

Conclusion—Our data demonstrate definitively that both H1R and H2R participate in the immediate systemic responses during histamine-associated pathophysiology and mechanistically support the utility of H2R-blocking therapeutics in alleviating symptoms of anaphylaxis.

Keywords

anaphylaxis; antihistamine; histamine; IgE

Histamine is a major product of activated mast cells and basophils. Acute allergic reactions requiring emergency room visits are associated with elevated plasma histamine levels (1). While antihistamines are an established therapy for many allergic diseases, these anti-allergic compounds block only the activity of histamine receptor 1 (H1R) (2) and histamine possesses four known receptors (H1R–H4R). Recent guidelines for the treatment for food allergy concluded that in the hospital-based setting, the adjunctive use of both diphenhydramine (an H1R antihistamine) and ranitidine (an H2R antihistamine) was beneficial (3). In support of this, previous clinical studies had demonstrated the beneficial effects of combined H1R/H2R blocking therapy on outcomes of acute allergic reactions in randomized, double-blinded, placebo-controlled trials (4), suggesting that the H2R may be contributing to acute allergic responses.

The rationale for inhibiting H2R in allergy is not clear. This receptor is best associated with acid production, reflux, and ulcers in the stomach, a site in which histamine is not produced by mast cells or basophils but by enterochromaffin-like cells that act via H2R on parietal cells to stimulate acid (5). However, H2R is expressed on many of the same cell types as H1R, including immune cells, endothelium, and smooth muscle cells (6). While studies have established the role of H1R histamine receptors in anaphylaxis using pharmacological inhibitors (7), there is controversy on the importance of H2R. Makabe-Kobayashi et al. (8), in addition to defining the critical importance of histamine in anaphylaxis using histamine-deficient mice, concluded that both H1R and H2R were important. However, this was based on the effects of relatively high, single doses of pyrilamine (H1R blocker) or cimetidine (H2R blocker). In contrast, Finkelman and colleagues recently showed that blocking platelet-activating factor (PAF) plus triprolidine (H1R blocker) was sufficient to prevent allergen-triggered anaphylactic shock (9), supporting previous findings that focused specifically on anaphylaxis-associated hypotension (10). However, such approaches are hindered by differences in effective doses between mice and humans and potential offtarget effects of pharmacological inhibitors. In this study, we took advantage of mice with genetic ablation of either H1R or H2R to provide complete loss of each receptor in an attempt to definitively establish the necessity for each histamine receptor. These mice have been previously reported and shown to have selective loss of the respective histamine receptors (11, 12). To address synergy and/or compensation, we also generated a H1R/H2R knockout (KO) strain that lacked both receptors by breeding mice of either single KO strain. All mice were on a C57BL/6 genetic background and confirmed to be deficient in expression of each specific receptor by RT-PCR on skin. No changes in expression of the other histamine receptors were observed in each case (data not shown).

Because histamine has been shown to be elevated in the blood of patients experiencing clinical anaphylaxis (1), we initially utilized a murine model of IgE-dependent anaphylaxis to determine the role of the histamine receptors in such responses. Mice were initially primed with intravenous injection of 50 μ g of ovalbumin (OVA)-specific murine IgE [TOe clone (13), generated by the Northwestern University Recombinant Protein Production Core Facility] and anaphylactic-like responses initiated 24 h later by intravenous injection of 40 μ g of OVA in 100 μ l of PBS. In wild-type (WT) mice, anaphylaxis was observed as a significant decrease in core body temperature (Fig. 1A) and observable symptom scores (Fig. 1B), as previously described (14) whereby 0 was assigned if no symptoms were evident, 1 through to 5 was given if symptoms were observed where 1 represents mild scratching and/or rubbing of the nose, head, or feet, scores of 2 and 3 represent intermediate symptoms, for example, edema around the eyes or mouth, pilar erection, and/or labored breathing, 4 represents significantly reduced motility, tremoring, and/or significant respiratory distress, and 5 represents death. In contrast, both H1R KO and H2R KO mice had clear protection against the decrease in body temperature ($P = 0.05$ by 2-way ANOVA on data in Fig. 1A), suggesting that both receptors contribute to these responses. H1R/H2R double KO mice demonstrated further protection than seen with either single KO strain ($P = 0.001$ by 2-way ANOVA on data in Fig. 1A) and were indistinguishable from C57BL/6 histidine decarboxylase KO mice (15), which lack the ability to synthesize histamine. This similarity between mice with no histamine and H1R/H2R KO mice suggests that the other histamine receptors are unlikely to be contributing to the immediate responses of anaphylaxis. Interestingly, some responsiveness persisted in both these strains, which may be due to PAF-mediated anaphylaxis, as previously demonstrated in mice (7). Despite this, there was significant improvement in the observable symptom score rankings in both strains (Fig. 1B). To rule out potential differences in mast cell activation, we also measured levels of the mast cell protease mMCP1 in serum from all groups, and compared with the vehicle group, this was significantly elevated and similar between WT and the histamine receptor-deficient strains (WT Vehicle 427 ± 119 pg/ml, WT IgE/OVA 3809 ± 857 pg/ml, H1R KO IgE/OVA 8823 ± 3275 pg/ml, H2R KO IgE/OVA 2483 ± 767 pg/ml, H1R/H2R KO IgE/OVA 8057 ± 2331 pg/ml). No differences in basal mMCP1 levels between any strain were observed either (data not shown).

To examine the receptor involvement in responses to histamine specifically, we next examined the responses seen upon direct delivery of histamine. As shown in Fig. 2, intravenous injection of 2 mg of histamine in 100 μ l of PBS was sufficient to evoke significant decreases ($P = 0.001$ by 2-way ANOVA) in core body temperature in WT mice but this was reduced to a similar amount in either H1R or H2R KO mice. In contrast, the responses in H1R/H2R double KO mice were statistically indistinguishable from mice receiving PBS alone by 2-way ANOVA.

Taken together, our data demonstrate that both H1R and H2R contribute to the systemic responses that occur during anaphylaxis and upon increased blood histamine levels. Interestingly, studies on the effects of histamine in isolated vascular vessels have suggested that histamine can elicit an endothelial-dependent vasodilation that is H1R driven and an endothelial-independent vasodilation that is H2R driven, likely via smooth muscle cells (16).

Consequently, the contribution of each receptor in anaphylaxis may involve tissue-specific mechanisms. The contribution of H2R in histamine-dependent responses that we have clearly demonstrated helps to mechanistically explain the observed therapeutic benefits from combination H1R/H2R blockade in acute anaphylaxis (4), as well as potentially explain the relative lack of effectiveness of H1R-targeted antihistamine compounds in the treatment for some other allergic diseases, including asthma.

References

1. Lin RY, Schwartz LB, Curry A, Pesola GR, Knight RJ, Lee HS, et al. Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. *J Allergy Clin Immunol.* 2000; 106(Pt 1):65–71. [PubMed: 10887307]
2. Simons FE, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol.* 2011; 128:1139–1150. [PubMed: 22035879]
3. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol.* 2010; 126(6 Suppl):S1–S58. [PubMed: 21134576]
4. Lin RY, Curry A, Pesola GR, Knight RJ, Lee HS, Bakalchuk L, et al. Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. *Ann Emerg Med.* 2000; 36:462–468. [PubMed: 11054200]
5. Sachs G, Prinz C, Loo D, Bamberg K, Besancon M, Shin JM. Gastric acid secretion: activation and inhibition. *Yale J Biol Med.* 1994; 67:81–95. [PubMed: 7502535]
6. Jutel M, Akdis M, Akdis CA. Histamine, histamine receptors and their role in immune pathology. *Clin Exp Allergy.* 2009; 39:1786–1800. [PubMed: 20085595]
7. Finkelman FD. Anaphylaxis: lessons from mouse models. *J Allergy Clin Immunol.* 2007; 120:506–515. quiz 516–507. [PubMed: 17765751]
8. Makabe-Kobayashi Y, Hori Y, Adachi T, Ishigaki-Suzuki S, Kikuchi Y, Kagaya Y, et al. The control effect of histamine on body temperature and respiratory function in IgE-dependent systemic anaphylaxis. *J Allergy Clin Immunol.* 2002; 110:298–303. [PubMed: 12170272]
9. Khodoun M, Strait R, Orekov T, Hogan S, Karasuyama H, Herbert DR, et al. Peanuts can contribute to anaphylactic shock by activating complement. *J Allergy Clin Immunol.* 2009; 123:342–351. [PubMed: 19121857]
10. Shibamoto T, Liu W, Cui S, Zhang W, Takano H, Kurata Y. PAF, rather than histamine, participates in mouse anaphylactic hypotension. *Pharmacology.* 2008; 82:114–120. [PubMed: 18583921]
11. Inoue I, Yanai K, Kitamura D, Taniuchi I, Kobayashi T, Niimura K, et al. Impaired locomotor activity and exploratory behavior in mice lacking histamine H1 receptors. *Proc Natl Acad Sci USA.* 1996; 93:13316–13320. [PubMed: 8917588]
12. Kobayashi T, Tonai S, Ishihara Y, Koga R, Okabe S, Watanabe T. Abnormal functional and morphological regulation of the gastric mucosa in histamine H2 receptor-deficient mice. *J Clin Invest.* 2000; 105:1741–1749. [PubMed: 10862789]
13. Sawada K, Nagai H, Baski Y, Yamaya H, Ikizawa K, Watanabe M, et al. The expression of murine cutaneous late phase reaction requires both IgE antibodies and CD4 T cells. *Clin Exp Allergy.* 1997; 27:225–231. [PubMed: 9061224]
14. Ganeshan K, Neilsen CV, Hadsaitong A, Schleimer RP, Luo X, Bryce PJ. Impairing oral tolerance promotes allergy and anaphylaxis: a new murine food allergy model. *J Allergy Clin Immunol.* 2009; 123:231–238. [PubMed: 19022495]
15. Ohtsu H, Tanaka S, Terui T, Hori Y, Makabe-Kobayashi Y, Pejler G, et al. Mice lacking histidine decarboxylase exhibit abnormal mast cells. *FEBS Lett.* 2001; 502:53–56. [PubMed: 11478947]
16. Jin H, Koyama T, Hatanaka Y, Akiyama S, Takayama F, Kawasaki H. Histamine-induced vasodilation and vasoconstriction in the mesenteric resistance artery of the rat. *Eur J Pharmacol.* 2006; 529:136–144. [PubMed: 16337938]

Figure 1.

H1R and H2R both contribute to anaphylactic responses. Mice were administered 50 μ g ovalbumin (OVA)-specific IgE intravenously and challenged 24 h later with 50 μ g OVA in 100 μ l PBS intravenously. Vehicle mice received PBS alone. Rectal body temperatures were determined at 10-min intervals (A), and symptom was scored at 20 min postchallenge. All measurements and assessments were made by two independent investigators, and data in A represent mean temperature $\pm$ SEM, while B shows individual symptom scores, $n = 6$ –10 mice from three independent experiments for both readouts.

Figure 2.

H1R and H2R both contribute to acute systemic responses to histamine. Mice of the specified strains were administered 2 mg histamine in 100 μ l PBS intravenously. Rectal body temperatures were determined at 10-min intervals. All measurements were made by two independent investigators, and data represent mean $\pm$ SEM, $n = 6-9$ mice from four independent experiments.