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The Role of Histamine H1 and H4 Receptors in Atopic Dermatitis: From Basic Research to Clinical Study

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ABSTRACT

Histamine plays important roles in inflammation and nervous irritability in allergic disorders, including atopic dermatitis (AD). It has been shown to regulate the expression of pruritic factors, such as nerve growth factor and semaphorin 3A, in skin keratinocytes via histamine H1 receptor (H1R). Furthermore, H1R antagonist reduced the level of IL-31, a cytokine involving the skin barrier and pruritus, in chronic dermatitis lesions in NC/Nga mice and patients with AD. Histamine plays roles in the induction of allergic inflammation by activating eosinophils, mast cells, basophils, and Th2 cells via histamine H4 receptor (H4R). H4R, in addition to H1R, is expressed on sensory neurons, and a decrease in scratching behaviors was observed in H4R-deficient mice and mice treated with a H4R antagonist. We found that the combined administration of H1R and H4R antagonists inhibited the itch response and chronic allergic inflammation, and had a pharmacological effect similar to that of prednisolone.

Although the oral administration of H1R antagonists is widely used to treat AD, it is not very effective. In contrast, JNJ39758979, a novel H4R antagonist, had marked effects against pruritus in Japanese patients with AD in a phase II clinical trial. Next generation antihistaminic agents possessing H1R and H4R antagonistic actions may be a potent therapeutic drug for AD.

KEY WORDS

allergic inflammation, atopic dermatitis, histamine H1 receptor, histamine H4 receptor, pruritus

ABBREVIATIONS

AD, atopic dermatitis; BMB, bone marrow-derived basophils; BMMC, bone marrow-derived mast cells; DC, dendritic cells; DRG, dorsal root ganglia; H1R, histamine H1 receptor; H2R, histamine H2 receptor; H3R, histamine H3 receptor; H4R, histamine H4 receptor; HDC, histidine decarboxylase; IL, interleukine; MDC, macrophage-derived chemokine; NGF, nerve growth factor; TARC, thymus and activation-regulated chemokine; TNCB, tri-nitro chlorobenzene; Sema3A, semaphorin 3A; TSLP, thymic stromal lymphopoietin.

INTRODUCTION

Atopic dermatitis (AD) is an allergic inflammatory disease characterized by intense pruritus, chronic eczematous plaques, and relapsing inflammation induced by repeated exposure to an antigen.¹ The prevalence of AD was reported to be approximately 3% in adults and 25% in children, and has increased by

2- to 3-fold during the last century in industrial countries.¹⁻³

Inflammation in AD skin involves mast cells, eosinophils, and Th2 cells, and is associated with histological abnormalities such as scaling, crusting, and lichenoid papules.⁴ The cytokine milieu of this inflamed skin exhibits Th2-dominant responses indicated by the production of Th2 cytokines including

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interleukin (IL)-4, IL-5, and IL-13, and Th2 chemokines such as thymus and activation-regulated chemokine (TARC/CCL17) and macrophage-derived chemokine (MDC/CCL22).⁵⁻⁸ Th2 responses are triggered by thymic stromal lymphopoietin (TSLP), which is produced by keratinocytes⁹ and epithelial cells.¹⁰ TSLP activates dendritic cells (DC)¹¹ or basophils,¹² and these cells induce the differentiation of Th2 populations as antigen-presenting cells.

Histamine is a well-known mediator of acute inflammatory and immediate hypersensitivity responses. Furthermore, it has recently been shown to affect chronic inflammation and regulate several essential events in immune responses.¹³ Four types of histamine receptors have been identified to date. Histamine H1 receptor (H1R) mediates the histamine-induced contraction of airway and vascular smooth muscle cells, and increases vascular permeability.¹⁴ Histamine H2 receptor (H2R) is involved in the release of gastric acid.¹⁵ H1R and H2R are expressed on many cell types including inflammatory and immune cells and modulate their functions. Histamine H3 receptor (H3R), which is primarily expressed in the nervous system, acts as a presynaptic autoreceptor in central and peripheral neurotransmission.¹⁶ Histamine H4 receptor (H4R), which was cloned in 2000, is mainly expressed on several hematopoietic cells and plays important roles in the histamine-induced activation of mast cells, eosinophils, monocytes, DC, and T cells.¹⁷⁻²⁰ In addition to H1R, H4R is now considered to be a new therapeutic target for AD, asthma, rhinitis and rheumatoid arthritis.²¹⁻²⁴

Vigorous pruritus is the most important issue requiring a therapeutic strategy in AD, more so than allergic inflammation. However, pruritus associated with AD is poorly controlled clinically. The mediators of pruritus have been extensively studied,²⁵ and histamine has been shown to be a potent pruritogen when applied to both normal skin in healthy individuals²⁶ and the lesional skin of AD patients.²⁷ However, although the itching associated with a nettle rash is potently alleviated by H1R antagonists, whether histamine is involved in the pruritus of AD has yet to be confirmed.

Thus, histamine exerts a range of effects on many physiological and pathological processes and new roles are still being elucidated. In this review, we aimed to briefly summarize current knowledge on H1R and H4R, and discuss the possibility of therapeutic targets regarding H1R and H4R antagonism both *in vivo* and in patients with AD.

H1R

H1R is expressed in many tissues and cells, including nerves, respiratory epithelia, vascular smooth muscle cells, endothelial cells, hepatic cells, DC and lymphocytes. H1R is coupled to G_q, which activates phospholipase C, and increases intracellular Ca²⁺ lev-

els.²⁸⁻³² As a consequence, histamine elicits the contraction of respiratory tract or vascular smooth muscles, increases vascular permeability, and induces the production of prostacyclin and platelet activating factor by activating H1R.^{32,33} Thus, almost all immediate hypersensitivity reactions, which include skin symptoms, such as erythema, pruritus, and edema, are elicited by the activation of H1R.¹⁵

The activation of H1R also affects the immune responses of various immune cells that play a role in allergic dermatitis. Histamine has been shown to enhance the production of MCP-1, RANTES, and GM-CSF in IFN- γ -stimulated keratinocytes.³⁴ It also upregulates the antigen-presenting capacity of DC, and leads to Th1 polarization through H1R.³⁵ H1R expression levels were previously shown to be higher in Th1 cells than in Th2, Th17, or Treg cells,³⁶⁻³⁹ whereas H2R is preferentially expressed on Th2 cells.⁴⁰ Cytokines such as IL-3 enhance H1R expression in Th1 cells, but not in Th2 cells.³⁶ Histamine was shown to directly augment Th1 responses by triggering H1R, while both Th1- and Th2-type responses were suppressed by H2R.³¹ In addition, histamine, via H1R, has a chemotactic effect on T cells,⁴¹ and decreases the suppressive functions of Treg cells by reducing the expression of CD25 and Foxp3.³⁹

Nerve growth factor (NGF) level in the skin horny layers of patients with AD is useful as a biomarker for disease severity, especially pruritus.⁴² H1R is also expressed in keratinocytes⁴³ and dermal dendritic cells⁴⁴ in the skin tissue, and histamine increases the production of NGF via H1R in human keratinocytes.⁴⁵ The secretion of NGF is caused by the phosphorylations of PKC, ERK and the activation of AP-1 from H1R. Furthermore, we confirmed that histamine regulated the expression of semaphorin 3A (Sema3A) via H1R, in mouse keratinocytes (Fig. 1A, B). Sema3A has been identified as a guidance molecule of nerve fibers and regulates the motility of dorsal root ganglia (DRG) growth cones and axonal morphogenesis.^{46,47} Sema3A expression levels in the epidermis were shown to be markedly lower in patients with AD than in healthy volunteers.⁴⁸ In human keratinocytes, the expression of Sema3A is changed by cellular Ca²⁺ concentration, so the activation of H1R, coupled to G_q, might be down-regulated them by Ca²⁺ mobilization.⁴⁹ Thus, histamine may be involved in the itch response in local skin lesions by increasing NGF production and decreasing Sema3A expression levels via H1R, in addition to the direct stimulation of sensory neurons.⁵⁰

Histamine was recently shown to induce the production of IL-31, which plays a role in pruritus and skin barrier function in AD.^{51,52} A previous study was reported that IL-31 was predominantly produced by Th2-skewed activated T cells *in vitro*.⁵³ Transgenic mice overexpressing IL-31 exhibit spontaneous pruritus and develop severe dermatitis.⁵⁴ In human dis-

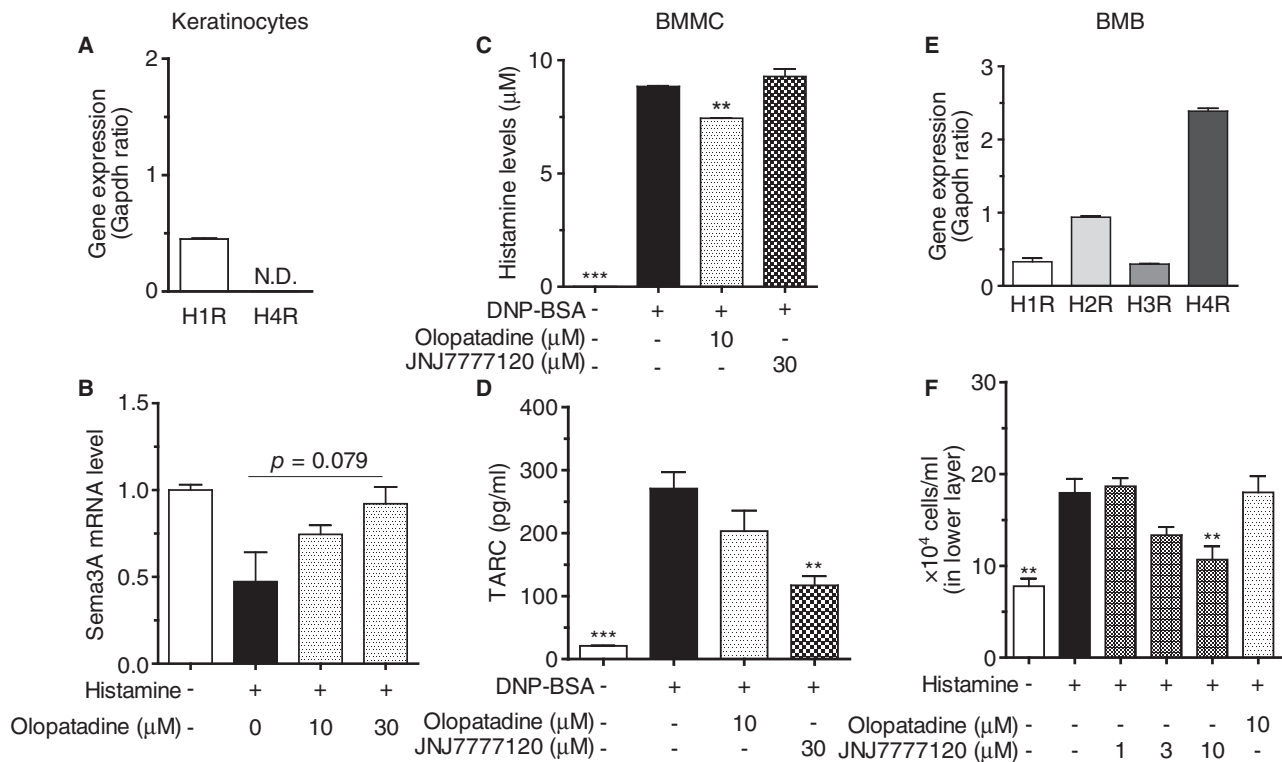


Fig. 1 The new roles of H1R and H4R-mediated pathways, keratinocytes, mast cells, and basophils *in vitro*. H1R and H4R mRNA levels were determined in the mouse keratinocyte cell line PAM212 (A). PAM212 cells were incubated for 30 min in medium containing olopatadine and then stimulated with histamine at 10 μM for 3 h, and the expression levels of Sema3A mRNA were then determined (B). Mouse bone marrow-derived mast cells (BMMC) were treated with olopatadine or JNJ7777120 for 30 min, and then stimulated with DNP-BSA for 24 hrs. Histamine (C) and TARC (D) levels were measured in the supernatant. Significance; ***P* < 0.01 and ****P* < 0.001 vs. DNP-BSA stimulation. The mRNA levels of histamine receptors were analyzed in bone marrow-derived basophils (BMB) by real-time PCR (E). Histamine was added to the bottom chamber in the chemotaxis assay for BMB. BMB treated with JNJ7777120 or olopatadine for 30 min were added to the top chamber. After incubation for 24 hrs, transwells were removed and the number of cells that infiltrated into the bottom chamber was counted (F). Significance; ***P* < 0.01 vs. histamine alone.

eases, IL-31 was significantly overexpressed in pruritic atopic dermatitis and, at its highest levels, in prurigo nodularis, one of the most pruritic forms of chronic skin inflammation.⁵² Olopatadine, an H1R antagonist, improved IL-31 levels in the lesioned skin of *Dermatophagoides farinae* applied dermatitis in NC/Nga mice.⁵⁵ Otsuka *et al.* also reported that the administration of cetirizine, an H1R antagonist, decreases IL-31 levels in the serum of AD patients.⁵⁶

Thus, histamine has the ability to induce several skin symptoms in AD, including pruritus, and affects immune responses. Nevertheless, evidence to show that the oral administration of H1R antagonists alleviates AD is lacking.⁵⁷

H4R

H4R is expressed not only on immune cells, but also on other cell types including intestinal epithelia, spleen, lung, synovial tissue, central nervous system, sensory neurons, and also cancer cells.⁵⁸⁻⁶⁴ H4R is

coupled to Gα_{i/o} proteins, therefore, the stimulation of H4R reduces forskolin-induced cAMP formation.^{65,66} This stimulation also leads to the activation of mitogen-activated protein kinase and enhanced Ca²⁺ mobilization.⁶⁷

H4R mediates the pro-inflammatory responses of histamine in both autocrine and paracrine manners. Histamine via H4R increases the expression of adhesion molecules as well as cell shape changes and rearrangement of the actin cytoskeleton, leading to the increased movement of eosinophils.¹⁸ Mast cells are a major source of, and also respond to histamine. Mast cells are attracted to allergic lesions by the histamine produced by dendritic cells during the effector stage.⁶⁸ The activation of H4R on mast cells results in Ca²⁺ mobilization and chemotaxis, without affecting degranulation, which enables the selective recruitment of effector cells and amplification of histamine-induced allergic responses.¹⁷ We recently elucidated a novel action of histamine that was mediated by H4R

using bone marrow-derived mast cells (BMMC).⁶⁹ H4R antagonists markedly inhibited the production of TARC by antigen-stimulated BMMC (Fig. 1C, D). Since histamine was released from BMMC stimulated with the antigen, the histamine released may have induced the production of these chemokines. TARC is a chemokine that acts through CCR4 expressed by Th2 cells, and is known to be an important mediator in human Th2-type immunity.^{70,71}

Similar to mast cells, basophils also express the high affinity IgE receptor FcεRI on their surface and release chemical mediators such as histamine following antigen stimulation.⁷² However, basophils and mast cells differ in several important aspects, such as anatomical localization, the production of cytokines, and antigen-presenting activity.⁷³⁻⁷⁵ Basophils have the ability to induce Th2-skewing with haptens and peptide antigens, but not protein antigens upon epicutaneous immunization.^{11,76} Shiraishi *et al.* demonstrated the histamine-induced chemotaxis of bone marrow-derived basophils (BMB), but not H4R-deficient BMB.⁷⁷ We also confirmed that BMB preferentially expressed H4R mRNA over those of the other histamine receptors (Fig. 1E), and the histamine-induced chemotaxis of BMB was blocked by an H4R antagonist, but not by an H1R antagonist (Fig. 1F). A recent study reported that the antigen-IgE mediated activation of basophils occurred in the peripheral blood of patients with AD.⁷⁸ Since basophils not only initiate allergic inflammation, but also play a role in maintaining the allergy march,⁷⁹ H4R may play important roles in the regulation of basophils in AD.

Among the Th subsets, the mRNA and protein of H4R are preferentially expressed in Th2 cells over Th1 cells and naive T cells.⁸⁰ The expression of IL-31 mRNA by stimulating H4R is upregulated though the activation of AP-1 in Th2 cells and peripheral blood mononuclear cells from patients with AD.⁸⁰ Additionally, Th17 cells polarized by IL-1β together with IL-23 also expressed H4R on the mRNA and protein levels. Since Th17 cells preferentially infiltrate the acute skin lesions of patients with AD,⁸¹ H4R may contribute to the pathogenesis of allergic inflammation by activating not only Th2 cells, but also Th17 cells.

Using H4R-deficient mice or H4R antagonist, H4R was shown to play roles not only in allergic inflammation, but also in pruritus.⁸²⁻⁸⁷ The anti-allergic effects of H4R antagonists were mainly evaluated in a dermatitis mouse model (Table 1). Dunford *et al.* clarified the involvement of H4R in the itch responses induced by allergic mechanisms.⁸² A decrease in scratching behaviors was observed in H4R-deficient mice or mice treated with the H4R antagonist, JNJ7777120.

Regarding the mechanisms of histamine-mediated pruritus, Thurmond *et al.* suggested that both H1R and H4R are expressed on C-afferent fiber terminals, and also that these antagonists may directly inhibit

the transmission of itching responses from the peripheral to central nervous system.⁸⁷ Rossbach *et al.* detected the expression of H1R, H3R, and H4R on skin innervating sensory neurons isolated from the DRG.⁸⁸ Using single-cell calcium imaging, they revealed that histamine induced an increase in calcium levels in a subset of skin-specific sensory neurons by activating H1R and H4R as well as inhibiting H3R. Furthermore, changes in fluorescence intensity accompanying the Ca²⁺ influx were stronger with the H4R agonist than with the H1R agonist and H3R inverse agonist. Therefore, H4R is considered to have essential roles in itch responses via C-fibers or/and DRG.

EFFECTS OF THE CO-ADMINISTRATION OF H1R ANTAGONISTS AND H4R ANTAGONISTS IN ALLERGIC DERMATITIS MODELS

Previously, it has been reported skin inflammation induced each antigen improved by antagonisms of H1R or H4R *in vivo*. H1R antagonists, used in clinical practice such as olopatadine,^{55,69,89} pyrilamine,⁹⁰ cetirizine⁸³ and fexofenadine,⁹¹ were confirmed the usefulness to allergic dermatitis models in mice. However, an antagonism of H1R has only limited effects in skin inflammation. Rossbach *et al.* reported that the combination of H4R and H1R antagonism had prophylactic effects on acute hapten-induced scratching, but not dermatitis.⁸³ We recently confirmed that co-administration of H1R and H4R antagonists exhibited therapeutic efficacy in chronic dermatitis.⁶⁹ When TNCB was repeatedly applied to NC/Nga mice with chronic dermatitis, H4R antagonist suppressed TNCB-induced scratching behavior, and the combination with an H1R antagonist had an additive effect. Such synergistic effects have also been reported in an acute inflammatory model by Rossbach *et al.*⁸³ and chemical-induced pruritus model by Dunford *et al.*⁸² We confirmed that the repeated administration of H1R and H4R antagonists inhibited both the itch response and chronic allergic inflammation, while the single administration of H4R and H1R antagonists also markedly inhibit scratching behaviors.⁶⁹ This combined administration potentiated anti-inflammatory effects, and had a pharmacological effect similar to that of prednisolone. More recently, Mahapatra *et al.* reported Th2-dependent antigen-specific skin inflammation using OVA-allergen attenuates by combination therapies with H1R and H4R antagonists, as well as hapten-induced model.⁹² These findings suggest that the antagonism of H4R is not only useful for pruritus and allergic inflammation *in vivo*, but also has superior effects if the antagonism of H1R is added. The combined treatment with H4R antagonist plus H1R antagonist potentiated the therapeutic effects similar to those of prednisolone in chronic dermatitis.

Table 1 Effects of H1R and/or H4R antagonists on dermatological disorders *in vivo*

Evaluation	Induction	Mouse	Compounds	Schedule	Results	Reference No.
Pruritus	Antigen-IgE, Histamine, Compound 48/80	CD-1	JNJ7777120, diphenhydramine	prophylactic	Significant inhibition was observed when JNJ7777120 was administered in conjunction with diphenhydramine, and this was more effective to that by JNJ7777120 alone.	82
Pruritus (& Dermatitis)	TDI	BALB/c	JNJ7777120, cetirizine	prophylactic	The combination of JNJ7777120 and cetirizine resulted in the strongest inhibition of scratching behavior but not allergic dermatitis.	83
Acute dermatitis	TNCB, TPA	BALB/c	Pyrilamine, thioperamide	prophylactic	In TNCB-induced biphasic ear swelling, pyrilamine and thioperamide inhibited early phase and late phase reaction, respectively.	21
Acute dermatitis	OVA + OVA primed Th2 cells	BALB/c	JNJ7777120, mepyramine	prophylactic	Mepyramine or JNJ7777120 reduced the infiltration of Th2 cells to the skin lesion. The levels of cytokines in skin lymph node-derived cells were reduced by the combined application.	92
Sub-acute dermatitis	TNCB	c57BL/6	JNJ7777120, olopatadine	prophylactic	Combined therapy with JNJ7777120 and olopatadine decreased serum IgE and Th2 cytokines more than monotherapy with olopatadine.	86
Sub-acute dermatitis	Derf	NC/Nga	Olopatadine	therapeutic	Olopatadine significantly suppressed scratching, and improved the dermatitis score	54
Chronic dermatitis	Spontaneous	Ds-Nh	Olopatadine	prophylactic	Olopatadine suppressed TSLP and Th2 cytokines levels in lesional skin.	89
Chronic dermatitis	Diet with low Mg ²⁺ and Zn ²⁺	HR-1	Fexofenadine	prophylactic	Fexofenadine significantly decreased a scratching frequency and the level of eotaxin in plasma.	91
Pruritus & Chronic dermatitis	TNCB	NC/Nga	JNJ7777120, olopatadine	therapeutic	JNJ7777120 attenuated scratching behavior and improved dermatitis and augmented by the combined treatment with olopatadine.	69
Pruritus & Chronic dermatitis	TNCB	HR-1	JNJ7777120, fexofenadine	therapeutic	JNJ7777120 reduced scratching behavior and ameliorated skin lesions, whereas fexofenadine had no such effect and did not reduce inflammation.	85

TDI, Toluene-2,4-diisocyanate; TNCB, 2,4,6-trinitro-1-chlorobenzene; TPA, 12-O-tetradecanoylphorbol 13-acetate; FITC, fluorescein isothiocyanate; Derf, *Dermatophagoides farinae*.

CLINICAL EFFECTS OF H1R ANTAGONISTS ON AD

To treat for AD, topical glucocorticoids, calcineurin inhibitor ointments, cyclosporine, and anti-histamine and anti-allergic agents are prescribed medical treatments in Japan.⁹³ Histamine levels were shown to be higher in the plasma and skin lesions of AD patients than in healthy donors.^{94,95} However, evidence for the efficacy of H1R antagonists as an oral drug is lacking and is generally not supported by randomized controlled trials. There is an only report that fexofenadine 60 mg twice daily for 7 days was significantly decreased the severity of pruritus compared with pla-

cebo.⁹⁶ On the other hand, the topical treatment of AD with H1R antagonists was also examined in clinical studies. Although their efficacies remain controversial,^{97,98} some H1R antagonists, such as doxepin,^{99,100} diphenhydramine,¹⁰¹ and loratadine,¹⁰² had beneficial effects on pruritus in AD. In human keratinocytes, histamine decreases the formulation of tight junctions and the expression of flaggrin, a gene responsible for AD, via H1R (Table 2).⁴³ As described above, histamine also regulates neuron guidance factors such as NGF and Sema3A via H1R, in epidermis. These findings indicate that H1R is partly involved in the pathogenesis of AD-lesional skin.

Table 2 Expression and functional characteristics of histamine, H1R, and H4R in healthy donors and atopic dermatitis patients

Donor	Sample	Expression	Functions	Reference No.
Healthy	Keratinocytes	H1R	Histamine suppresses epidermal keratinocyte differentiation and impaired skin barrier function via H1R.	43
Healthy	Keratinocytes	H1R	Promotion of RANTES and GM-CSF secretion and augmentation of the IFN- γ -induced release of the chemokines MCP1, RANTES, MIP3 α , IP-10, and GM-CSF.	34
Healthy	Th17 cells	H4R	Increased production of IL-17 and induction of AP-1 in Th17 cells by stimulation with histamine of an H4R agonist.	38
Healthy	Th2 cells	H4R	H4R is highly expressed on Th2 cells by IL-4 and activation with H4R upregulates IL-31 mRNA in Th2 cells.	80
Healthy	Langerhans cells	H4R	Increased migration from the epidermis and downregulation of the production of CCL2 via H4R activation.	103
Atopic dermatitis	Plasma	Histamine	Higher in patients with AD than in healthy volunteers.	94, 95
Atopic dermatitis	Lymphocytes	H4R	STAT1 phosphorylation and cleavage are regulated by H4R in human atopic and non-atopic lymphocytes.	62
Atopic dermatitis	Dendritic cells	H4R	Histamine or an H4R agonist downregulates the production of CCL2 and upregulates IFN- γ . H4R may contribute to the shift from a Th2 to Th1 milieu, as seen in the transition from acute to chronic lesions of AD.	104
Atopic dermatitis	Keratinocytes	H1R and H4R	Highly expression in keratinocytes of patients with AD, and induction of proliferation via activation with H4R.	105

CLINICAL TRIALS OF H4R ANTAGONISTS ON AD

H4R, in addition to H1R, is expressed on cells constituting the epidermis and not only on immune cells, obtained from healthy volunteers¹⁰³ and AD patients,¹⁰⁴ and have functional roles in these cells (Table 2). H4R is more abundantly expressed in keratinocytes from patients with AD than in those from healthy donors.¹⁰⁵ The H4R agonist, 4-methylhistamine, was shown to induce the proliferation of keratinocytes from patients with AD.¹⁰⁵ Thus, H4R is also involved in the pathogenesis of AD. Before now, anti-histamine drugs with H4R antagonism are unknown in clinic.¹⁰⁶ Only alcaftadine, which is an anti-histamine drug for treatment of allergic conjunctivitis, has an affinity with H4R ($K_i = 2.9 \mu\text{M}$), but it has high selectivity with H1R ($K_i = 3.1 \text{ nM}$).¹⁰⁷ It is considered alcaftadine has a no-effective toward H4R in clinic since it has high sensitivity of nearly 1,000-fold, compared with H1R to H4R.

The safety and efficacy of JNJ39758979, a selective and high affinity H4R antagonist, were recently assessed at 100 or 300 mg/day for 6 weeks in patients with AD.¹⁰⁸⁻¹¹⁰ The primary endpoint (Eczema Area and Severity Index score at week 6) was not significant, although both active groups showed numerical improvements over the placebo group. Significant symptomatic improvements were observed in patient-reported itch severity and duration. In addition, the effects of JNJ39758979 on histamine-induced itch in

healthy donors were evaluated in phase I study. Compared with placebo or cetirizine, which is an H1R antagonist, the reduction of pruritus score was significant for JNJ39758979.¹¹¹ Interestingly enough, JNJ39758979 was ineffective against wheal and flare reactions associated with intradermal histamine injection, while these effects were almost completely eliminated by cetirizine. These results suggested histamine induces flare response and pruritus by activation with H1R and H4R, respectively, in skin tissues of human. JNJ39758979 showed significantly anti-pruritic effects in human, but agranulocytosis occurred in two patients administered 300 mg in phase II trial. This was attributed to the off-target effects of JNJ39758979 and the sponsor terminated this clinical study. The finding obtained from clinical trials is that JNJ39758979 had an anti-pruritic effect in moderate AD patients, and healthy subjects with histamine challenge.

CONCLUSIONS

We summarized the usefulness of H1R and H4R antagonists to treat chronic allergic dermatitis in mice and AD patients in this review. Histamine exhibits various actions on skin disorders through H1R and H4R. Histamine regulates nerve fiber interventions by decreasing the expression of Sema3A mRNA and increasing NGF levels via H1R in keratinocytes, and directly activates sensory neurons via H1R and H4R. The increase in NGF levels and decrease in the expression of Sema3A was also been confirmed in the

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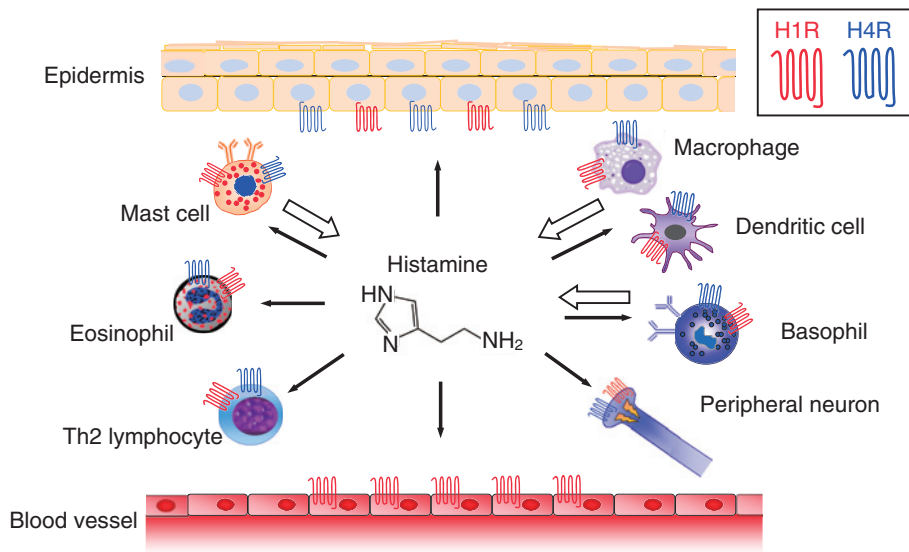


Fig. 2 H1R and H4R pathways in chronic allergic dermatitis.

skin lesions of AD patients, as well as *in vivo*. Furthermore, histamine, via H4R, activates the effector cells of allergic responses, such as mast cells, basophils, and eosinophils, and induces the production of TARC, which reflects the clinical severity of AD. Histamine also regulates the functions of not just Th2 cells but Th1 and Th17 cells, via various receptors. Thus, histamine affects various cells located in skin tissues via mainly H1R and H4R (Fig. 2). Especially, it is an interesting knowledge that IL-31, a cytokine which induces of pruritus and Th2-type allergic response as a new biomarker, is regulated via histamine H1R and H4R.

Topical glucocorticoids frequently cause skin atrophy and elicit side effects due to their systemic administration. We found that the co-administration of an H1R antagonist and H4R antagonist had potent inhibitory effects that were equal to those of steroids in a chronic allergic dermatitis mouse model, and JNJ 39758979 exhibited anti-pruritic effects in moderate AD patients. More recently, ZPL-3893787 for Ziarcopharm, which has entered into an agreement from Pfizer Inc., started phase I study for allergic diseases. Next generation antihistaminic agents with H1R and H4R antagonistic actions should be developed in the future to treat patients with AD.

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