

Histamine H4 Receptor in Allergic Dermatitis

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ABSTRACT

Allergic dermatitis, the common skin disease, includes chronic allergic contact dermatitis (CACD) and atopic dermatitis (AD), the Th2 dominant diseases. Histamine aggravates CACD in mice. Histamine H4 receptor (HH4R) is expressed on eosinophils, mast cells, T cells, natural killer cells, antigen presenting cells, basophils, keratinocytes and sensory neurons and is suggested to be related to allergic dermatitis. Administration of the HH4R antagonist JNJ777120 is effective to the murine CACD models. Furthermore, combination of JNJ777120 and the histamine H1 receptor antagonist olopatadine hydrochloride is a potent therapeutic target in chronic inflammatory skin diseases such as CACD and AD, since combined therapy is more effective than monotherapy.

Key words: Histamine H4 receptor (HH4R); Chronic allergic contact dermatitis (CACD); Atopic dermatitis (AD); HH4R antagonist; Combined therapy between HH4R and histamine H1 receptor antagonists

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INTRODUCTION

Allergic dermatitis includes allergic contact dermatitis (ACD) and atopic dermatitis (AD). A widely used murine model of human ACD is the delayed type hypersensitivity response to small organic haptens with potent sensitizing capacity^[1]. However, ACD is considered to be the Th1 dominant disease. In patients with chronic allergic contact dermatitis (CACD), repeated exposure to antigens through the skin is thought to contribute to the development of eczematous lesions. In murine model, repeated application of antigens results in antigen-specific hypersensitivity responses from a delayed- to an early-type response accompanied with accumulation of mast cells in the upper part of the dermis and elevation of serum IgE levels^[2] and develops CACD. AD, aggravated by chronic exposure to antigens, is a common and distinctive form of allergic skin diseases associated with eczematous lesions, early-type hypersensitivity responses, and increased IgE production in response to environmental allergens^[3,4]. Therefore, AD bears clinical, histological, and immunological similarities to CACD^[5,6]. Both CACD and AD are the Th2 dominant diseases and histamine aggravates CACD in mice^[7].

Histamine H4 receptor (HH4R) was cloned in human as the 4th histamine receptor^[8]. HH4R is suggested to be related to inflammatory reactions. Numerous different inflammatory cell are involved in pathogenesis of inflammatory skin diseases, including T cells, antigen presenting cells, granulocytes, keratinocytes. T cells play a pivotal role among immune effector cells in allergic dermatitis^[9]. This article introduces the functions of HH4R on cell types, the relationship between HH4R and allergic dermatitis, and the effects of the selective HH4R antagonist JNJ777120 in CACD.

HH4R ON CELL TYPES

1. Eosinophils

Human eosinophils express HH4R and histamine acts as chemoattractant for eosinophils^[8, 10]. Activation of HH4R by histamine primes eosinophils for increased chemotactic responses to eotaxin^[11]. HH4R mediates eosinophil cell shape change and upregulation of adhesion molecules CD11b/CD18 (Mac-1) and CD54 (ICAM-1) on eosinophils^[12]. The HH4R antagonist JNJ7777120 inhibits a migration of eosinophils into inflamed tissues^[13].

2. Mast Cells

Human mast cells express HH4R on the mRNA and protein levels and stimulation of this receptor in mast cells results in enhanced CXCL12-mediated recruitment of precursor mast cells into the dermis^[14-16]. Human mast cells respond to 4-methylhistamine (selective HH4R agonist) for sustained intracellular calcium mobilization, degranulation and cytokine production. They produce IL-4, IL-5, IL-6, IL-8, IL-13, IL-1beta and MCP-1^[17]. The stimulation of HH4R by the HH4R agonist JNJ28610244 enhances production of IL-6 via ERK and phosphoinositide 3-kinase activation in murine mast cells^[18]. HH4R mediates the lease of TNF-alpha and IL-8 in human mast cells via PI3K, Ca²⁺-Calcineurin-NFAT and MAPKs signaling pathways^[19]. The activation of HH4R by 4-methylhistamine causes the release of IL-13 and RANTES on human mast cells^[20].

3. T Cells

Human CD4 (+) T cells express HH4R. HH4R expression on Th2 cells is higher compared with Th1 cells and stimulation of HH4R with antigens (4-methylhistamine and clobenpropit) results in an induction of transcription factor AP-1^[21]. Th2 conditions is observed in AD and CACD. The number of Th17 cells is increased in peripheral blood of AD and associated with severity of AD^[22]. Th17 cells also express HH4R. Stimulation with histamine or HH4R agonist (4-methylhistamine) increases the production of IL-17 and induces AP-1 in Th17 cells^[23]. Messenger RNA expresses in human CD8 (+) T cells and stimulation of HH4R (clobenpropit) results in a release of IL-16^[24]. On the other hand, HH4R agonist (clobenpropit) blocks IFN-gamma and IL-5 production by antigen-specific T-cell lines^[25].

4. Natural Killer Cells

Natural killer (NK) cells affect dendritic cell maturation and function. NK cells may play a role in regulating dendritic cells in AD^[26]. NK cells express the protein of HH4R and chemotactic effects of histamine on NK cells are induced via HH4R^[27]. NK cells are detected in the lesional skin of patients with inflammatory skin diseases, where high levels of histamine are present. HH4R stimulation by HH4R agonist (ST1006) upregulates CCL3 and CCL4 at the mRNA level and in addition for CCL3 also at the protein level in human NK cells^[28]. HH4R agonist (ST1006) induces NK cell chemotaxis in vitro, which is inhibited with HH4R antagonist (JNJ7777120). In the murine model of allergic dermatitis, HH4R agonist (ST1006) increases the number of NK cells compared to just allergen challenged ears. Moreover, the number of NK cells is lower in ovalbumin-sensitized HH4R (-/-) mice^[29].

5. Antigen Presenting Cells

Antigen presenting cells, which include monocytes, dendritic cells and Langerhans cells, are the major components in the initiation

of allergic inflammation. After antigen is taken into and presented on these cells, cytokines and chemokines are secreted to generate a cytokine network. Human monocytes and monocyte-derived dendritic cells express HH4R and its stimulation by clobenpropit and 4-methylhistamine results in a suppression of IL-12, IL-27 and CCL2, leading to calcium influx and chemotaxis^[27, 30-32]. On the other hand, HH4R antagonist (JNJ7777120) inhibits the production of CCL17 and CCL22 in the human monocyte-derived Langerhans cells of AD patients^[33]. However, no evidence for the presence of HH4R in human monocyte is reported^[34]. Further studies to HH4R on antigen presenting cells are needed.

6. Basophils

Histamine plays roles in the induction of allergic inflammation by activating basophils via HH4R^[35]. Basophils express HH4R mRNA levels. Histamine and HH4R agonist (ST1006) initiate active migration of basophils. A reduction in FcεRI crosslinking-mediated surface expression of CD63 and CD203c is observed on basophils after pre-incubation with histamine or the HH4R agonist (ST1006)^[36].

7. Keratinocytes

Keratinocytes play an important role in inflammatory skin diseases. They induce the recruitment of various cell types to the skin lesion and regulate the production of inflammatory cytokines and chemokines. Keratinocytes on human epidermal tissue express HH4R^[37]. Outer root sheath keratinocytes of AD increase the expression of HH4R compared with keratinocytes of healthy donors^[38].

8. Sensory neurons

Skin innervating sensory neurons express HH4R. Histamine induces a calcium increase in a subset of skin-specific sensory neurons via HH4R. It is assumed that histamine excites histamine-sensitive afferents and elicits the sensation of itch via HH4R^[39].

THE RELATIONSHIP BETWEEN HH4R AND ALLERGIC DERMATITIS

HH4R is upregulated during differentiation of keratinocytes in the upper layer of epidermis versus keratinocytes in basal layer^[37]. Proliferation of foreskin and outer root sheath keratinocytes is blocked by the HH4R antagonist (JNJ7777120)^[38]. Histamine might promote epidermal hyperplasia via HH4R in allergic dermatitis. HH4R expression on Th2 cells is higher compared with Th1 cells and stimulation of HH4R (4-methylhistamine and clobenpropit) results in an induction of transcription factor AP-1 in Th2 cells, which are dominant in allergic dermatitis^[21]. Th17 cells, expressing HH4R, play a potential role in AD and the number of this cell type is associated with the severity of AD^[22]. Th17 function is one of the important factors regulating chronic allergic diseases such as CACD and AD^[40]. Histamine induces chemotaxis of eosinophils through HH4R^[12] and rapidly induces shape changes in eosinophils while at the same time enhancing their chemotactic response to chemokines through HH4R^[11, 12]. HH4R also mediates histamine-induced chemotaxis of mast cells in mouse^[14, 41]. HH4R is involved in pruritic responses in mice to a greater extent than H1 receptor^[42]. HH4R (-/-) mice show a clear amelioration of the skin lesions with a diminished influx of inflammatory cells and reduced epidermal hyperproliferation at ovalbumin-induced AD-like skin lesions. HH4R (-/-) mice have a reduced amount of ovalbumin-specific IgE, a reduced number of splenocytes and lymph node cells with a decreased number of CD4+

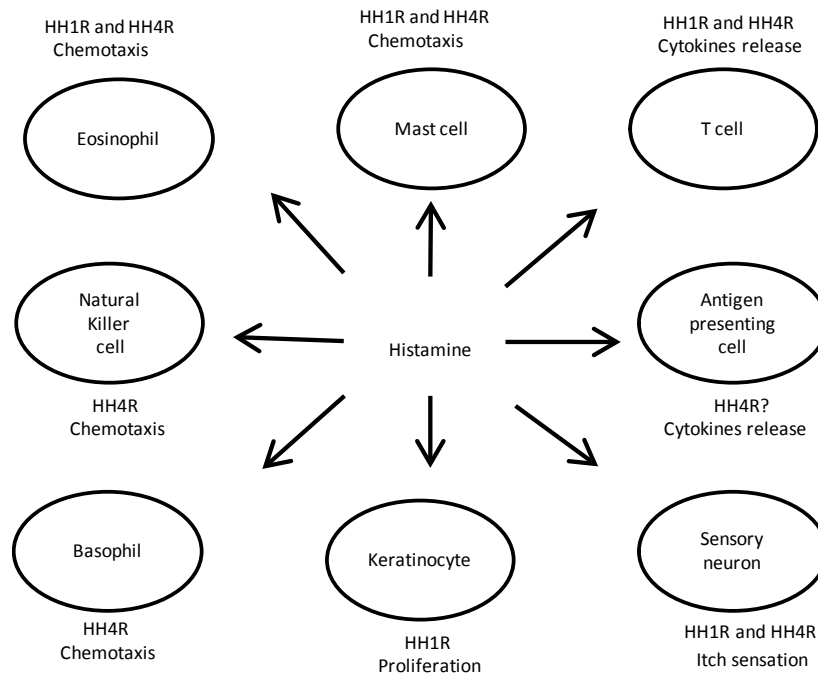


Figure 1 Remarkable effects of histamine via HH1R and HH4R in chronic allergic inflammation.

T cells^[43]. Taken together, these results strongly indicate that HH4R antagonism is effective for allergic dermatitis (Figure 1).

HH4R ANTAGONIST TO CACD

Treatment with JNJ777120, the HH4R antagonist, leads to a reduction in inflammation, mast cell, and eosinophil infiltration in the skin of repeatedly sensitized mice with FITC. This phenomenon is accompanied by a reduction in the levels of several cytokines^[44]. Levels of IL-4, IL-5 and IL-6 in skin lesions of CACD are decreased, whereas levels of IFN- γ and IL-12 are increased by HH4R antagonistic activity. Serum IgE levels decreases with the HH4R antagonist. JNJ777120 decreases the numbers of mast cells and eosinophils in eczematous lesions in the wild-type mice, while 4-methylhistamine, the HH4R agonist, increases counts for these cells in histidine decarboxylase (HDC) (-/-) mice. Eczematous lesions are ameliorated in the presence of JNJ777120 in the wild-type mice, while they are aggravated in the presence of 4-methylhistamine in HDC (-/-) mice^[45]. JNJ777120 inhibits the increases in thymus and activation-regulated chemokine/CCL17 and macrophage-derived chemokine/CCL22^[46].

Combined treatment of olopatadine, the histamine H1 receptor (HH1R) antagonist, and JNJ777120 reduces scratching counts and serum IgE level and its effects are as potent as that of prednisolone^[46]. Olopatadine plus JNJ777120 inhibits thymus and activation-regulated cytokine production in bone marrow-derived mast cells and decreases the infiltration of CD4⁺ cells in the skin^[46]. Furthermore, combined therapy further decreases serum IgE and IL-4 compared to olopatadine or JNJ777120 monotherapy. Skin levels of IFN- γ and IL-12, representative Th1 cytokines, are increased by the repeated challenge and tend to be reduced by olopatadine and increased by JNJ777120. Addition of olopatadine negates this JNJ777120 inverse effect^[47]. Marked epidermal hyperplasia with intercellular edema and intense dermal cell infiltration is observed after repeated challenge. These eczematous lesions are ameliorated by combined therapy of olopatadine and JNJ777120. Combined

therapy decrease epidermal thickness compared with olopatadine monotherapy. Furthermore, the number of eosinophils and mast cells are also decreased by combined therapy compared with olopatadine monotherapy^[47]. The combined administration of HH4R and HH1R antagonists inhibits the itch response and chronic allergic inflammation, and has a pharmacological effect similar to that of prednisolone^[35].

CONCLUSION

The above studies provide evidence for a pathogenetic and immunomodulatory role of HH4R in allergic inflammatory skin diseases. HH4R modulates the relevant cell populations by influencing chemotaxis and cytokine production. Therefore, HH4R or combination of HH4R and HH1R antagonists is a potent therapeutic target in chronic inflammatory skin diseases such as CACD and AD.

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