Histamine and Histamine Receptors in Allergic Dermatitis

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Contents

Abstract

In this chapter we will first introduce the pathophysiological process of several skin diseases including allergic dermatitis, a common skin disease, including chronic allergic contact dermatitis (CACD), and atopic dermatitis (AD). In CACD and AD patients, repeated skin exposure to antigens contributes to the development of chronic eczematous lesions. Repeated application of haptens on mice allows emulation of the development of CACD in humans. Further, we will focus on H1, H2, and H4 histamine receptors and their effects on CACD and AD. Histamine-deficient mice, with a knockout histidine decarboxylase (HDC)

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gene, were used to investigate the role of histamine in CACD and AD. Histamine induces infiltration of inflammatory cells, including mast cells and eosinophils, and elevates Th2 cytokine levels in CACD. Histamine promotes the development of eczematous lesions, elevates IgE serum levels, and induces scratching behavior in CACD. The administration of H1 or H4 receptor antagonists was effective to ameliorate these symptoms in murine CACD models. The combination of H1 and H4 receptor antagonists is a potential therapeutic target for chronic inflammatory skin diseases such as CACD and AD, since combined therapy proved to be more effective than monotherapy.

Keywords
Allergic dermatitis • Atopic dermatitis • Chronic allergic contact dermatitis • Histidine decarboxylase (−/−) mice

1 Introduction

Dermatitis is the most common disease in dermatology practice. Dermatitis is characterized by itching and soreness of variable intensity, and in variable degrees, a range of signs, including dryness, erythema, excoriation, exudation, fissuring, hyperkeratosis, lichenification, scaling, and vesiculation. Dermatitis can be called acute, subacute, or chronic, depending on its clinical and pathological features. Besides this classification, there is no international agreement on the subcategories of dermatitis; only dermatitis with specific names according to their distinguishing features is clinically considered.

Contact dermatitis is known as one of the most common types of dermatitis, with itch sensation (Thomson et al. 2002). Three types of contact dermatitis are known: (a) irritant contact dermatitis, (b) allergic contact dermatitis (ACD), and (c) photocontact dermatitis. (a) Irritant contact dermatitis is triggered by chemical or physical irritant factors. Chemical irritants including solvents, surfactant, acid, and alkalis are able to induce contact dermatitis. The most common physical irritant is low humidity due to air-conditioning (Morris-Jones et al. 2002). (b) ACD is clinically problematic, since it is a very common occupational- and environmental-related disease. Together with other forms of allergies, the ACD progresses in two stages: an initial sensitization phase, followed by an elicitation phase (Kimber et al. 2002). In metal allergy, one of the most representative forms of ACD, allergens include nickel, chromium, and cobalt. Phototoxic contact dermatitis is more common than photoallergic contact dermatitis and resembles severe sunburn. Photoallergic contact dermatitis or photocontact dermatitis resembles ACD on sun-exposed areas, although sometimes it may extend to covered areas as well (Lugović et al. 2007; Honari 2014).

Atopic dermatitis (AD) is a common, chronic or chronically relapsing, severely pruritic, eczematous skin disease. The incidence of AD is considered to be increasing worldwide (Williams et al. 1999), both the adolescent and adult types of AD

(Takeuchi and Ueda 2000). AD is a chronic inflammatory skin disease characterized by eczematous skin lesions and intense pruritus (Kabashima 2013). The immunological Th2 response has been found to play a key role in the pathogenesis of AD (Bieber 2010). The production of Th2 cytokines, namely, interleukin (IL)-4, IL-5, and IL-13, increases immunoglobulin (Ig) E production and/or eosinophil activation, subsequently amplifying the allergic inflammation (Brandt and Sivaprasad 2011; Guttman-Yassky et al. 2011). Levels of total IgE (Gebhardt et al. 1997) and peripheral eosinophil counts (Simon et al. 2004) correlate with AD severity.

In this chapter we will focus on the role of histamine in a murine AD model, especially in relation to T-helper cells, the activity of histamine on the scratching behavior, and subtypes of histamine receptors with type-specific activity.

2 Allergic Dermatitis

Allergic dermatitis includes ACD and AD. ACD basically occurs as a type IV allergic reaction. The causative agent invades the body percutaneously and is captured by epidermal antigen presenting cells, i.e., Langerhans cells. These cells migrate to the regional lymph nodes and induce T cell activation. Consequently, T cells proliferate in the lymph nodes achieving sensitization. When the same agent reinvades the skin, the sensitized T cells activate and release inflammatory cytokines leading to dermatitis. Among numerous different inflammatory cells involved in the pathogenesis of dermatitis, including antigen presenting cells, granulocytes, and keratinocytes, T cells play a pivotal role among immune effectors in allergic dermatitis (Novak et al. 2003). AD is defined as a disease in which the main lesion is an itching eczema with recurrent remissions and exacerbations. Most patients also show an atopic condition (Saeki et al. 2009). In most AD cases, in addition to type IV allergic reactions, type I allergic reactions (e.g., atopic conditions such as urticaria, allergic rhinitis, and asthma) are also involved.

A widely used mouse model of ACD is the delayed-type hypersensitivity response (type IV allergic reaction) to small organic haptens with potent sensitizing capacity (Grabbe and Schwarz 1998). As previously discussed, AD is predominantly orchestrated by Th2 cells, while ACD is considered to be a Th1 dominant disease. In patients with chronic allergic contact dermatitis (CACD), the repeated exposure to antigens through the skin is thought to contribute to the development of the eczematous lesions. In the murine model, repeated applications of an antigen result in antigen-specific hypersensitivity responses. The skin reaction in mice changes from a delayed- to an early-type response in correlation to the increased number of repeated applications of the allergen, and finally accompanied by the accumulation of mast cells in the upper part of the dermis and elevation of serum IgE levels (Kitagaki et al. 1995).

AD, aggravated by chronic exposure to antigens, is a common and distinctive form of allergic skin diseases associated to eczematous lesions, early-type hypersensitivity responses, and increased IgE production in response to environmental

allergens (Cooper 1994; Ohmen et al. 1995). AD bears clinical, histological, and immunological similarities to CACD (Wang et al. 2007; Man et al. 2008). Both CACD and AD are Th2 dominant diseases.

3 The Role of Histamine in Atopic Dermatitis

3.1 Pathogenetic Role of Histamine

The pharmacological assessment of the in vivo effects of histamine in the development of eczematous lesions was an issue prior to the development of histidine decarboxylase (HDC) knockout mice, since most observations involve the use of histamine receptor antagonists. To overcome this limitation, we produced histamine-deficient mice by disrupting the HDC gene (Ohtsu et al. 2001).

First, we observed a skin allergic reaction. Plasma extravasation after a challenge with compound 48/80, a compound which induces an immediate-type allergic response, was positive in HDC (+/+) mice but negative in HDC (−/−) mice (Ohtsu et al. 2002). On the other hand, contact hypersensitivity, a delayed-type allergic response, showed no difference in a model of thickening of the ear skin after trinitrochlorobenzene (TNCB) between HDC (+/+) and HDC (−/−) mice (Ohtsu et al. 2002; Seike et al. 2010).

A repeated epicutaneous application of sensitizing agents develops a skin reaction characterized by epidermal hyperplasia, accumulation of large numbers of mast cells and CD4+ T cells beneath the epidermis, and increase in the serum levels of antigen-specific IgE (Kitagaki et al. 1995), similar to the observations in AD (Kim et al. 2015). The contact hypersensitivity response shifts from a delayed-type hypersensitivity to an immediate-type response due to repeated applications (Kitagaki et al. 1995). The role of histamine in the extent of the skin reaction induced by repeated applications of contact sensitizing agents was investigated on HDC (−/−) mice. Histological examination of the skin reveals that mice display hyperplastic epidermis and infiltration of mast cells, CD4+ T cells, and eosinophils following repeated daily applications of diphenylcyclopropenone (DCP) to the skin. The magnitude of these changes was more significant in HDC (+/+) than in HDC (−/−) mice (Seike et al. 2005a, 2010). This finding suggests that histamine promotes the development of chronic eczematous-like lesions.

3.2 Histamine and Th2, Th1, Treg, and Th17

In a repeated challenge with TNCB, which is the model for CACD, the levels of Th2 cytokines IL-4 and IL-5 were higher in skin lesions of HDC (+/+) than of HDC (−/−) mice. On the other hand, IFN-γ and IL-12 levels, representative Th1 cytokines, showed no significant changes in skin lesion from HDC (+/+) or HDC (−/−) mice. Serum IgE levels in HDC (+/+) mice were higher than in HDC (−/−) mice (Seike et al. 2010). From these observations, together with another report

(Mahapatra et al. 2014), we can conclude that histamine seems to induce Th2 dominant allergic reactions in CACD.

Regulatory T cells (Tregs) are a subset of T cells which regulate effector T cells and lead to immune tolerance in order to reduce allergic reactions and play a role in the maintenance of immunological self-tolerance by actively suppressing self-reactive lymphocytes (Hori et al. 2003). Tregs play a role in ameliorating contact dermatitis by suppressing effector T cells (Ring et al. 2006). TGF-β1 is one of the main regulators of Treg recruitment in allergic lesions (Chen et al. 2003). Since the level of TGF-β1 and the number of Tregs in eczematous lesions are significantly higher in HDC (−/−) compared to HDC (+/+) mice, histamine is thought to decrease the levels of TGF-β1 and, therefore, its effect. This negative effect might help to produce the skin lesions by decreasing the number of Tregs cells (Tamaka et al. 2015).

Th17 cells, a distinct lineage of effector CD4+ T cells, are characterized by the production of IL-17 and IL-22 (Liang et al. 2006). IL-17 induces Th2 immune responses in murine AD model (Nakajima et al. 2014). Histamine might be an important regulator for Th17 recruitment in some cases, since increased Th17 levels are observed in the skin lesions in the CACD model of HDC (−/−) mice (Seike et al., unpublished data). However, in the arthritis model, it was demonstrated that the H4 receptor knockout mice and H4 receptor antagonist reduce the clinical score, which might be mediated by the reduction of IL-17 levels (Cowden et al. 2014). It was not clear whether the differential effect of histamine in CACD and arthritis is due to the differences between the models or to the specific activity of histamine and H4 receptor in allergic states. Further research is necessary to elucidate the mechanism by which histamine exerts its effect on Th17 cells.

3.3 Histamine-Induced Scratching Behavior

Pruritus has been defined as an unpleasant sensation that triggers a desire to scratch (Ikoma et al. 2011). Contact dermatitis is known as the common skin disease with itch sensation as a typical symptom (Nojima and Carstens 2003).

The role of histamine on scratching behavior and neuronal conditions has been extensively reported (Leknes et al. 2007; Nakano et al. 2008; Akiyama et al. 2009). We used HDC (+/+) and HDC (−/−) mice after daily applications of DCP to observe the long-term effects of histamine. Interestingly, scratching behavior was observed in HDC (+/+) but not in HDC (−/−) mice after DCP application (Seike et al. 2005b). A significant increase in c-Fos (+) cells was observed in lamina I in the dorsal horn of HDC (+/+) mice, whereas not in HDC (−/−) mice (Seike et al. 2005b). Therefore, the sensory cells in lamina I of the dorsal horn of HDC (+/+) mice are considered to be more excited when compared with those of HDC (−/−) mice. Moreover, substance P expression in the spinal dorsal horn has been shown to be increased with peripheral sensory stimulation after DCP treatment (Seike et al. 2005c). Since it was reported that mast cells around the nerve endings produce histamine stimulated by substance P (Erjavec et al. 1981), histamine

production might be responsible for the itch sensation in HDC (+/+) mice. E-cadherin, one of the synapse-related molecules, is expressed in the spinal dorsal horn by peripheral sensory stimulation induced in DCP-treated mice (Seike et al. 2005c). The E-cadherin expression is increased only in HDC (+/+) but not in HDC (−/−) mice. From these results we can conclude that histamine might induce E-cadherin expression either directly or indirectly. Therefore, not only the direct effect of histamine, as we will discuss further in detail, but also the indirect effect of histamine, e.g., nerve fiber proliferation and/or synapse formation, might augment the itchy sensation in this model (Seike et al. 2005b).

From these studies we concluded that scratching behavior is mainly mediated by histamine and followed by the afferent pathway of sensation connected to the central nervous system through lamina I of the spinal dorsal horn in a murine model of CACD (Seike et al. 2005b).

4 Histamine Receptors

Histamine is a ubiquitous chemical messenger, which exerts numerous functions mediated by, at least, four pharmacological distinct receptors. All histamine receptors are classified as G-coupling receptors with seven transmembrane domains (Hough 2001; Seifert et al. 2011). H1 receptors activate the PLC-IP3-Ca^{2+} pathway followed by the activation of PKC, eNOS, protein kinases, and PLA2, among other effectors. H2 receptors activate the cyclic AMP-dependent pathway, while H3 and H4 receptors activate MAP kinase, and activation of H4 receptors mobilizes Ca^{2+} ions stored inside the cells.

4.1 H1, H2, and H3 Receptors

Therefore, which kind of receptors are involved in the effect of histamine in the AD mouse model? We have previously showed that not only H1 receptors but also H4 receptors play a role in the induction of the lesion by using their specific antagonists (Seike et al. 2010; Matsushita et al. 2012). Periostin, a matricellular protein and a contributor to tissue remodeling, is a critical mediator for the amplification and persistence of allergic inflammation in a house dust mite extract-induced AD model (Masuoka et al. 2012). Histamine induces the expression of periostin in fibroblasts, and an H1 receptor antagonist blocks both periostin and collagen expression (Yang et al. 2014). Therefore, the contribution of histamine to AD through the H1 receptor might be related to periostin as well.

The activity of H2 receptor has been characterized in gastric wall cells, and its action is clinically applied for the treatment of peptic ulcer with anti-H2 blockers. In the skin, the H2 receptor is expressed in keratinocytes, macrophages, and lymphocytes (Akdis and Simons 2006). However, its function in the skin has yet not been fully understood.

H3 receptor is expressed in sympathetic and parasympathetic nerves, and it regulates the release of histamine, serotonin, acetylcholine, and other neurotransmitters (Sander et al. 2008). H3 receptor antagonists increase scratching behavior in ICR mice (Sugimoto et al. 2004) and mast cell-deficient mice (Hossen et al. 2003). Histamine induces calcium increase in skin-specific sensory neurons through the activation of the H1 and H4 receptors, as well as inhibition of the H3 receptor. The decreased threshold in the response of H3 receptor to antagonists is considered to activate H1 and H4 receptors on sensory neurons, which in turn results in the excitation of histamine-sensitive afferents and therefore elicits the itch sensation (Rossbach et al. 2011). The exact physiological role of the H3 receptor in the skin remains to be explored, although several researches suggest that H3 receptor is related to itch sensation and scratching behavior in allergic dermatitis.

4.2 H4 Receptor

Compared to the other histamine receptors, the discovery of a fourth histamine receptor was unexpected, since it was first proposed as an orphan receptor which role has been found later. H4 receptors are expressed primarily in immune cells, e.g., leukocytes and mast cells (Oda et al. 2000). In a murine Th-2 dependent skin inflammation model, H4 receptor mediates inflammation and pruritus (Cowden et al. 2010; Dunford et al. 2007; Thurmond et al. 2014). In the pruritus mouse model, the function of H4 receptor on mast cells or other hematopoietic cells seemed not to be directly related to the sensation (Dunford et al. 2007). Dunford et al. proved first that mast cell-deficient (WBBF1-W/W^v) mice showed the similar bouts of scratching behavior as the control ($WBB6F_1$-+/+) mice and second that H4 receptor knockout mice had reduced scratching bouts, which was not recovered even when the mice were reconstituted with the bone marrow cells of their wild-type counterpart. Since H4 receptors are expressed in dorsal root ganglion (DRG) neurons, the activation of afferent nerves related to the itchy sensation might be mediated by H4 type receptors (Rossbach et al. 2011).

4.3 Combined Effect of H1 and H4 Receptor Antagonists

Repeated application of haptens on the skin induces immediate hypersensitivity and produces a shift in the cutaneous cytokine milieu from Th1 to Th2 profiles (Kitagaki et al. 1997). In this model, the effects of histamine on the development of eczematous lesions were assessed using histamine-deficient mice (Seike et al. 2005a). The development of eczematous lesions in contact dermatitis was suppressed in HDC (−/−) compared to HDC (+/+) mice. Therefore histamine seems to be an important Th2 mediator in the eczematous lesion. Hence, which type of receptor plays a predominant role in these lesions?

Four types of histamine receptors have been reported to contribute to the pathophysiology of allergic dermatitis. H1 receptor antagonists inhibit murine

contact hypersensitivity but with low efficacy (Tokura et al. 2003). H2 receptor antagonists increase the contact hypersensitivity response (Belsito et al. 1990). H3 receptor antagonists have been suggested to contribute to the itchy sensation and scratching behavior, which has been already discussed in Sect. 4.1. H4 receptor antagonists reduce hapten-induced scratching behavior, but not ear swelling (Rossbach et al. 2009).

H1 receptor is definitely an important receptor in producing edema in skin diseases (Thurmond et al. 2004; Seike et al. 2005a), and these lesions were controlled, at least in part, by the effect of IL-4, IL-6, and macrophage inflammatory protein-2 (Hamada et al. 2006). On the other hand, H4 receptor by itself is a key receptor in the CACD model in mice (Seike et al. 2010). Eczematous lesions are ameliorated in the presence of H4 receptor antagonist JNJ7777120 in HDC (+/+) mice, while aggravated in the presence of H4 receptor agonist 4-methylhistamine in HDC (−/−) mice. In biochemical assays, IL-4, IL-5, and IL-6 in skin lesions and serum IgE levels are decreased, whereas IFN-γ and IL-12 levels in skin lesions are increased by the H4 receptor antagonist JNJ7777120 in this model. In histological assays, the number of mast cells and eosinophils in eczematous lesions is lower in HDC (+/+) mice after H4 receptor antagonist than in HDC (−/−) mice after H4 receptor agonist.

As previously explained, H1 and H4 receptor antagonists have beneficial effects on allergic inflammation, and the effect of the combined treatment was assessed in an AD model. The combined treatment with olopatadine and JNJ7777120, H1 and H4 receptor antagonists, respectively, reduces epidermal thickening reaction in the repeated TNCB staining CACD model (Matsushita et al. 2012). The number of eosinophils and mast cells were also decreased by the combined therapy compared to olopatadine monotherapy. Combined therapy further decreased serum IgE and IL-4 levels when compared to olopatadine or JNJ7777120 monotherapy. Interestingly, IFN-γ and IL-12 show a completely opposite response to H1 and H4 receptor antagonists, increased by H4 receptor antagonist JNJ7777120 and decreased by H1 receptor antagonist olopatadine. Since IFN-γ and IL-12 are typical Th1 cytokines, histamine acts oppositely on the regulation of the Th1 cytokine profile through H1 and H4 receptors. It was reported that H1 receptor knockout mice developed reduced allergen-specific skin reaction, and dendritic cells produced reduced amount of IL-12 upon allergic stimulation (Vanbervliet et al. 2011). There are not enough reports to conclude the effect of allergen-specific skin reaction of the H4 receptor knockout on Th1/Th2 balance. However, it was suggested that the effect of permanent knockout H4 receptor was different from the pharmacological blockade with H4 receptor antagonists (Rossbach et al. 2015). Rossbach et al. discuss in their report that the effect of H4 receptor antagonists was not strong enough to silence H4 dependent signaling. The combined treatment with olopatadine and JNJ7777120 reduces scratching counts and serum IgE levels, with potency comparable to prednisolone (Ohsawa and Hirasawa 2012). Olopatadine, together with JNJ7777120, inhibited thymus and activation-regulated cytokine production in bone marrow-derived mast cells and decreased the infiltration of CD4+ cells in the skin (Ohsawa and Hirasawa 2012). This last report also confirmed that the

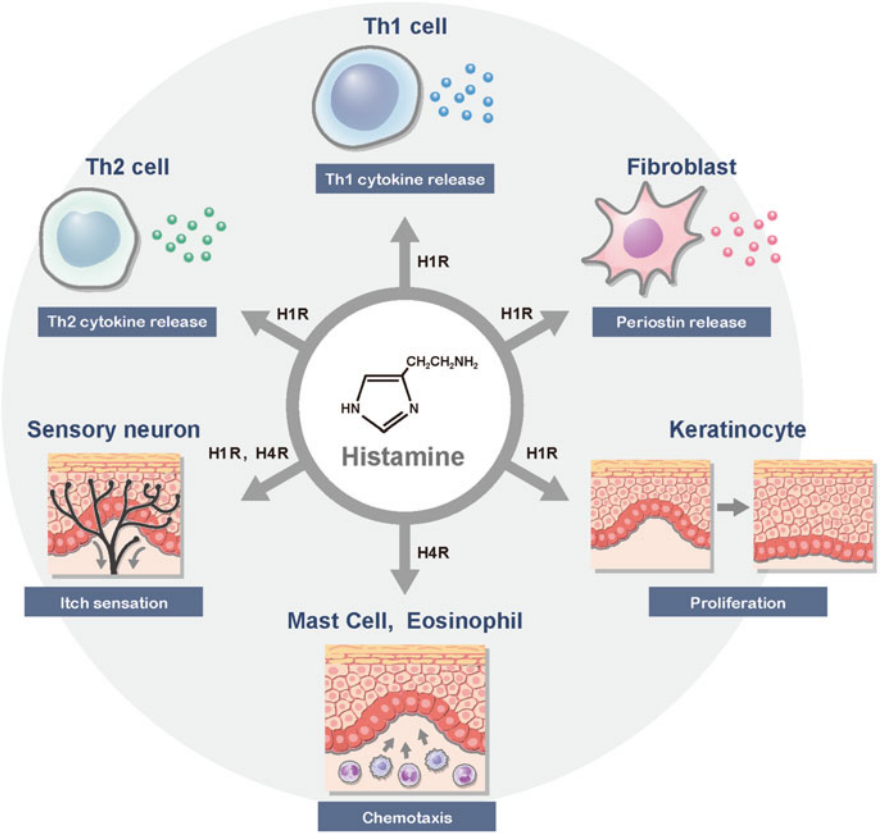

Fig. 1 Increasing effects of histamine through H1 and H4 receptors in skin allergic reaction. Histamine is involved in itch sensation of the sensory neuron via H1 and H4R (Andrew and Craig 2001; Seike et al. 2005b; Rossbach et al. 2011). Keratinocyte is proliferated by histamine via H1R (Seike et al. 2005a; Glatzer et al. 2013). H4R mediates chemotaxis of mast cell and eosinophils (Hofstra et al. 2003; Ling et al. 2004; Seike et al. 2010; Shiraishi et al. 2013). Histamine induces periostin release of fibroblast via H1R (Yang et al. 2014). Th1 (Noubade et al. 2007) and Th2 (Botturi et al. 2010) cytokine releases are induced by histamine via H1R

combined administration of olopatadine and JNJ7777120 inhibited the increase of IL-4 and IL-5 levels in skin lesions. H1 and H4 receptor antagonists synergistically suppressed Th2 cytokine release in the skin in an allergic dermatitis murine model. Combinatory various effects of histamine H1 and H4 receptors were summarized in Fig. 1.

5 Conclusion and Perspective

All of the above studies provide evidence of a pathogenetic and immunomodulatory role of histamine in chronic allergic inflammatory skin diseases. Mainly, H1 and H4 receptors modulate the relevant cell populations by influencing chemotaxis, cytokine release, and itch sensation produced independently or cooperatively. Therefore, a combination of H1 and H4 receptor antagonisms might be a potent therapeutical option for chronic inflammatory skin diseases such as CACD and AD. When new histamine receptor(s) are identified in the future, their therapeutic application and pathophysiological mechanism behind allergic dermatitis should be further investigated for a better clinical application.

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