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Histamine: Bridging Food and Atopic Dermatitis

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ABSTRACT

Atopic dermatitis is a most common chronic inflammatory skin diseases, and it is often characterized by itch, inflammation, and disruption of skin barriers. Itch associated with atopic dermatitis severely impacts the quality of life of individuals, families, and caregivers, and the incidence of itch is increasing. Here, we focused on the interplay between histamine, food, and itch mechanisms in atopic dermatitis. Histamine, a biogenic amine, plays a significant role in the pathogenesis of atopic dermatitis and related itch, and histamine levels are found elevated in atopic dermatitis individuals. A histamine-rich diet, such as ingesting foods rich in histamine and foods that trigger the cellular release of histamine, exacerbates atopic dermatitis symptoms, and the elimination of a histamine-rich diet attenuates the pathology. Further, we discussed the role of histamine receptors, specifically H1 and H4, in itch and inflammation associated with atopic dermatitis. Drugs such as antihistamines are effective in some cases, but fail to alleviate itch in atopic dermatitis, suggesting non-histaminergic itch pathways. In addition, we discussed enzymes such as diamine oxidase and histamine N-Methyltransferase, which are involved in the metabolism of histamine and, by inhibiting the activity of these enzymes leading to the accumulation of histamine, which, in turn, is responsible for atopic dermatitis and associated itch. This review provides intricate interactions between itch, diet, and histamine in atopic dermatitis and provide essential mechanistic insights and further in the development of future therapeutics.

Keywords: *Atopic dermatitis, Itch, Food, Histamine, G Protein-coupled receptors, histamine receptors, Diamine oxidase*

Introduction

Atopic dermatitis (AD) is an inflammatory skin condition (often named eczema) that causes itchy rashes in humans and animals[1]. The prevalence of disease depends on the patient's age, ethnic background, and geographical origin[2]. In recent years, the average number of cases in industrialized countries has more than doubled, with the disease impacting around 25% of children and 2% of adults worldwide [1]. People with AD have a higher risk of developing other conditions such as arthritis, asthma, depression, anxiety, allergic rhinitis, and sleep problems that negatively impact the patient's quality of life[3]. Recent data suggest that neural recruitment is involved early in activating allergic stimulation of AD and helps maintain the inflammatory cascade[4]. The exact cause/mechanism of AD is not well understood but several comorbidities, including food allergy, asthma, allergic rhinitis, and mental health disorders can impact AD. The first part of this review will focus on the relationship between AD and Histamine, types of food with histamine, and enzymes responsible for regulation of histamine that might be involved in initiation and aggravation of AD and associated itch. Itch is a major symptom associated with AD and the cellular release of histamine and its role in itch is well-established. Therefore, the second part of the review will focus on itch and its mechanisms as well as discussing the role of histamine receptors that have been linked to AD.

Relationship among histamine or histidine rich food and atopic dermatitis.

Foods can significantly trigger AD and food allergies, which have been linked to the disease [5]. Although food allergies and allergens are not necessarily the direct cause of atopic dermatitis, they can be indirectly involved in the aggravation of the disease. One study in humans shows that ingesting moderate or high amounts of histamine-hydrochloride may aggravate eczema in a subgroup of patients with AD[6-8]. Common allergens in AD are mostly high protein foods, cow's milk, eggs, and fermented foods [5, 7-9]. Most of these foods contain the chemical compound histamine that is involved in the aggravation of AD. However, a review from Bath-Hextall et al suggested no benefit of egg and milk free diet in unselected participants with atopic eczema [10]. The authors also remain open that this may be due to small population size and may be these individuals are not allergic to these substances in the first place. Along with an increase of histamine level in plasma, an increase in the level of skin histamine has been reported among patients of acute AD[11]. Histamine is a biogenic amine, formed by the action of the enzyme histidine decarboxylase on proteinogenic amino acids, 1-histidine. Histamine plays a crucial role in many physiological and pathophysiological processes. Histamine regulates gastric acid secretion in the stomach, acts as a neurotransmitter, and mediates anaphylaxis in allergic conditions[12]. In mammals, histamine is known to be present in all tissues, primarily the skin connective tissue, lung, and most of the gastrointestinal tract[13], and involved in functional execution through primarily four types of histamine receptors that have been identified and characterized; they are H1, H2, H3, and H4 receptors[14]. Excess histamine release in the body either through cellular release or via histamine-rich food[15] can lead to the flare-up of atopic dermatitis[16-18]. Although the link between AD and diet has been unclear for a long time, some connections between AD and food have been proposed based on diet elimination/ supplementation that helps to reduce or improve AD conditions in a subgroup of patients[19]. Several reports suggest that histamine and its four receptors are linked to atopic dermatitis and itch[20]. Blood plasma histamine levels are higher in AD patients[21], and enhanced release has been observed in the skin of AD individuals[22]. Their study and others suggest a possible association between high histamine diet and AD[23, 24].

In an elimination approach, recent study aimed to investigate the relationship between histamine and atopic dermatitis[25]. The study included atopic dermatitis and healthy individuals and was conducted in a hospital setting. The researchers

collected skin biopsies from all participants and analyzed the samples for histamine levels. They used immunohistochemistry methods to determine the amount of histamine in the skin samples. They also recorded the severity of eczema symptoms in each participant, as well as other clinical information such as age, sex, and history of allergies. In addition, in the group of the atopic dermatitis patients, researchers also treated them with an antihistamine (cetirizine) for a period of four weeks, and then re-assessed the histamine levels in the skin and the symptoms of eczema. Participants were given the antihistamine in oral form and at a daily dose of 10 mg. The results showed that histamine levels were significantly higher in the skin of participants with atopic dermatitis compared to those without the condition. This confirms previous findings that histamine plays a key role in eczema symptoms. Furthermore, the eczema symptoms improved significantly in patients treated with antihistamine. The itching, redness and inflammation of the skin was all reduced in the group of patients treated with antihistamines. The study concludes that histamine is involved in the development of the eczema symptoms and that antihistamines may be an effective treatment for atopic dermatitis. The study also highlights the importance of understanding the underlying mechanisms of eczema in order to develop new and more effective treatments. The study is important because it provides more evidence that histamine is involved in the pathology of eczema, and that antihistamines may be effective in reducing symptoms of eczema. The study also provides a rationale for further research in the field, including the development of more specific and targeted antihistamine treatments for eczema.

In another study, a six-year-old boy was admitted to the hospital with severe AD for the evaluation of food as a triggering factor for his skin disease. In a food challenge test, he showed a positive result of exacerbated eczema score for both eczema area and severity index (EASI) score and the visual analog scale (VAS) when he was on 200 g of pork diet compared to eating 60 g of pork. Interestingly, keeping him on a balanced and low-histamine dietary regimen showed improvement in AD symptoms and that lasted for more than seven months[26]. This suggest a low-histamine, balanced diet could be helpful for AD patients and histamine rich diet aggravate AD without having any issues of food allergy.

Almost one percent of the human population worldwide is affected by histamine intolerance[27,28]. Certain lactic acid bacteria with the hdcA (Histidine decarboxylase) gene can convert the amino acid histidine into histamine[29]. The main histamine-producing bacterial strain in wine transformation belongs to the genera Oenococcus, lactobacillus, and pediococcus[29]. Analysis of several sample collections from different wineries shows that these bacteria are present in almost all wines at an exceedingly high level. Also, hdcA was detected in most of the unstable plasmid in strains of Oenococcus[29]. Therefore, histamine is produced in the body in large amounts due to the food and drinks containing these bacteria that transform histidine into histamine using enzyme decarboxylase.

Histamine is found in large amounts in many commercial soybean products like tofu, tempeh, tamari, and sufu (fermented soybean), etc. In the case of sufu samples, very high histamine levels (700 mg/kg) were found, which is very unhealthy for a patient. Biogenic amines present in soybean products are not a risk for healthy consumers, but patients who take drugs with monoamine and diamine oxidase inhibitors can suffer adverse health effects by eating such high-histamine foods[30]. Several cases of scombroid fish (tuna, mackerel, swordfish, kingfish, etc) poisoning occur after consuming these fish which are rich in the amino acid histidine[31,32]. Urinary excretion analysis of patients sick with scombroid fish poisoning shows high-level histamine and its metabolite[32].

The primary dietary sources high in histamine are fermented foods, beverages like kefirs, kombucha, yogurt, frozen and smoked fish and fruits such as strawberries and cherries. Vegetables that are high in histamine are spinach, eggplant, and potato. Chili powder, cinnamon, and cloves are found to be very

high in histamine[27,28,33-36]. Certain foods are not necessarily high in histamine but act as a histamine-trigger food, such as citrus fruits, alcohol, and nuts[27, 36,37]. Other common foods such as cheese, blue cheese, and parmesan cheese also have very high histamine. This may not be an issue in healthy individuals with normal histamine-degrading enzyme levels. However, these foods with high histamine can further aggravate symptoms of atopic dermatitis in patients with histamine intolerance (HIT)[35,38]. They are unable to degrade even normal levels of histamine from food let alone food with higher histamine. This is due to their deficiency in enzymes that help destroy of ingested histamine[35]. A recent report demonstrated a link between a histamine diet and AD. In this report, 36 patients were placed on a low histamine diet for one week, 12 of the 36 patients showed significant improvement in atopic dermatitis after one week of the low histamine diet intake, which suggests only a small subset of AD patients to show a correlation of low histamine diet and an improvement of symptoms in AD patients[6]. Briefly, the role of histamine in the maintenance of AD is linked to our daily intake of food, and this might occur in most AD individuals, but the role of types of food described above in the causation of itch is still largely unknown. In addition to diet, histamine plasma levels did not decrease in AD individuals, suggesting that these large group react differently and the release of histamine in this group is either due to decreased histamine metabolism or due to continuous release of histamine through IgE mediated reaction is not yet clear[6].

In mammalian skin L-histidine is incorporated into filaggrin, which is a skin barrier protein and linked to AD etiology. To evaluate the therapeutic role of L-histidine in AD patients, the authors conducted a randomized, double-blind, placebo-controlled, crossover, nutritional supplementation pilot study[39]. Daily single oral l-histidine administration for 4 weeks significantly reduced AD symptoms by both physician assessment using the SCORing AD tool and patient self-assessment using the Patient Oriented Eczema Measure tool compared to the placebo. The authors further demonstrated the L-histidine effects on proflaggrin processing and skin barrier functions on HaCaT keratinocytes culture and in organotypic skin-equivalent cultures. On keratinocytes cells they showed L-histidine increases filaggrin protein formation and in organotypic skin model they illustrated that L-histidine enhances the barrier function. Both these in vitro observations correlate with evidence from the clinical nutritional pilot study that oral l-histidine may have therapeutic benefits in AD. In another clinical pilot study by a completely independent group on two different age groups (Adults and Young Children) with AD, the author showed oral L-histidine if effective for AD management[40]. A single dose of L-histidine was given to adults (4gm daily) and in young children (0.8 gm) supplementation over periods of 4 wk. (adults) or 12 wk. (young children). Compared to the placebo L-histidine reduced AD in both adult and young children by using SCORing AD tool. The supplementation is well tolerated and has potential as a safe intervention for long-term use in the management of AD, but some adverse events have been reported suggesting continuous safety evaluation for long-term usage.

Involvement of histamine regulating enzymes in atopic dermatitis

Histamine intolerance is a condition that can be further aggravated in HIT patients by histamine-rich foods, which either cause histamine release or blocks the diamine oxidase[36,41]. It can further lead to many disorders of the gastrointestinal system, skin, lungs, cardiovascular system, and brain. Dermatology problems that can arise are rashes, itch, urticaria, dermatitis, psoriasis, rosacea, etc.[35,42]. Diamine oxidase is the main enzyme for the metabolism of dietary histamine and is responsible for the catabolism of extracellular histamine, whereas histamine N-Methyl transferase (HNMT) is responsible for catabolizing histamine in intracellular spaces of cells[36]. Various Single-nucleotide polymorphisms (SNPs) show correlations between inflammatory and neoplastic gastrointestinal diseases like food allergy, Crohn's and Colitis, etc. However, no significant association is seen by investigating HNMT alleles and patients

with inflammatory and gastrointestinal diseases[36,43-45]. On the contrary, some studies show an association between HNMT polymorphisms and AD in children. A study to evaluate the association between HNMT polymorphisms and AD in children concluded that polymorphisms in HNMT appear to confer susceptibility to AD in Korean children[46]. A study has been shown reporting Thr105Ile, a functional polymorphism of HNMT is linked with alcoholism in two ethnically distinct population[47]. In another study, association of food additives and HNMT T939C and HNMT Thr105Ile gene polymorphism was established[48]. In CNS, histamine acts as a neurotransmitter and has been shown to be involved in reward function and in the etiology of addition and stress. In the periphery it is considered as mediators, but it will be interesting to explore the role of histamine in the CNS in chronic AD condition.

Structurally the diamine oxidase (DAO) enzyme with 700 amino acids is proposed to be a dimer of 92 kDa encoded by *AOC1* gene[49-51]. The association of low DAO and increased plasma histamine was shown in atopic eczema [52]. In a separate study, high histamine amounts in plasma combined with reduced histamine degradation influenced the clinical score in AD[53]. Recently, an experiment with 14 patients with allergic conditions like food hypersensitivity, coeliac disease, etc., was investigated for serum DAO level and clinical response to DAO supplementation. These patients were placed on histamine-rich food. Their results indicate that 10 out of 14 patients had reduced serum DAO activity <10 U/ml, which suggests probably histamine intolerance. Moreover, 13 out of 14 patients showed significant relief in disturbances related to food intolerances with the intake of DAO supplementation[41]. Measuring DAO activity in serum is useful in determining histamine intolerance[41]. Furthermore, histamine plays a major part in food, and wine intolerance and lack of DAO in AD patients with intolerance to food or wine causes worsening symptoms in atopy[15].

Based on the influence of active ingredients of certain drugs on the activity of human diamine oxidase, many substances can be designated as DAO inhibitors[54]. Chloroquine and clavulanic acid are such drugs that showed the greatest inhibition potential of up to 90 percent. Other medications like Verapamil, have an inhibition rate of almost 50 percent. Drugs like Diclofenac, metoclopramide, suxamethonium, and thiamin have a very low inhibition rate[54].

A correlation between atopic eczema and decreased DAO activity was observed in patients with high blood serum histamine levels. Their blood DAO activity and histamine concentration were evaluated with a radio extraction radioimmunoassay. Their results showed the presence of wheals, which were 35 percent larger in diameter in almost 47% of patients. These patients have significantly low DAO activity and high histamine levels compared to the experiment's healthy people. The authors have cautiously indicated a possible correlation between decreased DAO activity in allergic patients[55].

Histamine receptors involved in atopic dermatitis

Histamine receptors belong to the family of GPCR with seven transmembrane domains and an intracellular second messenger system to transduce extracellular signals through the TRPV1 channel[16,56]. Since the beginning of the twentieth century, the synthesis of various histamine receptor antagonists has played a therapeutic role in treating of a wide variety of diseases like AD, asthma, pruritus, allergic rhinitis, and inflammation[57-60]. However, antihistamine drugs' failure to block histamine's complete action initiated a research program that started at the laboratory of SmithKline and French in Welwyn Garden City, U.K (1960), under the direction of James Black. He intended to confirm heterogeneity in histamine receptors (HRs) and discover an antagonist of the histamine receptor. HRs stay in equilibrium in relation to their active and inactive states[61]. Various techniques, including immunohistochemistry, flow cytometry, and western blots, are generally used to analyze HRs[62]. H1, H2, and H4 receptors are involved in chronic allergic contact dermatitis (CACD) and

atopic dermatitis[63]. The study shows that in ovalbumin-induced AD-Skin lesions, analyzed in H4R knockout mice; the results showed a significant reduction in the severity of skin lesions, reduced inflammatory cells, and lessened hyper-proliferation at the skin lesion site[20]. Previously, it was considered that either H1R or H4R is involved in skin inflammation. However, the use of H1R antagonists only shows limited improvement in skin inflammation. It is now confirmed that co-administration of H1R and H4R antagonists ameliorated chronic allergic inflammation in ovalbumin-induced AD-like skin lesions in a mouse treated with H1R inverse agonist mepyramine and or with H4R antagonist JNJ-39758979[64] and also the itch associated with AD. Conventional treatment with glucocorticoids leads to skin atrophy and has side effects. However, co-administration of H1R and H4R antagonists has an inhibitory effect equal to those of steroids in a chronic allergic dermatitis mouse model. In summary, HRs play an essential role in **alleviating AD but are often inefficient in treating itch associated with AD because of the involvement of histamine-independent pathways.** With this finding, next-generation antihistaminic agents using H1R and H4R antagonistic actions can be useful in developing treatments for AD patients[65].

Neural Pathways for itch

One of the common symptoms in AD is itch and various endogenous mediators have been identified as primary triggers that can cause itch[66]. Itch has been classified into four main clinical categories based on pathophysiological, anatomical, and psychological components and is further named neurogenic, pruritogenic, neuropathic, and psychogenic[67]. This section will discuss relevant literature that has been proposed to identify neural mechanisms of itch associated with AD. A labeled line theory suggests that the itch-specific neuronal fibers are in the continuum from the skin to the dorsal root ganglia (DRG)[9]. Itch is classified into two major subtypes based on histaminergic and non-histaminergic pathways. The histaminergic pathway is dependent upon the TRPV1-positive (via histamine or endothelin-1) and TRPV1-negative (via histamine) nerve fibers[16,17,68,69]. The non-histaminergic pathway usually the pruritogens other than histamine (protease-activated receptor agonist, cysteine protease, and Serotonin, and their effect are mediated through TRPA1 channels[70-73]. Once the sensory neurons are activated or depolarized, they release neurotransmitters/neuropeptides through the central afferents of the DRG into the spinal cord. The message is further propagated through interneurons that expressed natriuretic polypeptide receptor A (NPRA) in the spinal cord through projection neurons that expressed gastrin-releasing peptide receptor (GRPR) for the chemical-induced itch to the brain[9,74]. The brain finally decoded these messages in the somatosensory cortex[75].

A pruritogen is a mediator that provokes the sensation of itch in the skin, followed by an interaction with molecular detectors. The majority of these molecular detectors are either pruritic receptors (they are generally G-protein coupled receptor -GPCR-) and ion channel receptors (TRPV1, TRPV3, and TRPA1) that are acting downstream of the GPCR to activate the sensory neurons and involved in the propagation of itch[20,76-80]. Histamine-mediated itch happens through HR. The four histamine GPCRs include H1, H2, H3, and H4 receptors. The H1 and H4 receptors conveyed itch neurotransmission directly through the DRG sensory neurons via the TRPV1 channel [16,17]. In conclusion, we propose an increase in plasma histamine levels due to a histamine-enriched diet is linked with AD, but antihistamines remain ineffective in alleviating itch in AD individuals except a few[25]. The ineffectiveness of antihistamines is possibly explained due to the involvement of other non-histaminergic itch pathways at the periphery or possibly through central mechanisms.

Some of the practical clinical, diagnostic, and therapeutics considerations suggestion for individuals with atopic dermatitis. Dietary recommendations include diets with low histamine and identify and avoid trigger foods high in histamine, including fermented products, citrus fruits, alcohol, nuts, and certain types of fish. Diagnostic recommendations include measuring DAO activity in serum to diagnose

histamine intolerance. Lastly, for therapeutic options, considering L-histidine supplementation for atopic dermatitis management and including DAO supplements may alleviate symptoms in histamine-intolerant individuals.

Conclusion

Several reports suggest a link between food and atopic dermatitis, but the mechanistic insight into these relationships is still unclear. The role of dietary influence on the accumulation of high histamine in the body has been established and observed by showing the lowering of histamine in the diets, which provides relief to a subgroup of AD patients. Atopic dermatitis drastically affects a patient's quality of life and can lead to several other diseases; therefore, it is imperative to understand the complex biological mechanism (s) in AD. Mechanisms of action behind food and their metabolites involved in AD pathogenesis and associated itch need to be identified, which might help develop better treatment methods. More research needs to be done to establish a direct role of food in the pathogenesis of AD and itch.

Table 1. Gene polymorphisms that are linked to food allergy and AD

Gene	SNP	Relationship	References
DAO	C2970G	Food allergy	45
HNMT	314C>T 939A>G	AD, Food additive, alcohol	46, 81 48

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