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CLINICAL REPORT

Exogenous Histamine Aggravates Eczema in a Subgroup of Patients with Atopic Dermatitis

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Food and beverages may contain high amounts of histamine and thus may cause symptoms after ingestion. The aim of this study was to investigate the role of ingested histamine in atopic dermatitis. Patients with atopic dermatitis had to maintain a histamine-free diet for one week. Consecutively, double-blind, placebo-controlled provocations were performed with histamine-hydrochloride and placebo. The clinical outcome was assessed by determination of the SCORAD. Before and 30 min after each provocation blood was collected for measurement of plasma histamine levels and diamine oxidase activity. Thirty-six patients with atopic dermatitis completed the diet. Twelve of 36 showed a significant improvement of the SCORAD after one week of the diet. After provocation tests 11 of 36 showed aggravation of eczema. Plasma histamine was significantly higher in patients with atopic dermatitis compared with controls ($p < 0.001$), whereas diamine oxidase activity was similar in both groups. Our data indicate that ingestion of moderate or high amounts of histamine-hydrochloride may aggravate eczema in a subgroup of patients with atopic dermatitis. Plasma histamine and diamine oxidase activity were not associated with the clinical response to histamine. ***Key words: atopic dermatitis; diamine oxidase; histamine intolerance.***

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Atopic dermatitis (AD) is a chronic relapsing skin disease characterized by dryness of the skin, eczema and pruritus (1). Worldwide nearly 10–20% of children and 1–3% of adults are affected (2). The majority of affected individuals live in urban regions in industrialized countries (3). Hereditary disposition is a major cause of the disease (1). The severity of the symptoms is variable and can be triggered by various factors, including food allergens or by non-allergic food hypersensitivity reactions (4). Previous studies indicated that many adult patients report a food-related aggravation of skin symptoms (2, 5). In infancy and childhood, IgE-mediated food allergies are often relevant for worsening the eczema, whereas non-IgE-mediated reactions caused by food additives are less frequent (4). In up to 35% of children with AD aggravation of the eczema after the intake of food allergens such as milk, egg or wheat has been reported in severely affected children (6).

Histamine is a biogenic amine and the product of decarboxylation of the amino acid L-histidine. Food and beverages may contain biogenic amines in relevant amounts as a result of microbial contamination. Therefore, spoiled or fermented foods may contain high levels of biogenic amines (7). In particular, food items that undergo microbial ripening, such as cheese, salami, sauerkraut or red wine, may contain high levels of histamine. Histamine concentrations may vary widely, not only between different food varieties but also within single foods (7, 8).

Histamine intolerance belongs to the group of non-IgE-mediated hypersensitivity reactions and is a pharmacological food intolerance. There are currently no valid *in vitro* tests for proving histamine intolerance; thus, double-blind, placebo-controlled food challenge (DBPCFC) remains the gold standard for the diagnostic work-up of non-IgE-mediated food intolerances (9).

Biogenic amines are metabolized by specific enzymes (10). The histamine-degrading enzymes are diamine oxidase (DAO) and histamine methyltransferase (HMT). DAO is localized primarily in the jejunal mucosa and represents the first barrier for ingested histamine (8, 10, 11). The second enzyme, HMT, is localized mainly in the lung tissue and degrades the remaining histamine, which is passed into the bloodstream. Recently, it has been proposed that histamine intolerance is characterized by a deficiency or a reduced activity of DAO. Consequently, the ingestion of histamine, which is generally tolerated by healthy individuals, may more frequently lead to adverse reactions in histamine-intolerant patients (10, 11).

The possible impact of histamine on the local, but also systemic, immune response in the skin has been suggested by recent studies showing that histamine favours a Th1 response (12–14).

The aim of this study was to evaluate the role of ingested histamine as an aggravating factor in adult patients

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with AD. To investigate the histamine metabolism in this group in more detail the plasma histamine levels and DAO activity were determined and compared with those of a control group with healthy skin.

METHODS

Subjects

Subjects were recruited from the Allergy-Centre-Charité at the Department of Dermatology and Allergology, Charité. Patients with AD aged between 18 and 65 years were enrolled in this study. AD was diagnosed by the criteria of Hanifin & Rajka (15). A group of age- and sex-matched skin healthy volunteers served as controls. The study was approved by the local ethics committee and all participants gave informed consent before starting the study.

Study design

Patients with AD had to maintain a histamine-free diet for 2 weeks. The food restriction was based on a diet low in preservatives, colourings, antioxidants and other additives, as well as naturally occurring substances such as salicylates, benzoates or aromatic compounds, as described previously (4). In addition, foods with high amounts of histamine, such as fish, ripened cheese, smoked meat and alcohol were prohibited. No influence of a histamine-free diet on the skin of healthy controls was expected and, therefore, no diet was performed.

Patients and control subjects were not allowed to receive antihistamine medication throughout the study. The use of topical glucocorticoids was allowed on demand. During the second week oral provocations were performed. At intervals of 48 h three provocations were performed with capsules containing histamine-di-hydrochloride or placebo capsules containing mannite silicon dioxide. For titration two different dosages of histamine-di-hydrochloride were given, a lower dose with 0.75 kg^{-1} body weight and a higher dose with 1.5 mg kg^{-1} body weight according to the literature (16). Subjects were clinically observed for at least one hour after the challenges. Subjects with a severe immediate reaction after the first dose did not receive the second dose of histamine.

Skin status

At the beginning of the study, before and 48 h after each provocation the skin status of patients with AD was assessed by the same dermatologist using the Severity Scoring of Atopic Dermatitis (SCORAD) (17). As late-phase skin reactions arise within 24 and 48 h, an interval of 48 h was considered appropriate between the provocation tests, both for assessing positive skin reactions or for being sure no reaction occurred and the provocation can be continued. A clinically relevant improvement or aggravation of skin symptoms was defined as a change of ≥ 10 SCORAD points, respectively.

Blood samples

Blood samples for determining plasma histamine and serum DAO activity were drawn at the start of the study, before and 30 min after each histamine challenge.

Measurement of plasma histamine was performed by enzyme-linked immunoassay (ELISA) (Immunotech, Marseille, France) according to the manufacturer's recommendations. The expected reference value for healthy controls was < 10 nM. The DAO activity was determined by applying the C^{14}-putrescine method as described previously (18).

Statistical analysis

A two-factorial non-parametric analysis for longitudinal data (19) was performed to compare the time course of SCORAD, DAO and plasma histamine, respectively between the groups (i.e. patients with AD and controls).

The influence of diet or provocation within groups was evaluated by Wilcoxon-tests. p-values ≤ 0.05 were considered statistically significant. Calculations were performed with SPSS 11.0 (SPSS Inc, Chicago, IL, USA) and SAS (SAS Institute Inc, Cary NC, USA). Results are given as median (25–75% percentile) or as mean ± standard deviation (SD).

RESULTS

Subjects

Fifty-eight adult subjects with AD were recruited. Thirty-six completed the diet phase and underwent the DBPCFC (mean age 32 ± 1.4 years; 28 women, 8 men). The baseline SCORAD was 45 (38–49) points. Nineteen skin healthy individuals were included in the study as a control group (mean age 29 ± 1.3; 13 women, 6 men).

Improvement in skin status with histamine-free diet in patients with AD

The SCORAD decreased significantly after 7 days' diet in the AD group. The assessed median decline of SCORAD considering the whole group was –10% ($n = 36$; $p < 0.001$). During the challenge with both amounts of histamine (0.75 and 1.5 mg kg^{-1} body weight) an aggravation of skin symptoms was observed. No urticaria-like skin reactions were observed in any of the patients. Considering our criterion that a clinical relevant improvement of skin symptoms was defined as decrease of ≥ 10 SCORAD points, 12 of 36 patients with AD were considered as diet-responders because the SCORAD before diet was 47 (45–51) points and decreased significantly to 31 (31–35, $p = 0.002$) points after the diet. The histamine provocations in this group led to a significant increase in the SCORAD to 44 (33–49, $p = 0.037$) points after the first and to 53 (44–60, not significant) points after the second challenge. In the diet-non-responder group the SCORAD before and after diet was 42 (30–49 before, 34–47 after diet) points. After the first challenge, the SCORAD decreased to 37 (29–45) points and reached 39 (28–49) points after the second challenge, each change was not statistically significant (Fig. 1).

No significant change in the skin status was observed after placebo challenge in both subgroups (data not shown).

Systemic reactions

In some patients with AD, but also in healthy controls, the histamine provocation led to immediate systemic reactions. The severity of the symptoms varied from

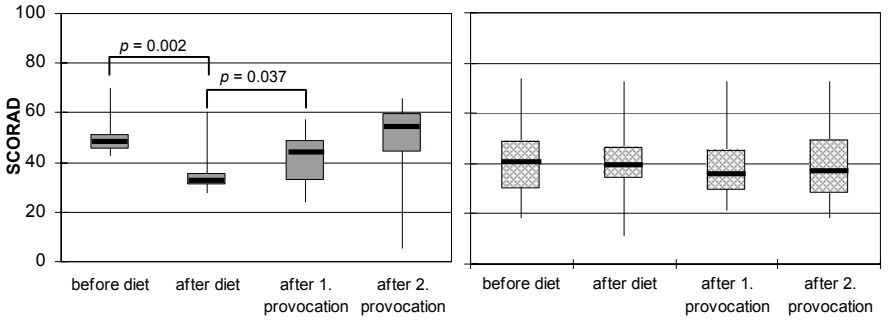

Fig. 1. SCORAD of patients with atopic dermatitis (AD). Classification in diet-responder (left, $n=12$), difference between before and after diet is –15.8 (–20.5 to –9.5), % change: –31.2 (–42.0 to –13.6); diet-non-responder (right, $n=24$), difference between before and after diet is –2.0 (–5.4 to –0.5), % change: –4.2 (–10.8 to –0.7). Median is shown as a black line, ends of the box represent 25% and 75% percentile, respectively. Outliers are not depicted.

mild (flush, headache, vertigo) to severe reactions (hypotension). Because of severity of the systemic reactions after the low-dose histamine provocation (0.75 mg kg^{-1} body weight) and the treatment with antihistamines, 2 patients with AD dropped out of the study. After the high dose histamine provocation (1.5 mg kg^{-1} body weight) 8 patients with AD had to stop the study because of hypotension. By contrast, within the control group only mild systemic reactions such as flush occurred, which did not require medical treatment.

Plasma histamine

The plasma histamine levels in subjects with AD were significantly higher compared with the control group ($p<0.001$; Fig. 2). At the beginning of the study the plasma histamine level in the patients with AD was 5.33 (3.95–9.44) nM and in the control group 3.06 (1.67–4.84) nM. In the patients with AD a significant increase in plasma histamine (median) was detected after the first histamine provocation from 5.39 to 6.91 nM ($p=0.002$) and after the second one from 6.10 to 8.57 nM ($p=0.029$), whereas the placebo provocation (3. provocation, Fig. 2) did not result in significant altered plasma histamine levels. In the control group only the high-dose provocation with histamine (2. provocation, Fig. 2) led to a significant increase in plasma histamine levels from 3.44 to 5.38 nM ($p=0.004$).

Significant differences in plasma histamine levels were observed neither for diet-responders vs. diet-non-responders nor for subjects with eczematous skin reaction vs. individuals without skin reaction (data not shown).

Diamine oxidase activity

The overall DAO activity did not differ significantly between patients with AD compared with controls. At the beginning of the study the DAO activity of the patients with AD was 10 (5.8–18.7) U ml^{-1} and of the healthy control group 14 (12.1–19.1) U ml^{-1}. Analysing the course of DAO activity within each group during the whole study period, there was no statistically significant change in the AD group detectable. In the control group a significant decrease of DAO activity (13 (1.5–33.1) before to 11 (4.2–30.4) after the provocation; $n=19$; $p=0.043$) was detected after the high histamine intake (1.5 mg kg^{-1} body weight). The diet-responder group also showed a significant decrease in DAO activity after the high histamine dose provocation ($p=0.036$, data not shown). Considering gender, no statistically significant differences between women and men regarding the analysed parameters (SCORAD, plasma histamine levels or DAO activity) were observed (data not shown).

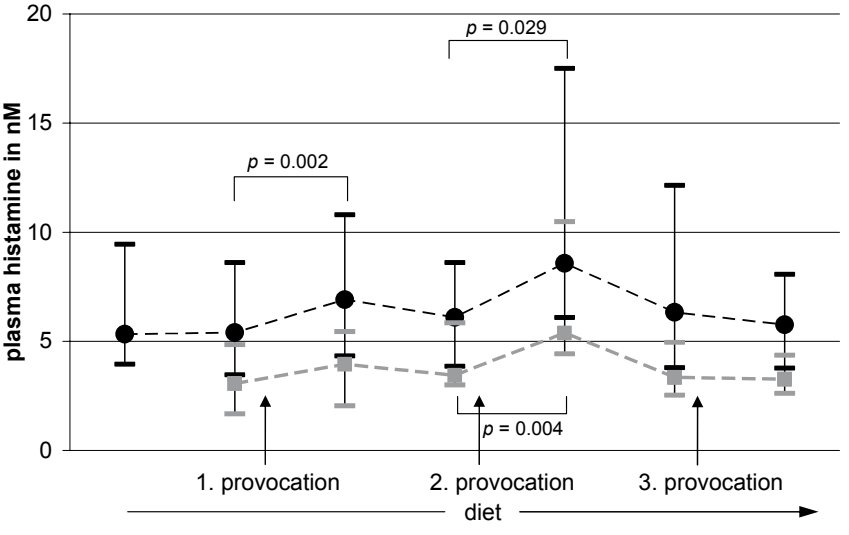

Fig. 2. Plasma histamine levels in both study groups during the study period (median; 25% and 75% percentile). Dots indicate patients with atopic dermatitis (AD) ($n=36$), squares indicate controls ($n=19$). Arrows indicate time-point of provocation with histamine-di-hydrochloride (1. provocation = 0.75 and 2. provocation = 1.5 mg kg^{-1} body weight) and placebo (3. provocation). Patients with AD showed a significant increase in plasma histamine after the first and second provocation ($p=0.002$ and $p=0.029$, respectively). In controls only the high-dose provocation (2. provocation) led to a significant increase ($p=0.004$).

DISCUSSION

Non-IgE-mediated hypersensitivity reactions against food have previously been shown to play a role in the skin status of adult patients with AD (4). The correlation between the ingestion of food rich in biogenic amines, e.g. histamine, and non-IgE mediated food hypersensitivity reactions is still not clarified in detail. Currently, no scientific background for dietary recommendations, concerning biogenic amines in patients with AD exists (20).

In this study the impact of a defined histamine intake on the skin status of adult patients with AD was examined. From the 58 initially recruited patients with AD, 36 completed the study. The main reason for this high drop-out rate was the fact that the patients were unable to adhere to the histamine-free diet. It is known that any kind of elimination diet can be difficult to manage in everyday life. Suspected food hypersensitivity was not among the main inclusion criteria. Therefore, for some patients it might have been difficult to maintain a histamine-free diet. However, our results indicate that approximately 30% of adult patients with AD benefit from a histamine-free diet with an improvement in the eczema. Correspondingly, we divided the study population into a diet-responder and a diet-non-responder group. In total, 81% of patients with AD had elevated total IgE and multiple type-I-sensitizations and 19% had normal IgE-levels. The observed distribution corresponds with the frequency stated in the literature regarding extrinsic (70–80%) and intrinsic (20–30%) AD among the adult patients with AD (21). The type of AD was independent of the response to the histamine-free diet. We identified diet-responders and non-diet-responders in both types of AD (data not shown).

The intake of high amounts of histamine caused a clinical relevant worsening of eczema in the diet-responder group only. This data strengthens recent observations that histamine has immune-modulating functions and may promote T-cell dependent cytokine production (12, 13). Histamine has diverse effects on Th1 and Th2 cells, as shown previously (12). Whether differences in histamine receptor (HR) expression in the skin of patients with AD might be relevant is currently under investigation. However, our clinical observations suggest a role of histamine in the inflammatory process of the skin, either directly or indirectly. As histamine receptors H1R and H2R and recently H4R are observed on monocyte-derived dendritic cells, these may also be activated by histamine (14, 22).

The elevated plasma histamine levels in patients with AD in comparison to the control subjects confirm the assumption that histamine is an important mediator for eczema aggravation in AD. Thus, antihistamines may support the treatment of AD. For example, the study by Kawashima et al. (23) showed that the daily intake of 120 mg fexofenadine, a non-sedating H1R antagonist, significantly decreased pruritus and had a positive effect on the skin status in patients with AD. However, other well-conducted studies suggest inefficiency of antihistamines in the therapy of AD (24). This implicates that higher dose of antihistamines may be required to achieve sufficient efficacy or other HR as H1R are needed to be targeted to achieve clinical efficacy. On the other hand, it should also be considered that the inflammation in the skin and pruritus in particular are not exclusively dependent on histamine. Other mediators like interleukin (IL)-31 (25) or neuropeptides like substance P (26) can promote the inflammatory process and mediate itch as well. Such factors may also be responsible for the observation that only a subgroup of patients with AD benefit from a histamine-free diet.

With our study design no decrease in plasma histamine was detected in the diet-responder group. Perhaps a longer diet phase would have been required to achieve this. On the other hand, one can speculate that the diet phase was sufficient to reduce histamine levels in the skin. This hypothesis can be addressed, e.g. by microdialysis of the skin before and after the diet phase.

Earlier studies by Wantke et al. (18) have shown that antihistamines such as diphenhydramine can enhance DAO activity *in vitro*. It is not known whether DAO activity is important in the pathogenesis of AD. If this is the case, it would be an additional therapeutic approach. Following this hypothesis one can speculate whether the intake of DAO as a drug will result in a reduction in plasma histamine levels and will therefore be of therapeutic interest for patients with AD. However, this needs to be confirmed by prospective clinical trials.

The relation between plasma histamine and DAO activity is not yet clarified. We observed increased plasma histamine levels in severely affected patients with AD compared with the control group and compared with the patients with AD with mild eczema. Whether this elevated plasma histamine level in patients with AD is a result of decreased histamine metabolism or whether it indicates an ongoing histamine release via IgE-mediated reactions, or both, needs to be clarified in future studies.

Systemic reactions, ranging from mild to severe, were observed in both study groups. Our data shows that within the healthy control group only mild symptoms such as flush occurred, which did not last longer than 5–10 min. In contrast, 10 patients with AD had severe reactions after histamine intake, such as hypotension. All these individuals with systemic reactions after histamine provocation had no decreased DAO activity, indicating that there is no direct correlation between DAO levels and clinical hypersensitivity to histamine. A recent study suggested a significant correlation of reduced DAO activity and severity of eczema in patients with AD (27). In contrast, we did not find significantly lower DAO levels in patients with AD, as measured at 7 time-points, compared with healthy controls. However, a significant correlation between plasma histamine levels and severity of eczema was observed.

Whether and to what extent other mechanisms of histamine degradation are also important, e.g. activity of HMT, the second histamine degrading enzyme is not exactly known (28, 29).

Finally, a selection bias has to be anticipated, since patients who suffer from food hypersensitivity were more likely to complete the study. Additionally, the sex distribution was not equal because we performed a random inclusion without stratification. Only 8 men vs. 28 women were randomized. Thirdly, the ratio of women to men among the AD and the control group differ (AD group = 3.5; control group = 2.1).

In summary, we conclude from our data that high amounts of ingested histamine may aggravate eczema in approximately 30% of patients with AD. Because no direct correlation between DAO activity, plasma histamine levels and skin reactions were observed, these parameters are not predictive to indicate the presence of either histamine intolerance or a role of histamine for an aggravation of eczema in AD.

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