Evidence for a reduced histamine degradation capacity in a subgroup of patients with atopic eczema

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Background: A diminished histamine degradation based on a reduced diaminoxidase activity is suspected as a reason for non–IgE-mediated food intolerance caused by histamine. Atopic eczema (AE) is often complicated by relapses triggered by IgE-mediated allergy to different kinds of food. However, in a subgroup of patients with AE, allergy testing proves negative, although these patients report a coherence of food intake and worsening of AE and describe symptoms that are very similar to histamine intolerance (HIT).

Objectives: It was the aim of our study to evaluate symptoms of HIT in combination with diaminoxidase levels in a total of 360 individuals consisting of patients with AE (n = 162) in comparison with patients with HIT (n = 124) without AE and healthy control volunteers (n = 85).

Methods: Histamine plasma level was determined with an ELISA and diaminoxidase serum activity with the help of radio extraction assays using [3H]-labeled putrescine-dihydrochloride as a substrate. Detailed clinical evaluations of characteristic features of AE and HIT were performed.

Results: Reduced diaminoxidase serum levels leading to occurrence of HIT symptoms like chronic headache, dysmenorrhea, flushing, gastrointestinal symptoms, and intolerance of histamine-rich food and alcohol were significantly more common in patients with AE than in controls. Reduction of both symptoms of HIT and Severity Scoring of Atopic Dermatitis could be achieved by a histamine-free diet in the subgroup of patients with AE and low diaminoxidase serum levels.

Conclusion: Higher histamine plasma levels combined with a reduced histamine degradation capacity might influence the clinical course of a subgroup of patients with AE.

Clinical implications: As HIT emerges in a subgroup of patients with AE, a detailed anamnestic evaluation of food intolerance and HIT symptoms complemented by an allergological screening for food allergy, a diet diary, and, in confirmed suspicion of HIT, measurement of diaminoxidase activity and a histamine-free diet should be undertaken. (J Allergy Clin Immunol 2006;117:1106-12.)

Key words: Atopic eczema, histamine, diaminoxidase, food intolerance, allergy

Numerous undesirable reactions to alcoholic beverages, food, drugs, and other substances are characterized by allergy-like signs and symptoms such as chronic headache, diarrhea, vomiting, flush, urticaria, asthma, and others. Histamine and other biogenic amines are present to varying degrees in many foods. Histamine content increases by maturing and fermentation processes.[1,2] The main enzyme for metabolism of ingested histamine is diaminoxidase,[2-6] a copper-containing amino oxidase[7-10] with a molecular mass of 90 kd. It has been proposed that diaminoxidase as a secretory protein[11,12] might be responsible for scavenging extracellular histamine after mediator release. Conversely, histamine N-methyltransferase (HNMT), the second important enzyme inactivating histamine, is a cytosolic protein[13] that can convert histamine only in the intracellular space of cells.[14,15]

A diminished histamine degradation based on a reduced diaminoxidase activity is suspected as a reason for non–IgE-mediated food intolerance caused by histamine.[16-23] Histamine is a potent mediator of numerous biological reactions such as the degranulation of mast cells in consequence of IgE-mediated allergen challenge of these cells in several allergic diseases. Via different histamine receptors, histamine causes smooth muscle contraction, vasodilatation, extravasation of plasma from capillaries, and stimulation of gastric acid secretion and nociceptive nerves. Together, these mechanisms are responsible for the typical symptoms such as diarrhea, headache,[24] hypotension, arrhythmias, urticaria,[25-27] pruritus, flushing, and even asthma[16,22,28] after ingestion of histamine-rich food,[16] alcohol,[21,22,29] or drugs releasing histamine or blocking diaminoxidase.[18,28,30] Symptoms can be reduced with a histamine-free diet[20,31,32] or can be eliminated by H1-blocker premedication.[16,17,21,24]

Atopic eczema (AE) is a chronic inflammatory skin disease that shows a wide variety of clinical pictures and that is often complicated by relapses of AE caused by different kinds of food. In a high number of patients with AE, IgE-mediated food hypersensitivities can be confirmed by skin prick tests, analysis of allergen specific IgE against food allergens in the sera, atopy patch tests, or oral allergen challenge.[33,34] However, in a subgroup of patients with

Abbreviations used	
AE:	Atopic eczema
FA:	Food allergy
HIT:	Histamine intolerance
HNMT:	Histamine-N-methyltransferase
SCORAD:	Severity Scoring of Atopic Dermatitis

AE, allergy testing proves negative, or the allergy-like symptoms and the type of sensitizations present in the individual patient cannot be linked with the type of food and beverages ingested.[35] Nevertheless, these patients report a coherence of food intake and worsening of AE and describe symptoms that resemble histamine intolerance (HIT).

Therefore, it was the aim of our study to evaluate whether HIT might be of relevance in a subgroup of patients with AE.

METHODS
Characterization of patients

A total of 162 adult AE[36] patients (age range, 14-86 years; average age, 31.42 ± 12.95 years; 106 female and 56 male) from the Department of Dermatology in Bonn, Germany, were analyzed regarding atopic status, and the severity of the disease was evaluated according to the Diepgen score,[37] the criteria of Bos,[38] the criteria of Hanifin and Rajka,[39] and the Severity Scoring of Atopic Dermatitis (SCORAD) system,[40] respectively. In parallel, typical clinical symptoms of HIT and a history of food intolerance were evaluated with a standard questionnaire. Food intolerance was defined as non–IgE-mediated reaction to histamine-rich food such as worsening or development of the aforementioned HIT symptoms or worsening of pruritus and eczema. For control purposes, 85 healthy donors without any history of HIT or AE (age range, 17-63 years; average age, 30.58 ± 10.31 years; 57 female and 28 male) and 124 donors with a clinical manifestation of HIT without AE (age range, 6-75 years; average age, 48.43 ± 15.21 years; 101 female and 23 male) were investigated. The diagnosis of HIT was defined as patients reporting 2 or more positive symptoms of HIT and an improvement of these symptoms as a result of a histamine-free diet. In parallel, diaminoxidase serum levels were evaluated in these patients. The protocol was approved by the local ethics committee.

Analysis of total serum IgE, allergen-specific IgE

Total serum IgE and allergen specific IgE against *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), birch pollen, Timothy grass pollen, cat dander, hazelnut, peanut, milk, egg, apple, *Aspergillus fumigatus*, *Candida albicans*, *Malassezia sympodialis*, and codfish in the sera were analyzed with an Immulite 2000 System (DPC Biermann, Bad Nauheim, Germany).

Quantitative determination of the diaminoxidase activity in serum

Diaminoxidase activity assay was performed according to the manufacturer's instructions (Immunodiagnostik AG, Bensheim, Germany). Briefly, serum samples were collected and centrifuged for 10 minutes at approximately 1000*g* and stored at −20°C. Diaminoxidase activity was determined quantitating the reaction product,

and radiolabeled putrescine-dihydrochloride was used as substrate. The resulting 3H-thymidine-labeled pyrolline was extracted selectively from the matrix by a liquid extraction step. Finally, radioactivity was determined by a β-counter. The signal detected was directly proportional to the activity of diaminoxidase in the sample, which was calculated according to a standard curve.[41] According to the literature, diaminoxidase activity lower than 3 U/mL was considered decreased.[23]

Analysis of laboratory parameters

Plasma level of histamine was evaluated according to the manufacturer's instructions (Immunotech, Marseille, France).

The amount of eosinophilic cationic protein in the sera of the volunteers was evaluated with the Immulite 2000 System. Serum tryptase levels were determined with the UniCAP System (Pharmacia Diagnostics, Uppsala, Sweden).

Zinc levels in the sera of the patients were measured quantitatively by atomic absorbtion spectrometry after deproteination of the serum with acetic acid (Bioscientia, Ingelheim, Germany). Copper serum levels and vitamin B_6 plasma levels were determined according to the manufacturer's instructions (copper: HITADO Diagnostic Systems, Möhnesee Delecke, Germany; vitamin B_6: Immunodiagnostik AG, Bensheim, Germany).

Conduction of histamine-free diet in a subgroup of patients with AE and HIT

A subgroup of patients with AE and HIT and low diaminoxidase activity (n = 17) underwent intensive nutritional consulting and histamine-free diet combined with intake of oral antihistamines once a day over a period of 2 weeks. Alcohol and long matured or fermented food rich in histamine like old cheese, fish, hard cured sausages, bread products containing yeast, vegetables like spinach, tomatoes, histamine-liberating fruits like citrus fruits, and other histamine-rich food had to be strictly avoided. In parallel, symptoms of HIT and AE were documented with the help of a standardized diet diary. At the beginning and after 2 weeks of the histamine-free diet, the objective and subjective SCORAD was evaluated in each patient. Serum diaminoxidase activity was compared in 5 patients before and after diet.

Statistical analysis

Statistical analysis using the Wilcoxon test was performed with SPSS 12.0 for Windows (SPSS, Chicago, Ill). Calculated values shown were means ± SDs. In addition, the frequencies of the different parameters between the different groups were compared by using the χ^2 test and the Mann-Whitney U test.

RESULTS
Symptoms of HIT occur in a subgroup of patients with AE

To analyze the frequency of HIT in patients with AE, we evaluated the occurrence of classical symptoms of HIT in patients with AE selected randomly by a standard questionnaire.

Symptoms of HIT such as chronic headache ($P = .003$; $\chi^2 = 8.556$), premenstrual headache and dysmenorrhea ($P = .002$; $\chi^2 = 9.295$), flushing ($P < .001$; $\chi^2 = 24.67$), gastrointestinal symptoms such as diarrhea, cramps, and meteorism ($P < .001$; $\chi^2 = 38.89$) and intolerance of food rich in or releasing histamine ($P < .001$; $\chi^2 = 51.85$) and alcohol ($P < .001$; $\chi^2 = 18.485$) occurred significantly more often in patients with AE than in controls
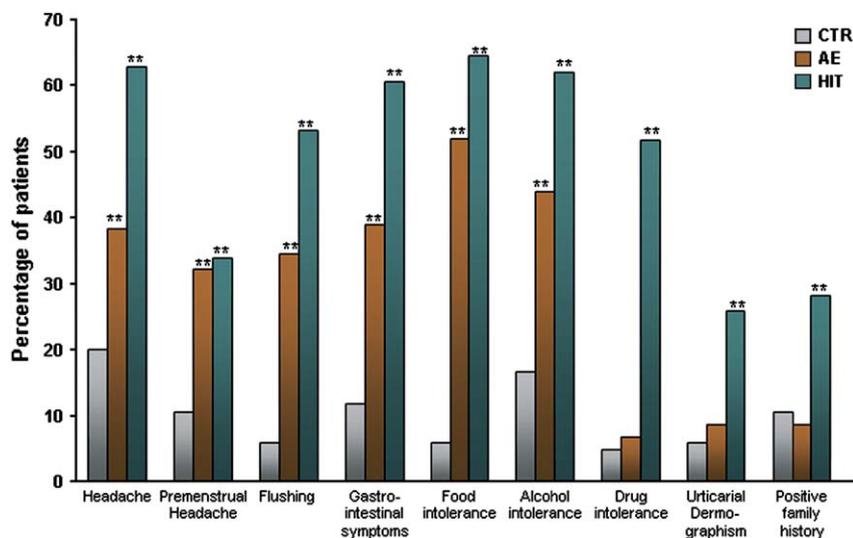
FIG 1. Symptoms for HIT are high in patients with AE. Symptoms of HIT in patients with a suspected HIT without AE (*HIT*; n = 124), patients with AE (n = 162), and healthy controls (*CTR*; n = 85) are shown. The percentage of patients showing symptoms and or low diaminoxidase activity is depicted on the *x-axis*. **P < .01 in comparison with healthy control group (CTR).

TABLE I. Low and normal diaminoxidase (DAO) activity in serum from patients with suspected HIT, patients with AE, and a healthy control group (CTR)

	Total number	Low DAO		Normal DAO			
	n	n	%	n	%	*P* value*	χ^2
CTR	85	0	0	85	100		
AE	162	31	19.14	131	80.86	<.001	18.6
HIT	124	25	20.16	99	79.84	<.001	19.466

*Statistical analysis has been performed with the χ^2 test.

(Fig 1). Drug intolerance (P = .52; χ^2 = 0.425), urticarial dermographism (P = .44; χ^2 = 0.588), and a positive family history regarding HIT symptoms (P = .62; χ^2 = 0.25) did not differ significantly from the control group (Fig 1).

Reduced diaminoxidase serum level in a high number of patients with AE

To evaluate the histamine degradation capacity of patients with AE, we performed analyses in which we measured the diaminoxidase activity in the sera of patients with AE in comparison with healthy volunteers and patients with HIT but without AE. We observed both a significantly lower mean of the diaminoxidase activity in patients with AE (P < .001) compared with controls and a higher total number of patients with AE displaying a reduced diaminoxidase serum level in comparison with healthy controls (P < .001; χ^2 = 18.6; Table I; Fig 2, *A*).

Histamine plasma levels in patients with AE and patients with HIT were significantly elevated compared with control persons (P < .05 for AE and P < .01 for HIT; Fig 2, *B*). Patients with AE and symptoms of HIT and low diaminoxidase activity had higher histamine levels than patients with AE without HIT, although this did not

reach statistical significance. An additional sensitization toward food allergens (hazelnut, peanut, milk, egg, apple, and codfish; P = .0031; χ^2 = 8.731) and occurrence of headache (P = .035; χ^2 = 4.454) and gastrointestinal symptoms (P < .0001; χ^2 = 16.6) could be observed in a significant higher number of patients with AE with low diaminoxidase activity compared with those patients with AE with normal diaminoxidase activity (Table II).

Modified levels of vitamin B$_6$, copper, or zinc were not associated with reduced diaminoxidase levels in patients with AE

Vitamin B$_6$ is a postulated cofactor of diaminoxidase,[42] and copper and zinc occupy the active sites in the recombinant enzyme.[9] It has been shown in some studies that a deficiency of vitamin B$_6$, copper, or zinc might lead to a reduced histamine degradation capacity. To exclude an AE-related malnutrition or deficiency of vitamin B$_6$, copper, or zinc as a reason for the reduced histamine degradation capacity, we next analyzed the vitamin B$_6$ plasma and copper and zinc serum levels in parallel to the diaminoxidase activity in a subset of patients with AE (n = 21), patients with HIT without AE (n = 18), and healthy

controls (n = 16). As a result, vitamin B_6, copper, and zinc serum levels were not reduced in patients with AE and did not differ significantly from vitamin B_6, copper, and zinc serum levels in healthy controls or patients with HIT without AE.

Histamine-free diet leads to improvement of symptoms of HIT and SCORAD in patients with AE

To investigate the effect of orally ingested histamine on the clinical status of patients with AE, 17 patients with AE and low diaminoxidase activity with symptoms of HIT were put on a histamine-free diet and given an oral antihistamine once daily. After 2 weeks, a significant improvement of HIT symptoms such as headache, flushing, and gastrointestinal symptoms occurred in most of the patients (Fig 3). Moreover, a significant reduction of both objective and subjective SCORAD was observed (Fig 4). In addition, diaminoxidase activity increased in 3 of 5 patients after the diet, whereas diaminoxidase activity remained unchanged in 2 of 5 patients.

DISCUSSION

Histamine intolerance is caused by a disproportion of the quantity of histamine and the capacity of histamine degradation. This can be a result of histamine overload and/or diaminoxidase deficiency. Exceeding the individual histamine tolerance gives rise to concentration-dependent histamine-mediated symptoms.[43,44] In sensitive patients, symptoms occur even after oral ingestion of small amounts of histamine that are well tolerated by healthy persons. Symptoms can manifest in multiple organs like gastrointestinum, lung, skin, cardiovascular system, and brain according to the expression of histamine receptors.

There are primary and acquired forms of HIT that may result from gastrointestinal diseases,[27,45] competitive inhibition of biogenic acids, or diaminoxidase-blocking drugs.[18,30,46] Elevated histamine concentrations[47] and diminished diaminoxidase activities were found in the colonic mucosa of patients with food allergy (FA).[45,48,49] Furthermore, a low HNMT activity has been observed in both FA[48] and asthma bronchiale.[50]

Here we describe a significantly higher number of symptoms of HIT in a subgroup of patients with AE that might be caused by a reduced histamine degradation capacity in these patients. From the clinical picture, HIT in AE patients represents most of the typical symptoms for classic HIT except for a higher level of drug-induced symptoms of HIT in patients with HIT without AE. Interestingly, most of the patients with classic HIT reporting drug-intolerance related to HIT also had a positive family history for HIT. Together, this might indicate that in a subgroup of patients with HIT, a genetic background, such as functionally relevant single nucleotide polymorphisms in gene regions encoding histamine degrading enzymes, might underlie the reduced histamine degrading capacity.
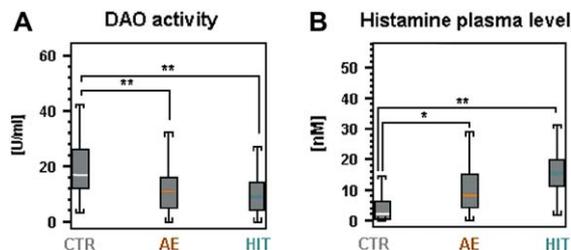

FIG 2. A, Diaminoxidase (DAO) activity in U/mL in serum from patients with suspected HIT, AE, and a healthy control group (*CTR*). SDs are given. *$P < .05$; **$P < .01$. **B,** Histamine levels (normal < 10 nmol/L) are higher in patients with AE and HIT than in controls. SDs are given. *$P < .05$; **$P < .01$.

Polymorphism of the diaminoxidase has been found associated with inflammatory intestinal diseases including FA,[51-53] whereas polymorphism of the HNMT gene associated with low enzyme activity has been reported for patients with asthma.[50,54] Variants of the diaminoxidase or HNMT gene in patients with AE or in primary HIT without inflammatory or allergic diseases have not been investigated yet.

In contrast with the classic HIT, which shows a clear female predominance, symptoms of HIT in patients with AE seem to be independent of the sex of the patient, and no positive family history of HIT was observable. In addition, no differences in serum IgE levels, severity of AE, or the association of rhinitis and asthma between patients with AE with and without HIT could be found (Table II), indicating that AE-associated HIT most likely occurred independently from these parameters. Histamine plasma levels were significantly higher in patients with AE and highest in patients with AE with HIT compared with those without HIT. An additional sensitization toward food allergens could be observed in a significant higher number of patients with AE with low diaminoxidase activity compared with those with normal diaminoxidase activity, supporting the finding that FA can coexist with an impaired histamine degradation capacity,[45] both related to an altered gastrointestinal mucosal barrier.[55,56]

Elevated basal plasma histamine levels[57,58] and increased spontaneous histamine release toward different stimuli[59-61] and after food challenge[55] have been shown in patients with severe AE compared with normal subjects. Reduced type B monoamine oxidase and diaminoxidase activities in AE have been reported in previous studies.[57,62]

Assuming the absence of gastrointestinal diseases or diaminoxidase blocking drugs, an acquired functional impairment of diaminoxidase might be a result of cofactor deficiency or the presence of inhibiting factors. Vitamin B_6 and copper levels, cofactors of diaminoxidase, were normal in our study and previous studies,[42,62] supporting the thesis of diaminoxidase inhibition.

Although elevated histamine concentrations correlated with a high total histamine degradation capacity in colonic biopsies of patients with FA,[63] and diaminoxidase lymph activity in rats was raised after histamine-injection, further histamine administration resulted in comparatively

TABLE II. Comparison of patients with AE with and without low diaminoxidase serum levels and symptoms of HIT*

Group	IgE Serum level, kU/L†	Objective SCORAD†	Subjective SCORAD†	Diepgen score†	Asthma (%)‡	Allergic rhinitis (%)‡	FA (%)‡	Tryptase, µg/L†
AE without HIT (n = 131)	788.07 ± 1018.35	27.79 ± 16.35	34.0 ± 19.96	21.67 ± 5.78	30.53 (n = 40)	66.41 (n = 87)	22.14 (n = 29)	4.82 ± 2.2 (n = 29)
AE with HIT (n = 31)	614.15 ± 923.28	21.587 ± 14.91	27.62 ± 19.439	22.6 ± 5.2561	25.81 (n = 8)	74.19 (n = 23)	48.39 (n = 15)	3.89 ± 1.63 (n = 4)
P value	.367	.056	.114	.538	.604	.404	.003	.483
χ^2					0.269	0.696	8.731	

Group	Headache‡ n	%	Premenstrual headache‡ n	%	Flushing‡ n	%	Gastrointestinal symptoms‡ n	%	Food intolerance‡ n	%	Alcohol intolerance‡ n	%	Drug intolerance‡ n	%	Urticarial dermographism‡ n	%
AE without HIT (n = 131)	45	34.35	28	32.56	44	33.59	41	31.3	69	52.57	55	41.98	9	6.87	11	8.4
AE with HIT (n = 31)	17	58.84	6	23.08	12	38.71	22	70.97	15	48.39	17	54.84	2	6.45	3	9.68
P value	.035		.357		.59		<.0001		.667		.195		.934		.82	
χ^2	4.454		0.849		0.291		16.6		0.184		1.677		0.007		0.052	

*For numerical parameters (IgE serum level, objective and subjective SCORAD, and Diepgen Score), means ± SDs are depicted.
†Statistical analysis was performed with the Mann-Whitney U Test.
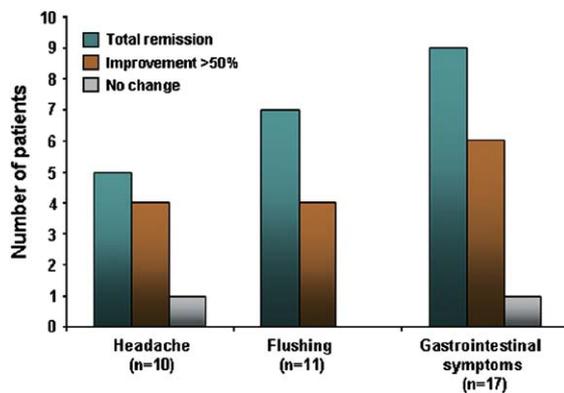‡Statistical analysis was performed with the χ^2 test.

FIG 3. Improvement of symptoms of HIT after 2 weeks of histamine-free diet in patients with AE and HIT and low diaminoxidase activity.

FIG 4. Objective (extent and severity of eczema) and subjective (including pruritus and sleep loss) SCORAD improves in patients with AE and HIT and low diaminoxidase serum levels after 2 weeks of histamine-free diet (n = 17). SCORAD value is depicted on the *x-axis* together with the SEM.

smaller increases, implicating only a limited secretion of diaminoxidase from the intestinal mucosa.[64] In addition, substrate inhibition of recombinant human diaminoxidase has been observed for elevated histamine levels.[9,65] Because the diaminoxidase has also been shown to be inhibited by its degradation product, imidazole acetic acid,[66,67] a negative feedback loop inducing an endogenous inhibition of diaminoxidase caused by high histamine levels might occur in patients with AE. Together, these mechanisms might lead to a generally reduced histamine degradation capacity in patients with AE (Fig 5). However, further investigation of these mechanisms is needed.

Because HIT in patients with AE often occurred in association with food allergy, a careful and detailed anamnestic evaluation of the symptoms and causative factors would be indispensable for the exact diagnosis. Interestingly, a
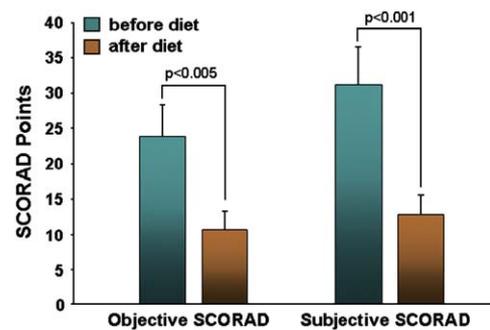
histamine-free diet and antihistamines are capable of improving both HIT-specific and AE-specific symptoms in patients with low diaminoxidase capacity. Omitting orally ingested histamine leads to a regeneration of the diaminoxidase-producing jejunal enterocytes and therefore an increase of enzyme activity, which could also be observed in a subgroup of patients with AE in our study.[32] Supporting the beneficial effect of a histamine-free diet observed in our study, another research group performed a double-blind, placebo-controlled histamine challenge in patients with AE after 2 weeks of a histamine-free diet and reported an aggravation of eczema as well as development of systemic reactions like flush, headache, or dizziness in patients with AE after provocation (Fiedler EM et al, unpublished data, 2005).

From the pathophysiological point of view, 2 different therapeutic strategies for patients with AE and
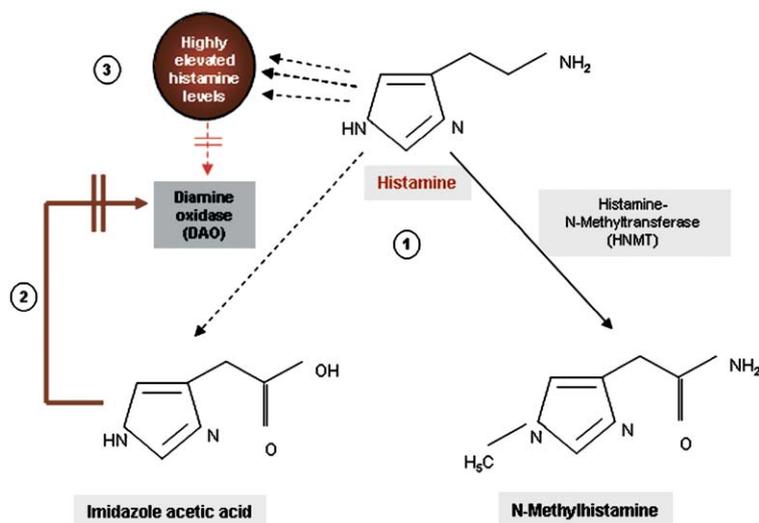
FIG 5. Pathway of histamine degradation. *(1)* Normal histamine degradation pathway by diaminoxidase (DAO) and HNMT. *(2 + 3)* Potential mechanisms responsible for the development of histamine intolerance in patients with AE. *(2)* Enhanced histamine levels might lead to a high histamine degradation mediated by DAO and blockage of DAO by imidazole acetic acid. *(3)* Substrate inhibition on DAO might occur by elevated histamine levels.

AE-associated HIT arise: first, the reduction of the histamine release and histamine levels by a histamine-free diet and antihistamines, and second, the substitution of the enzyme itself or cofactors promoting the activity of diaminoxidase such as vitamin B_6, copper, zinc, or vitamin C in patients with a deficiency on this level. In a recent study, no additional effect could be seen with a histamine-free diet in patients with HIT by add-on medication with antihistamines.[32] Therefore, premedication with antihistamines seems to be advisable only in dietary errors or before exposition to drugs inhibiting diaminoxidase.

In view of our data, we propose that higher histamine plasma levels occurring in AE combined with a reduced histamine degradation capacity might be of relevance for the clinical course of a subgroup of patients with AE. Whether the deficiency in histamine degradation observed in AE results from polymorphisms in the diaminoxidase gene or represents a rather secondary phenomenon, such as an inhibition of diaminoxidase caused by the continuous allergen-induced histamine release in AE, remains to be elucidated.

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