Histamine and histamine intolerance[1–3]

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ABSTRACT

Histamine intolerance results from a disequilibrium of accumulated histamine and the capacity for histamine degradation. Histamine is a biogenic amine that occurs to various degrees in many foods. In healthy persons, dietary histamine can be rapidly detoxified by amine oxidases, whereas persons with low amine oxidase activity are at risk of histamine toxicity. Diamine oxidase (DAO) is the main enzyme for the metabolism of ingested histamine. It has been proposed that DAO, when functioning as a secretory protein, may be responsible for scavenging extracellular histamine after mediator release. Conversely, histamine *N*-methyltransferase, the other important enzyme inactivating histamine, is a cytosolic protein that can convert histamine only in the intracellular space of cells. An impaired histamine degradation based on reduced DAO activity and the resulting histamine excess may cause numerous symptoms mimicking an allergic reaction. The ingestion of histamine-rich food or of alcohol or drugs that release histamine or block DAO may provoke diarrhea, headache, rhinoconjunctival symptoms, asthma, hypotension, arrhythmia, urticaria, pruritus, flushing, and other conditions in patients with histamine intolerance. Symptoms can be reduced by a histamine-free diet or be eliminated by antihistamines. However, because of the multifaceted nature of the symptoms, the existence of histamine intolerance has been underestimated, and further studies based on double-blind, placebo-controlled provocations are needed. In patients in whom the abovementioned symptoms are triggered by the corresponding substances and who have a negative diagnosis of allergy or internal disorders, histamine intolerance should be considered as an underlying pathomechanism. *Am J Clin Nutr* 2007;85:1185–96.

KEY WORDS Histamine intolerance, histamine, diamine oxidase, food intolerance, allergy

INTRODUCTION

Histamine intolerance results from a disequilibrium of accumulated histamine and the capacity for histamine degradation. The main enzyme for metabolism of ingested histamine is diamine oxidase (DAO) (1–5). An impaired histamine degradation based on a reduced DAO activity and the resulting excess of histamine may cause numerous symptoms mimicking an allergic reaction. Ingestion of histamine-rich food (6), alcohol (7–9), or drugs (10–13) that release histamine or block DAO may provoke diarrhea, headache (14), congestion of the nose, asthmatoid wheezing (6, 8, 15), hypotension, arrhythmia, urticaria (16, 17), pruritus, flushing, and other conditions in these patients. Approximately 1% of the population has histamine intolerance, and 80% of those patients are middle-aged (18). Because of the multifaceted symptoms, the existence of histamine intolerance is frequently underestimated, or its symptoms are misinterpreted. Clinical symptoms and their provocation by certain foods and beverages appear similar in different diseases, such as food allergy and intolerance of sulfites, histamine, or other biogenic amines (eg, tyramine). Therefore, the differentiation of the causal agent in adverse reactions to food, alcohol, and drugs is a difficult challenge. There is poor evidence of adverse reactions to these agents based on double-blind, placebo-controlled (DBPC) provocations (19). However, a better understanding of the pathophysiology, clinical picture, trigger factors, and diagnostic tools may help to clarify the confusing debate surrounding histamine intolerance.

HISTAMINE AND HISTAMINE METABOLISM

Histamine (2-[4-imidazolyl]ethylamine) was discovered in 1910 by Dale and Laidlaw (20), and it was identified as a mediator of anaphylactic reactions in 1932 (21). Histamine belongs to the biogenic amines and is synthesized by the pyridoxal phosphate (vitamin B-6)–containing L-histidine decarboxylase (HDC) from the amino acid histidine. It is synthesized by mast cells, basophils, platelets, histaminergic neurons, and enterochromaffine cells, where it is stored intracellularly in vesicles and released on stimulation. Histamine is a potent mediator of numerous biologic reactions. Besides the well-known triggering of degranulation of mast cells by crosslinking of the FcεRI receptor by specific allergens, several other nonimmunologic stimuli, such as neuropeptides, complement factors (ie, C3a and C5a), cytokines, hyperosmolarity, lipoproteins, adenosine, superoxidases (22), hypoxia, chemical and physical factors (eg, extreme temperatures, traumas) (23), or alcohol and certain food and drugs, may activate mast cells.

Histamine exerts its effects by binding to its 4 receptors [histamine 1 receptor (H1R), H2R, H3R, and and H4R] on target cells in various tissues (**Figure 1**, **Table 1**). It causes smooth

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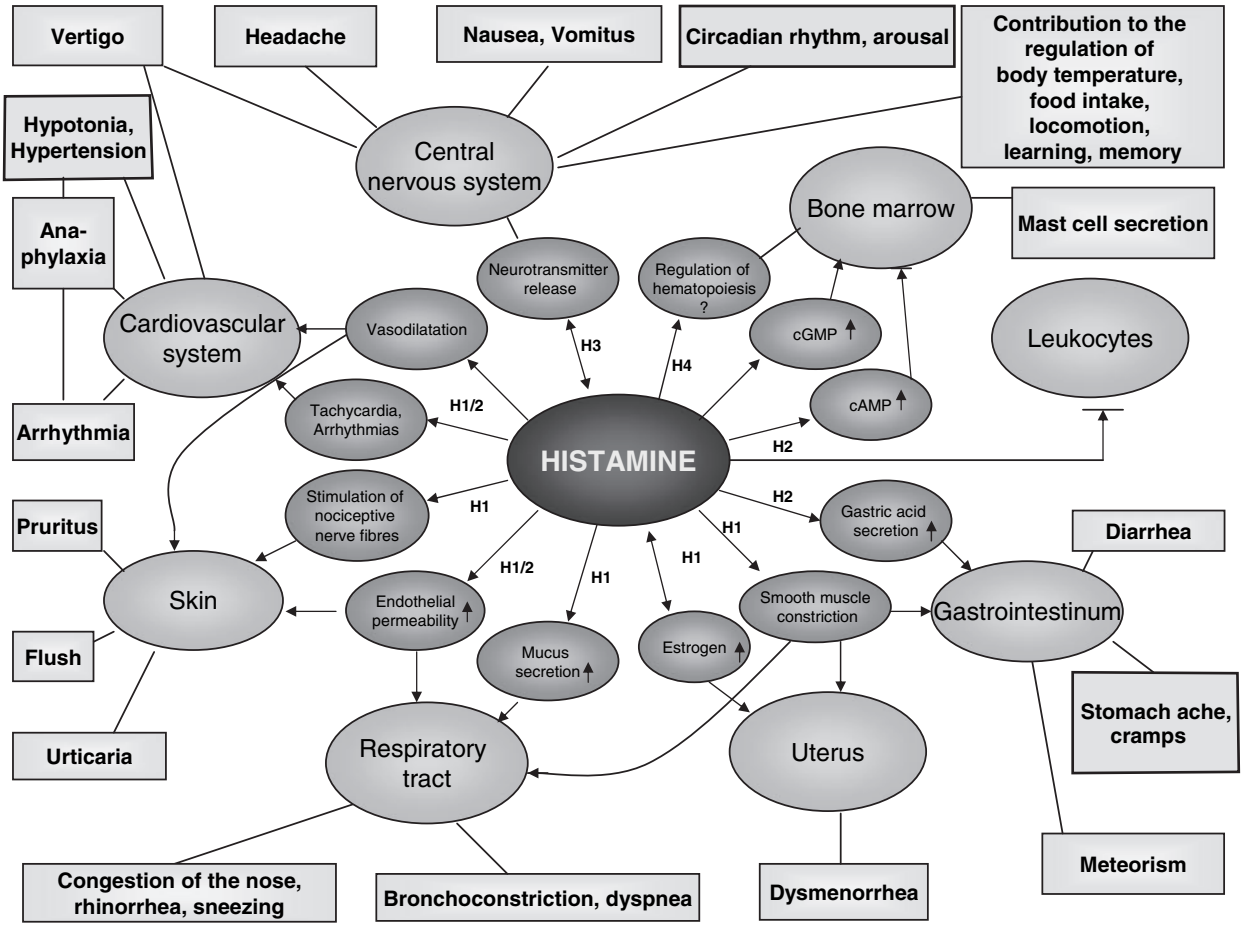

FIGURE 1. Summary of histamine-mediated symptoms. Adapted with permission from Maintz L et al. Dtsch Artzebl 2006;103:A3477-83.

muscle cell contraction, vasodilatation, increased vascular permeability and mucus secretion, tachycardia, alterations of blood pressure, and arrhythmias, and it stimulates gastric acid secretion and nociceptive nerve fibers. In addition, histamine has been known to play various roles in neurotransmission, immunomodulation, hematopoiesis, wound healing, day-night rhythm, and the regulation of histamine- and polyamine-induced cell proliferation and angiogenesis in tumor models (24, 25) and intestinal ischemia (26). Histamine can be metabolized in 2 ways: by oxidative deamination by DAO (former name: histaminase) or by ring methylation by histamine-*N*-methyltransferase (HNMT) (27) (**Figure 2**, **Table 2**). Whether histamine is catabolized by DAO or HNMT is supposed to depend on the localization of histamine. The DAO protein is stored in plasma membrane–associated vesicular structures in epithelial cells and is secreted into the circulation on stimulation (28, 29). Therefore, it has been proposed that DAO may be responsible for scavenging extracellular histamine (eg, after ingestion of histamine-rich food) after mediator release. Conversely, HNMT, the second most important enzyme inactivating histamine, is a cytosolic protein (30), which can convert histamine only in the intracellular space of cells (31, 32). Thus, the enzymes do not seem to compete for the substrate, although they have a similar affinity for histamine and they are expressed in some overlapping tissues. HNMT has a slightly higher affinity for histamine [Michaelis-Menten constant (k_M): 6–13 μmol/L] than does DAO (k_M: 20 μmol/L). In mammals, DAO expression is restricted to specific tissues; the highest activities are shown for small bowel and colon ascendens (4, 5, 33) and for placenta and kidney (28, 31). Lower DAO activity has been discussed as a potential indicator of intestinal mucosa damage in inflammatory and neoplastic diseases (17, 24, 34) and in persons undergoing chemotherapy (35). HNMT is widely expressed in human tissues; the greatest expression is in kidney and liver, followed by spleen, colon, prostate, ovary, spinal cord cells, bronchi, and trachea (36). HNMT is regarded as the key enzyme for histamine degradation in the bronchial epithelium (37).

TABLE 1
Histamine effects according to plasma histamine concentration (ng/mL)

Histamine	Clinical effect
0–1	Reference
1–2	↑ Gastric acid secretion
	↑ Heart rate
3–5	Tachycardia, headache, flush, urticaria, pruritus
6–8	↓ Arterial pressure
7–12	Bronchospasm
≈100	Cardiac arrest

ETIOPATHOGENESIS OF HISTAMINE INTOLERANCE

Different mechanisms have been proposed as causing histamine intolerance (38). Histamine intolerance can develop

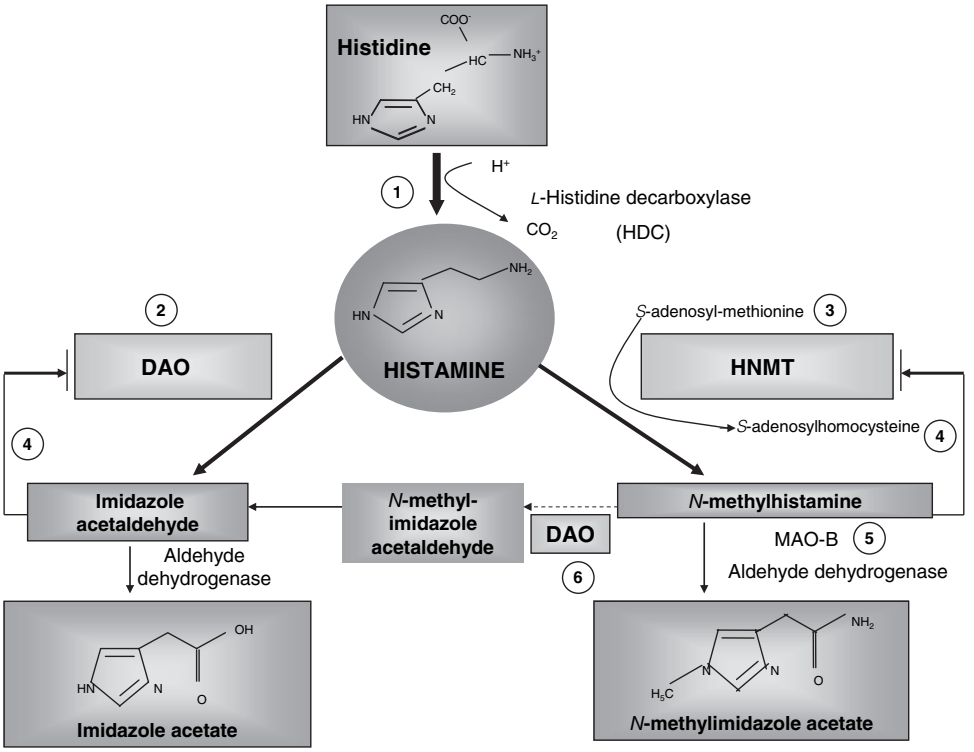

FIGURE 2. Summary of the histamine metabolism. The biogenic amine histamine is synthesized by decarboxylation of the amino acid histidine catalyzed by L-histidine decarboxylase (HDC) (1). Histamine can be metabolized by extracellular oxidative deamination of the primary amino group by diamine oxidase (DAO) (2) or intracellular methylation of the imidazole ring by histamine-*N*-methyltransferase (HNMT) (3). Therefore, insufficient enzyme activity caused by enzyme deficiency or inhibition may lead to accumulation of histamine. Both enzymes can be inhibited by their respective reaction products in a negative feedbackloop (4). *N*-Methylhistamine is oxidatively deaminated to *N*-methyl-imidazole acetaldehyde by monoamine oxidase B (MAO B) (5) or by DAO (6). Because the methylation pathway takes place in the cytosolic compartment of cells, MAO B (5) has been suggested to catalyze this reaction in vivo (35).

through both increased availability of histamine and impaired histamine degradation. Underlying conditions for increased availability may be an endogenous histamine overproduction caused by allergies, mastocytosis, bacterias, gastrointestinal bleeding, or increased exogenous ingestion of histidine or histamine by food or alcohol. Other biogenic amines, such as putrescine, may also be involved in displacing histamine from its mucosal mucine linkage, which results in an increase of free absorbable histamine in circulation. However, the main cause of histamine intolerance is an impaired enzymatic histamine degradation caused by genetic or acquired impairment of the enzymatic function of DAO or HNMT. Gastrointestinal diseases with altered enterocytes also may cause decreased production of DAO (17, 33, 39). Yet another cause can be competitive inhibition of histamine degradation of DAO by other biogenic amines, alcohol (7–9), or drugs (10, 12, 40). Acquired histamine intolerance may be transient and therefore reversible after the elimination of causes, such as by discontinuing DAO-blocking drugs. DAO inhibits the transepithelial permeation of exogenous histamine (41, 42), and impaired DAO activity results in increased enteral histamine uptake with consequent increased plasma histamine concentrations (10, 41) and corresponding symptoms. Increased amounts of histamine metabolites may also inhibit HNMT, the second enzyme metabolizing histamine (6, 43).

THE GENETIC BACKGROUND OF HISTAMINE INTOLERANCE

Recently, a potential genetic background of a reduced histamine metabolism has also been investigated. The human DAO gene spans ≈10 kbp and is located on chromosome 7q35 (27) Various single-nucleotide polymorphisms (SNPs) in the DAO gene have been shown to be associated with inflammatory and neoplastic gastrointestinal diseases, such as food allergy (44), gluten-sensitive enteropathy, Crohn disease, ulcerative colitis, and colon adenoma (45–47). No significant difference in the distribution of the investigated HNMT alleles could be shown between patients with gastrointestinal diseases and control subjects (45, 47), but a functional relevant polymorphism of the *HNMT* gene (chromosome 2q22) has been described for white asthma patients (48). Conversely, this association could not be observed in Japanese (49), German pediatric (50), and East Indian (51) populations. Thus, histamine intolerance seems to be acquired mostly through the impairment of DAO activity caused by gastrointestinal diseases or through the inhibition of DAO, but the high interindividual variations in the expression of DAO in the gut and the association of SNPs in the DAO gene with gastrointestinal diseases provide evidence for a genetic predisposition in a subgroup of patients with histamine intolerance (27).

CLINICAL PICTURE

Basal plasma histamine concentrations of 0.3 to 1.0 ng/mL are considered normal (52). Exceeding the individual histamine tolerance gives rise to concentration-dependent histamine-mediated symptoms (15, 53, 54) (Table 1). Even healthy persons may develop severe headache or flushing due to ingestion of massive amounts of histamine as is known from studies of scromboid poisoning (55). It has been shown that inhibition of

TABLE 2
Characteristics of the histamine-degrading enzymes diamine oxidase (DAO) and histamine *N*-methyl-transferase (HNMT)[1]

	DAO	HNMT
Gene		
Gene map locus	Chromosome 7q35	Chromosome 2q22
Gene	10 kbp, 5 exons, 4 introns	35 kbp, 6 exons
Associated with SNPs	Inflammatory and neoplastic gastrointestinal diseases such as food allergy, gluten-sensitive enteropathy, Crohn disease, ulcerative colitis, and colon adenoma	Asthma
Protein	Soluble homodimeric glycoprotein of M_R 200 000 with subunits of 70–125 kDa; 750 amino acid residues	Soluble, cytosolic protein of M_R 33 000 with subunits of 29–34 kDa; 292 amino acid residues
Enzyme		
Group	Copper-containing amine oxidases	Methyltransferases
Active form	Homodimer with the active-site cofactor 2,4,5-trihydroxyphenylalanine quinone (Topa quinone)	Monomer with a 2-domain structure
Enzyme kinetics (k_m)	Histamine, 20 μmol/L Putrescine, 350 μmol/L Spermidine, 3 mmol/L	Histamine, 6–13 μmol/L *S*-adenosyl-L-methionine, 6–10 μmmol/L
Optimum pH	7.2	7.5–9.0
Inhibititors	Copper-chelating agents, eg cyanide Carbonylgroup reagents, eg, aminoguanidine, semibarbacide	Reaction products: *N*-methylhistamine, *S*-adenosyl-L-homocysteine Sulphydryl groups: p-chloromercuriobenzoate
Major expression	Intestine, kidney, placenta	Highest: kidney and liver; considerable: spleen, colon, prostate, ovary, spinal cord cells, trachea, and bronchi; to a smaller amount, nearly ubiquitous expression
Storage	Plasma membrane–associated vesicular structures in epithelial cells, secretion into the circulation upon stimulation	Cytosolic compartment of the cells
Function	Extracellular scavenger of histamine and other diamines by oxidative deamination of the primary amino group of histamine	Intracellular histamine inactivation by methylation of the imidazole ring

[1] SNPs, single-nucleotide polymorphisms; kbp, kilobase pair; M_R, molecular weight; kDa, kiloDalton; k_M, Michaelis-Menten constant.

DAO followed by oral histamine administration may induce severe and even life-threatening reactions, such as hypotension, bronchospasm, or shock (10, 43). Recurrent anaphylactic reactions have been reported in patients with hyperhistaminemia (56). In histamine-sensitive patients with reduced DAO activity, symptoms occur even after the ingestion of the small amounts of histamine that are well tolerated by healthy persons. Symptoms can be manifest via the abovementioned actions of histamine in multiple organs, such as the gastrointestinum, lung, skin, cardiovascular system, and brain, according to the expression of histamine receptors. Typical symptoms of histamine intolerance include gastrointestinal disorders, sneezing, rhinorrhea and congestion of the nose, headache (14, 57), dysmenorrhea, hypotonia, arrhythmias (58, 59), urticaria (16, 60), pruritus, flushing, and asthma (7, 8).

Histamine and headache

Headache can be induced dose-dependently by histamine in healthy persons as well as in patients with migraine (53, 61). Histamine-induced headache is a vascular headache caused mainly by nitrate monoxide (62). Histamine releases endothelial nitrate monoxide upon stimulation of H1R, which is also expressed in the large intracranial arteries (63). In migraine patients, plasma histamine concentrations have been shown to be elevated both during headache attacks and during symptom-free periods. An increase in the number of brain mast cells is associated with pathologic conditions such as migraine, cluster headache, and multiple sclerosis (64). Many migraine patients have histamine intolerance evidenced by reduced DAO activity, triggering of headache by food rich in histamine (eg, long-ripened cheese or wine), and the alleviation of headache (ie, disappearance of symptoms) under a histamine-free diet (57, 65) and therapy with antihistamines (66).

Histamine and gastrointestinum

Besides headache, gastrointestinal ailments including diffuse stomach ache, colic, flatulence, and diarrhea are leading symptoms of histamine intolerance. Elevated histamine concentrations and diminished DAO activities have been shown for various inflammatory and neoplastic diseases such as Crohn disease (17), ulcerative colitis (67), allergic enteropathy (39), food allergy (33, 68, 69), and colorectal neoplasmas (24). In the colonic mucosa of patients with food allergy, a concomitant reduced HNMT (70) and an impaired total histamine degradation capacity (THDC) (69) have been found (33), so that the enzymes cannot compensate each other. Therefore, an impaired histamine metabolism has been suggested to play a role in the pathogenesis of these diseases.

Histamine and airways

During or immediately after the ingestion of histamine-rich food or alcohol, rhinorrea or nasal obstruction may occur in patients with histamine intolerance; in extreme cases, asthma attacks also may occur. Reduced HNMT activity has been shown for patients with food allergy (70) and asthma bronchiale (71).

TABLE 3
Foods rich in histamine[1]

Food categories	Histamine		Recommended upper limit for histamine		Tyramine	
	mg/kg	*mg/L*	*mg/kg*	*mg/L*	*mg/kg*	*mg/L*
Fish (frozen/smoked or salted/canned)			200		ND	
Mackerel	1–20/1–1788/ND–210					
Herring	1–4/5–121/1–479					
Sardine	ND/14–150/3–2000					
Tuna	ND/ND/1–402					
Cheese			No recommendation			
Gouda	10–900				10–900	
Camembert	0–1000				0–4000	
Cheddar	0–2100				0–1500	
Emmental	5–2500				0–700	
Swiss	4–2500				0–700	
Parmesan	10–581				0–840	
Meat			No recommendation			
Fermented sausage	ND–650				ND–1237	
Salami	1–654				-	
Fermented ham	38–271				123–618	
Vegetables						
Sauerkraut	0–229		10		2–951	
Spinach	30–60					
Eggplant	26					
Tomato ketchup	22					
Red wine vinegar	4					
Alcohol						
White wine		ND–10		2		1–8
Red wine		ND–30		2		ND–25
Top-fermented beer		ND–14				1.1–36.4
Bottom-fermented beer		ND–17				0.5–46.8
Champagne		670				

[1] ND, not detected. Data taken from references 13, 73, 75, 78, and 86.

Histamine and food

Histamine and other biogenic amines are present to various degrees in many foods, and their presence increases with maturation (1, 72). The formation of biogenic amines in food requires the availability of free amino acids, the presence of decarboxylase-positive microorganisms, and conditions allowing bacterial growth and decarboxylase activity. Free amino acids either occur as such in foods or may be liberated by proteolysis during processing or storage (73). Numerous bacterias and some yeast display high HDC activity and thus have the capacity to form histamine. Histidine is generated from autolytic or bacterial processes (74). Therefore, high concentrations of histamine are found mainly in products of microbial fermentation, such as aged cheese (75), sauerkraut, wine (76), and processed meat (77, 78) (**Table 3**) or in microbially spoiled food. Thus, histamine, tyramine, putrescine, and cadaverine serve as indicators of hygienic food quality (73). Tyramine and putrescine also may lead to intolerance reactions in combination with histamine. Possible explanations may be the inhibition of DAO by other amines (43) or the promotion of histamine liberation from the mucosa by putrescine (34).

Intolerance of tyramine that has vasoconstrictive properties that lead to hypertensive crisis and headache has been known mostly in patients taking monoamine oxidase (MAO)–inhibiting drugs. Orally administered tyramine in doses of 200 to 800 mg has been shown to increase systolic blood pressure by 30 mm Hg in otherwise unmedicated subjects. Conversely, in patients taking MAO-inhibiting drugs, the pressor sensitivity was 7- to 56-fold that in patients not taking MAO-inhibiting drugs (79). Eight DBPC studies have investigated the effect of tyramine on migraine. Two studies showed positive results in migraine patients who were sensitive to foods that are high in tyramine ($n = 45$) (19) or who had wine-provoked migraine ($n = 19$) (80); 6 studies showed negative results with 97 (81), 80 (82), 25 (83), and 65 (84) patients. The 2 positive studies and 2 of the negative studies were regarded as inconclusive (19) because of a lack of randomization (79), questionable blinding (80), or inappropriate selection of migraine patients without a history of suspected tyramine intolerance (81, 82). Conversely, in 2 conclusive studies of migraine patients with a positive or negative dietary history, 125 mg oral tyramine did not precipitate more headaches than did placebo.

In addition to histamine-rich food, many foods such as citrus foods are considered to have the capacity to release histamine directly from tissue mast cells, even if they themselves contain only small amounts of histamine (**Table 4**). In vitro studies of persons with a history of pseudoallergic reactions to food have shown a fragility of duodenal mast cells with massive degranulation in the presence of histamine-releasing substances that is significantly greater than that shown by control subjects (85). However, clinical studies using oral challenge tests to support the

TABLE 4
Foods with suggested histamine-releasing capacities[1]

Plant-derived	Animal-derived	Other
Citrus fruit	Fish	Additives
Papaya	Crustaceans	Liquorice
Strawberries	Pork	Spices
Pineapple	Egg white	
Nuts		
Peanuts		
Tomatoes		
Spinach		
Chocolate		

[1] Data were taken from reference 21.

hypothesis for the histamine-releasing capacity of foods are required (22).

Alcohol, especially red wine, is rich in histamine and is a potent inhibitor of DAO (9, 86). The relation between the ingestion of wine, an increase in plasma histamine, and the occurrence of sneezing, flushing, headache, asthma attacks, and other anaphylactoid reactions and a reduction of symptoms by antihistamines has been shown in various studies (7, 8, 14, 65, 87, 88). However, among the multitude of substances contained in wine, other biogenic amines such as tyramine (80) and sulfites (89) have been supposed to contribute to symptoms summarized as "wine intolerance" or "red wine asthma" (19, 89, 90). In DBPC wine tests with healthy persons (91) and in patients with chronic urticaria and wine intolerance (92), the histamine content did not influence wine tolerance. In the latter group, an increase in plasma histamine could be shown, paradoxically, after ingestion of the histamine-poor wine. In these patients, the ethanol metabolite acetaldehyde has been discussed as a histamine-releasing substance (92). However, the high percentage of responses to the placebo (87%) could be responsible for the absence of an effect in this study (19). Another randomized DBPC oral wine challenge in patients with a history of red wine–provoked asthma ($n = 18$) found no relation between wine tolerance and the wine's content of histamine or other amines but did find a greater bronchoconstrictive response to wine with a high sulfite content (89). Sulfiting agents are widely used as antioxidants and preservatives in foods, beverages, and pharmaceuticals. Adverse reactions with a presumed relation to sulfites include anaphylactic shock, bronchospasm, urticaria, angioedema, nausea, abdominal pain, diarrhea, stroke, and death (93). Sulfite hypersensitivity has been reported mainly in patients with chronic asthma; the estimated prevalence is 5–10% in all patients (94). Asthmatic reactions have been attributed to reflex activation of the parasympathetic system by the irritating effect of sulfites, possibly enhanced by a deficiency of sulfite oxidase. Besides this pseudoallergic mechanism, in at least some cases of sulfite hypersensitity, an immunoglobulin E (IgE)–mediated immediate-type allergic reaction must be considered (95). Sulfites may be contained in wine, but they are also contained in foods that are poor in histamine, such as fruit juice, frozen vegetables, and lettuce. Thus, in patients reporting intolerance to wine, a careful history of reactions to other foods rich in histamine or sulfites should be taken. In patients who are suspected of having sulfite intolerance, skin testing and a DBPC challenge with capsules containing increasing doses of bisulfite or placebo should be performed.

In contrast to an IgE–mediated food allergy, in which the ingestion of even a small amount of the allergen elicits symptoms, in histamine intolerance, the cumulative amount of histamine is crucial. Besides variations in the amount of histamine in food according to storage and maturation, the quantity consumed, the presence of other biogenic amines, and the additional intake of alcohol or DAO-blocking drugs are pivotal factors in the tolerance of the ingested food. Generally, an upper limit of 100 mg histamine/kg in foods and of 2 mg histamine/L in alcoholic beverages has been suggested (96). This threshold may be too high, considering the occurrence of histamine-mediated symptoms after oral ingestion of 75 mg histamine in 5 of 10 females without a history of histamine intolerance (15).

However, most of the positive studies for intolerant reactions to sulfite, histamine, and other biogenic amines do not fulfill the current scientific criteria for providing substantiated evidence of the clinical effect of these foods. Nevertheless, patients who have a conclusive history of adverse reactions to food, alcohol, drugs containing histamine, other biogenic amines, and sulfite but without proof of IgE exist. In such patients, a DBPC provocation of the suspected causal agents under close supervision by experienced specialists should be performed after exclusion of other causal diseases and informed consent of the patients—if the provocation is not unreasonably hazardous, considering the grade of the anaphylactoid reaction. Because of the great effort, time, and costs or because of patients' fear of a repeated reaction, DBPC provocations often are not performed in clinical practice, even when they are indicated.

Histamine and drugs

The effect of drugs as specific DAO inhibitors and their capacity to induce histamine intolerance have been shown in various studies with human placental DAO and in animal experiments (10, 40, 97, 98). A clinically relevant activity via histamine release or inhibition of DAO has been observed for various drugs (10, 40, 97, 98) (**Table 5**). Therefore, the intake of drugs, especially long-term medication, should be considered in interpretation of histamine intolerance symptoms and DAO concentrations.

Other associated diseases

Reduced DAO activity—or, rather, reduced DAO release—after the application of heparin could be shown to be a marker of tissue damage in patients with chronic renal failure (99, 100), viral hepatitis (101), or gut failure and of endotoxemia in patients with liver cirrhosis (102). Reduced DAO activity has also been shown in patients with chronic urticaria as a typical histamine-mediated disease (60) combined with a reduced tolerance for infused histamine (16) and an improvement of urticaria by maintaining a histamine-free diet (103).

Histamine and atopic eczema

Higher basal plasma histamine concentrations (104, 105) and increased spontaneous histamine release toward different stimuli (106–108) and after food challenges (109) have been shown in patients with severe atopic eczema (AE) than in control subjects. In addition, reduced DAO activities have been shown in a subgroup of AE patients (104, 110, 111). Thus, these patients have a significantly greater occurrence of chronic headache, dysmenorrhea, flushing, gastrointestinal symptoms, and intolerance to

TABLE 5
Drugs releasing histamine or inhibiting diamine oxidase

Substance class	Agent interfering with the histamine metabolism
Contrast media	
Muscle relaxants	Pancuronium, alcuronium, D-tubocurarine
Narcotics	Thiopental
Analgetics	Morphine, pethidine, nonsteroidal antiinflammatory drugs, acetylsalicylic acid, metamizole
Local anesthetics	Prilocaine
Antihypotonics	Dobutamine
Antihypertensive drugs	Verapamil, alprenolol, dihydralazine
Antiarrhythmics	Propafenone
Diuretics	Amiloride
Drugs influencing gut motility	Metoclopramide
Antibiotics	Cefuroxime, cefotiam, isoniazid, pentamidin, clavulanic acid, choroquine
Mucolytics	Acetylcysteine, ambroxol
Broncholytics	Aminophylline
H2-receptor antagonists	Cimetidine
Cytostatics	Cyclophosphamide
Antidepressants	Amitriptyline

alcohol and food than do control subjects. Reduction of both the symptoms of histamine intolerance and the severity score of atopic dermatitis (SCORAD) has been shown in a subgroup of patients with AE and low DAO serum activity who were following a histamine-free diet for 2 wk (111). Orally ingested histamine has been shown to aggravate eczema in AE patients in a DBPC provocation (112). A feedback inhibition of DAO through its degradation product imidazole acetic acid (113, 114) or substrate inhibition (115, 116) caused by the elevated histamine concentrations in AE may be a pathomechanism of a reduced histamine degradation capacity in a subgroup of patients with AE.

Histamine and sexual steroids

In the female genital tract, histamine is mainly produced by mast cells, endothelial cells, and epithelial cells in the uterus and ovaries. Histamine-intolerant women often suffer from headache that is dependent on their menstrual cycle and from dysmenorrhea. Besides the conctractile action of histamine, these symptoms may be explained by the interplay of histamine and hormones. Histamine has been shown to stimulate, in a dose-dependent manner, the synthesis of estradiol via H1R; meanwhile, only a moderate effect on progesterone synthesis was observed (117). The painful uterine contractions of primary dysmenorrhea are mainly caused by an increased mucosal production of prostaglandine F2α stimulated by estradiol and attenuated by progesterone. Thus, histamine may augment dysmenorrhea by increasing estrogen concentrations. And, in reverse, estrogen can influence histamine action. A significant increase in weal and flare size in response to histamine has been observed to correspond to ovulation and peak estrogen concentrations (118). In pregnancy, DAO is produced at very high concentrations by the placenta (119, 120), and its concentration may become 500 times that when the woman is not pregnant (120). This increased DAO production in pregnant women may be the reason why, in women with food intolerance, remissions frequently occur during pregnancy (14).

PRACTICAL CONSEQUENCES

Because of the multifaceted symptoms in multiple organs, a detailed history of the basal histamine-mediated symptoms, any triggering of symptoms after the intake of histamine-rich food or drugs interfering with the histamine metabolism, and concomitant gastrointestinal diseases or allergies is indispensable for diagnosis of histamine intolerance (**Figure 3**). Clinically, histamine-induced symptoms cannot always be assigned to the underlying pathomechanism. A massive intake of histamine from decomposed fish may result in the same symptoms as are seen in a person with an IgE-mediated fish allergy. Histamine actions may be possible causes of endogenous cell activation, increased exogenous uptake, decreased histamine degradation, or a combination of these mechanisms. An occult systemic mastocytosis should be excluded by measurement of the serum tryptase. Diagnosis of histamine intolerance is set by presentation of $\geq$2 typical symptoms of histamine intolerance (122) and improvement by histamine-free diet and antihistamines. The diagnosis of allergy using using the skin-prick test for food allergens or determination of specific IgE should be carried out to exclude food allergy. The diagnosis of allergy usually proves to be negative because histamine intolerance is a pseudoallergy. Keeping of a diet diary has proven useful in tracking significant improvement of symptoms with a histamine-free diet and relapses in histamine intolerance after dietary errors.

In a patient with clinical suspicion of histamine intolerance (ie, $\geq$2 typical symptoms), improvement of symptoms by histamine-free diet or antihistamines, DAO may be determined in serum (123) or tissue biopsy (32). Several radioextraction assays (REA) have been developed for the determination of the enzymatic activity of DAO by using [3H]- or [^{14}C]-labeled putrescinedihydrochloride as a substrate (124, 125). Determination of the HNMT activity is based on transmethylation of histamine by *S*-adenosyl-L [methyl-^{14}C] methionine (126). Furthermore, the total histamine degradation capacity can be measured (69). Plasma activity of DAO, which generally is relatively low, may be increased by the liberation of tissue-bound DAO through an injection of heparin (127–132), which was the main method used before the development of more sensitive assays. Serum DAO concentrations showed no significant daily variations and no significant sex differences (97). In patients with a DAO activity Histamine intolerance is presumably highly likely in patients with DAO activity $<$3 U/mL, likely (but less likely) in patients with DAO activity $<$10 U/mL, and improbable in patients with DAO activity $\geq$10 U/mL (18, 131).

Conversely, in some patients with a clear clinical picture of histamine intolerance, normal DAO activities have been observed, so that an additional determination of histamine concentrations and interpretation of laboratory data in view of the clinic seem advisable. Histamine can be measured in plasma or in urine, as can its degradation product *N*-methylhistamine (53, 132). Deficiency of the DAO cofactors vitamin B-6, copper, and vitamin C, which are thought to supplement histamine degradation (133), has been discussed as being controversial (14). Elevated histamine concentrations, reduced DAO activities, or both are classically found in histamine intolerance. A DBPC histamine provocation after a 4-wk histamine-free diet is considered the gold

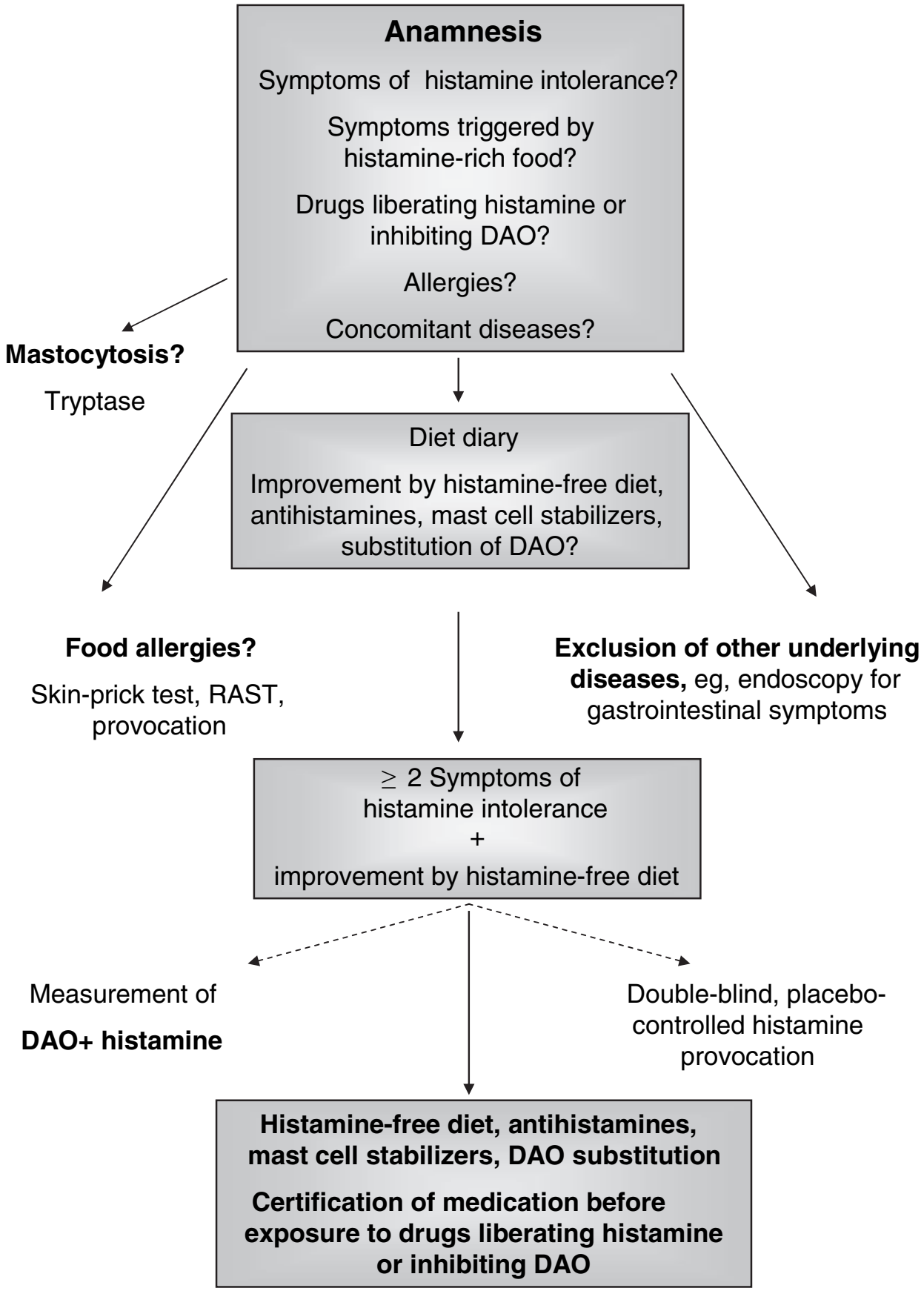

FIGURE 3. Diagnostic pathway for histamine intolerance. Adapted with permission from Maintz L et al. Dtsch Artzebl 2006;103:A3477-83.

standard in diagnosis. Because the amount of histamine in natural food varies pronouncedly according to storage and maturation, the provocation can be performed with alternate administration of capsules containing increasing doses of histamine-dihydrochloride (0.75 and 1.5 mg/kg body wt, respectively) and placebo capsules (112). Blood pressure and heart rate should be continuously controlled, and positive reactions (eg, hypotonia, tachycardia, urticaria, or other symptoms of an anaphylactoid reaction) should be immediately treated by a physician. Afterward, symptoms should be evaluated by using a standardized symptom-scoring system.

Therapy is based on the consequent conduction of a histamine-free diet. Alcohol and long-ripened or fermented (and therefore histamine-rich) food, such as aged cheese, cured meat, and yeast products; histamine-rich food, such as spinach or tomatoes; or histamine liberators, such as citrus fruit, should be avoided (65, 134); the histamine-free diet can be complemented with adjuvant administration of H1 and H2 antagonists. Most antihistamines have no influence on DAO activity, although inhibition of DAO by cimetidine and dihydralazine and increased activity by diphenhydramine have been observed (97). In patients consuming a strictly histamine-free diet, no additional benefit due to an intake of antihistamines could be observed (57). An increase in DAO activity with the histamine-free diet was shown in migraine patients (57). In addition, histamine degradation can be supported by the administration of vitamin C (133) and vitamin B-6, which leads to an increase in DAO activity (14, 135). Positive effects have been reported for mast cell stabilizers and pancreatic enzymes (136), especially with respect to gastrointestinal symptoms. Because of the frequent intolerant reactions toward drugs that interfere with the histamine metabolism, their intake should be avoided. Recently, capsules containing DAO isolated from pig kidneys have been generated to supplement the lack of endogenous human DAO in patients with histamine intolerance. These capsules contain only stabilizers—ie, cellulose, sucrose, solanum tuberosum, polyacrylic acid, cellulose gum, triethyl citrate, and potato starch. Patients who are suspected of having histamine intolerance should be given a certificate noting that condition and stating that the administration of contrast and other drugs that release histamine should be avoided. If the administration of theses drugs is unavoidable (137), prior medication with antihistamines is recommended.

CONCLUSIONS

In patients with typical symptoms of histamine intolerance that are triggered by histamine-rich food and alcohol, with intolerance of drugs that liberate histamine or block DAO, and with a negative diagnosis of allergy or internal disorders, histamine intolerance should be considered. A histamine-free diet, if necessary, supported by antihistamines or the substitution of DAO, leads to an improvement of symptoms. However, further studies investigating histamine intolerance due to DBPC provocations are indispensable.

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