

Histamine and histamine intolerance^{1–3}

Laura Maintz and Natalija Novak

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, asthmatic 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 enterochromaffin 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, superoxide (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 H4R] on target cells in various tissues (**Figure 1**, **Table 1**). It causes smooth

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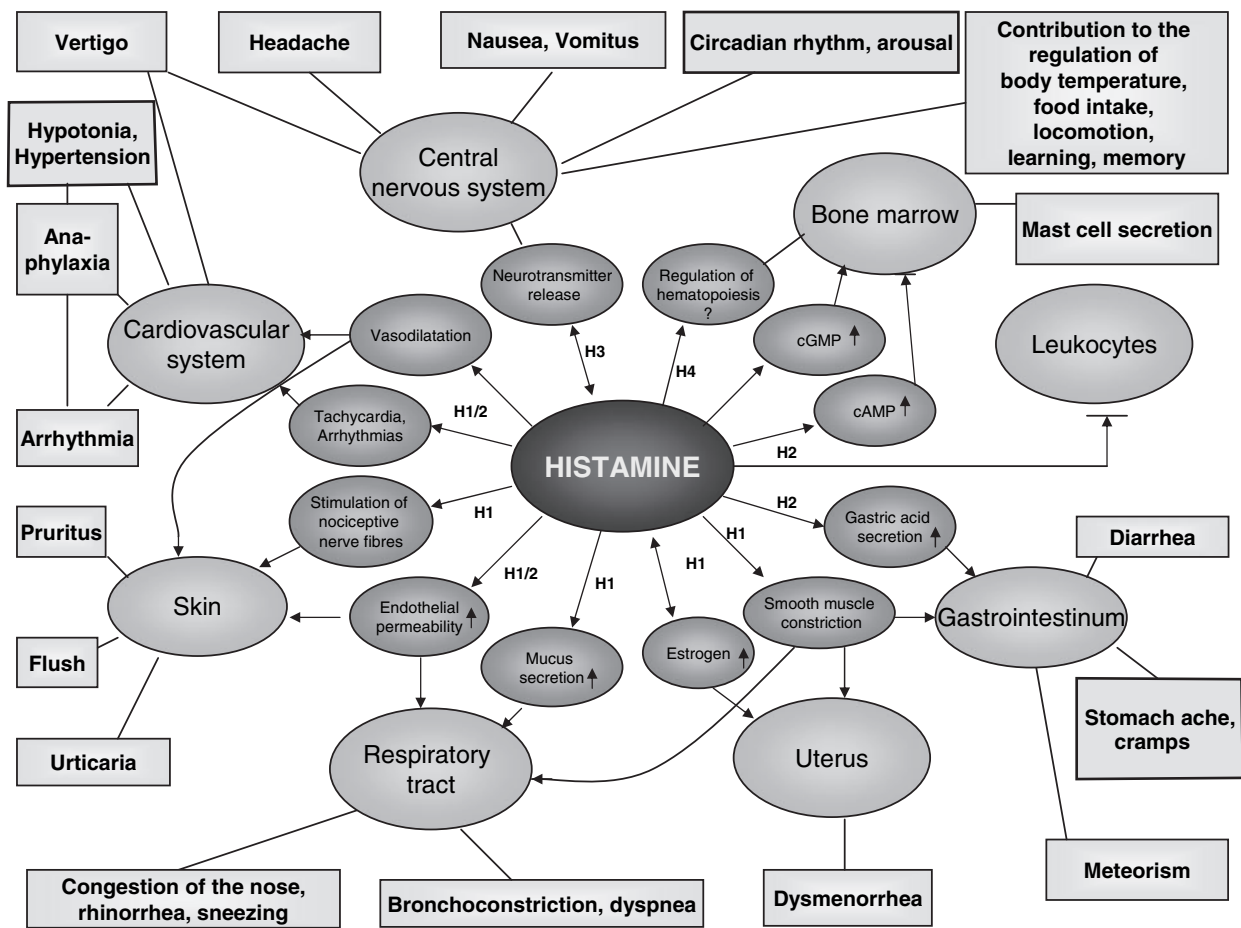


FIGURE 1. Summary of histamine-mediated symptoms. Adapted with permission from Maintz L et al. Dtsch Arztebl 2006;103:A3477-83.

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 $\mu\text{mol/L}$] than does DAO (k_M : 20 $\mu\text{mol/L}$). 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

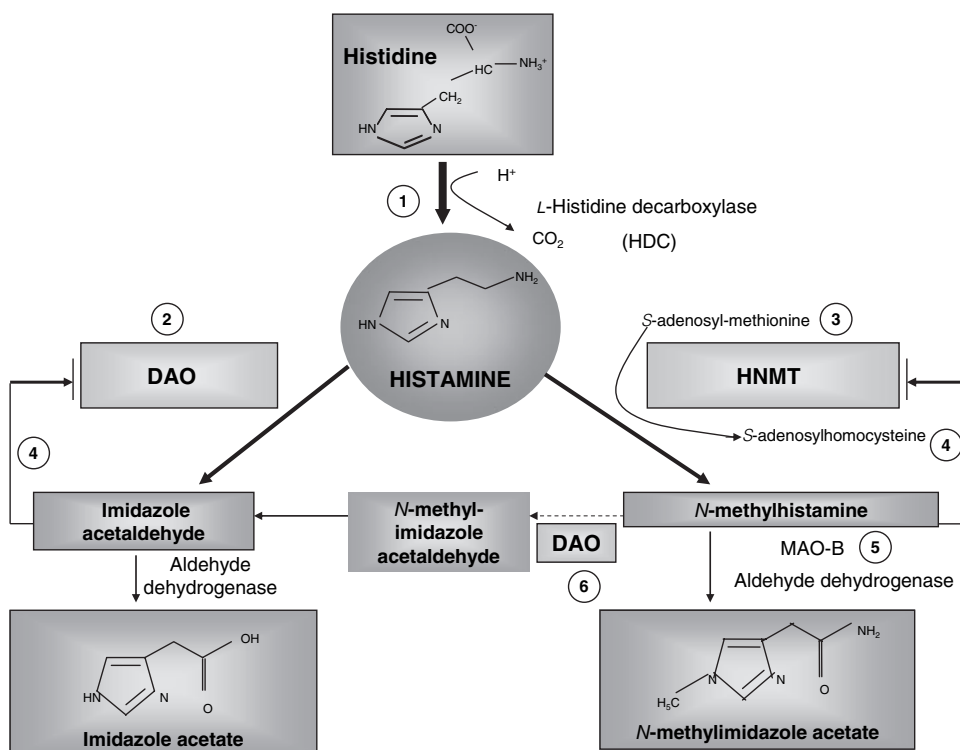


FIGURE 2. Summary of the histamine metabolism. The biogenic amine histamine is synthesized by decarboxylation of the amino acid histidine catalyzed by L-histidine decarboxylase (HDC) (1). Histamine can be metabolized by extracellular oxidative deamination of the primary amino group by diamine oxidase (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 feedback loop (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, bacteria, 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 2Characteristics 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 (<i>k_m</i>) | Histamine, 20 μmol/L Putrescine, 350 μmol/L Spermidine, 3 mmol/L | Histamine, 6–13 μmol/L <i>S</i> -adenosyl-L-methionine, 6–10 μmmol/L |
| Optimum pH | 7.2 | 7.5–9.0 |
| Inhibitors | Copper-chelating agents, eg cyanide Carbonylgroup reagents, eg, aminoguanidine, semibarbicide | Reaction products: <i>N</i> -methylhistamine, <i>S</i> -adenosyl-L-homocysteine Sulphydryl groups: p-chloromercuribenzoate |
| 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 gastrointestinal tract, 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 gastrointestinal

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 neoplasms (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, rhinorrhea 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 3Foods rich in histamine¹

| 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 | | | 10 | | 2–951 | |
| Sauerkraut | 0–229 | | | | | |
| 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 4Foods with suggested histamine-releasing capacities¹

| 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 hypersensitivity, 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 |
| Antihypototics | Dobutamine |
| Antihypertensive drugs | Verapamil, alprenolol, dihydralazine |
| Antiarrhythmics | Propafenone |
| Diuretics | Amiloride |
| Drugs influencing gut motility | Metoclopramide |
| Antibiotics | Cefuroxime, cefotiam, isoniazid, pentamidine, clavulanic acid, choroquine |
| Mucolytics | Acetylcysteine, ambroxol |
| Broncholytics | Aminophylline |
| H ₂ -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 contractile 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 F_{2α} 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 ≥ 2 typical symptoms of histamine intolerance (122) and improvement by histamine-free diet and antihistamines. The diagnosis of allergy 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, ≥ 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 [¹⁴C]-labeled putrescinedihydrochloride as a substrate (124, 125). Determination of the HNMT activity is based on transmethylation of histamine by S-adenosyl-L [methyl-¹⁴C] 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 ≥ 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

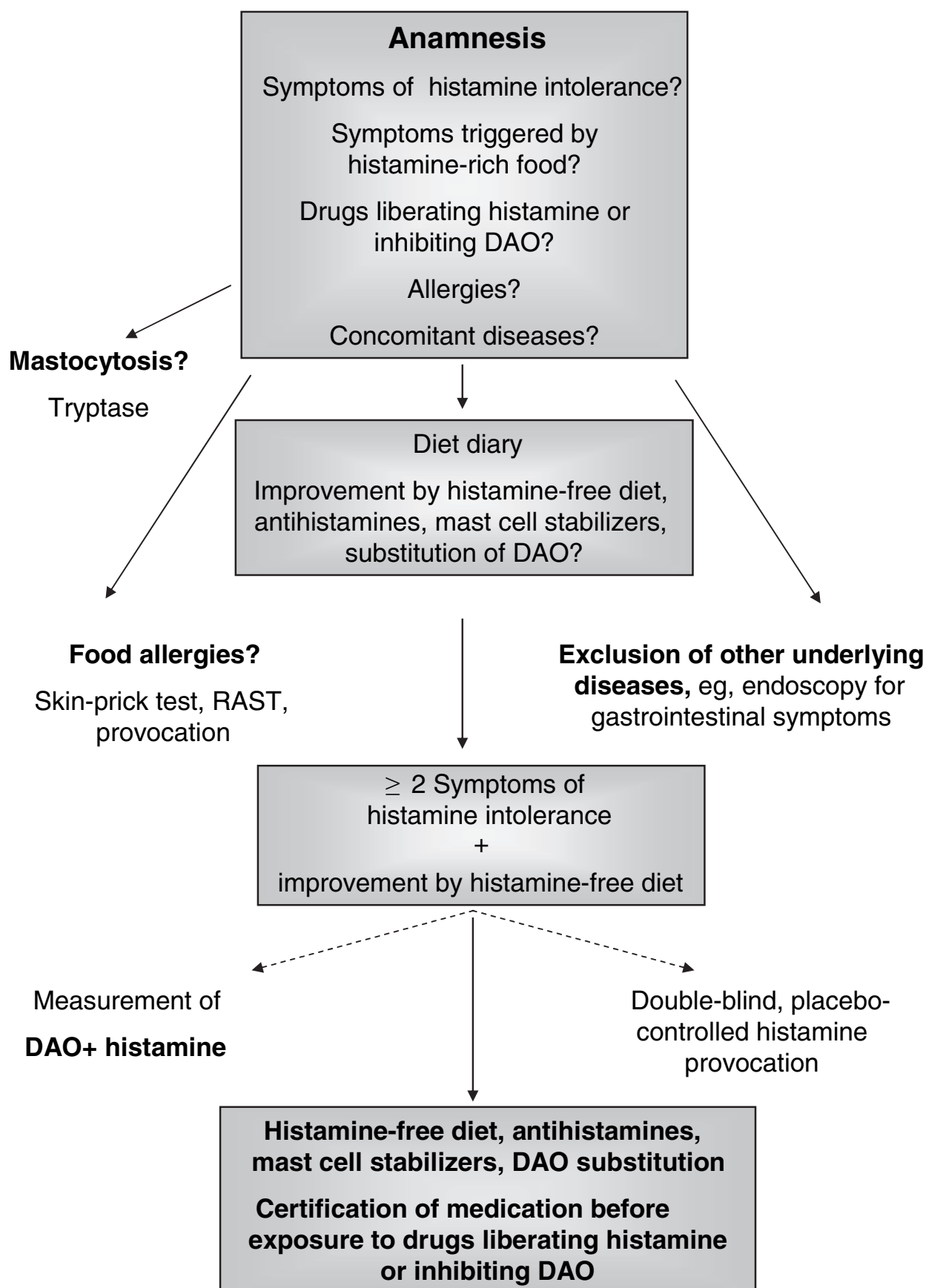



FIGURE 3. Diagnostic pathway for histamine intolerance. Adapted with permission from Maintz L et al. Dtsch Arztebl 2006;103:A3477-83.

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 these 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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REFERENCES

- Silla Santos MH. Biogenic amines: their importance in foods. *Int J Food Microbiol* 1996;29:213–31.
- Bieganski T, Kusche J, Feussner KD, Hesterberg R, Richter H, Lorenz W. Human intestinal diamine oxidase: substrate specificity and comparative inhibitor study. *Agents Actions* 1980;10:108–10.
- Bieganski T, Kusche J, Feussner KD, Hesterberg R, Richter H, Lorenz W. The importance of human intestinal diamine oxidase in the oxidation of histamine and/or putrescine. *Arch Immunol Ther Exp (Warsz)* 1980;28:901–6.
- Bieganski T, Kusche J, Lorenz W, Hesterberg R, Stahlknecht CD, Feussner KD. Distribution and properties of human intestinal diamine oxidase and its relevance for the histamine catabolism. *Biochim Biophys Acta* 1983;756:196–203.
- Bieganski T. Biochemical, physiological and pathophysiological aspects of intestinal diamine oxidase. *Acta Physiol Pol* 1983;34:139–54.
- Sattler J, Hafner D, Klotter HJ, Lorenz W, Wagner PK. Food-induced histaminosis as an epidemiological problem: plasma histamine elevation and haemodynamic alterations after oral histamine administration and blockade of diamine oxidase (DAO). *Agents Actions* 1988;23:361–5.
- Wantke F, Gotz M, Jarisch R. The red wine provocation test: intolerance to histamine as a model for food intolerance. *Allergy Proc* 1994;15:27–32.
- Wantke F, Hemmer W, Haglmüller T, Gotz M, Jarisch R. Histamine in wine. Bronchoconstriction after a double-blind placebo-controlled red wine provocation test. *Int Arch Allergy Immunol* 1996;110:397–400.
- Zimatkin SM, Anichtchik OV. Alcohol-histamine interactions. *Alcohol Alcohol* 1999;34:141–7.
- Sattler J, Lorenz W. Intestinal diamine oxidases and enterol-induced histaminosis: studies on three prognostic variables in an epidemiological model. *J Neural Transm Suppl* 1990;32:291–314.
- Wantke F, Hemmer W, Focke M, Stackl W, Gotz M, Jarisch R. Are adverse effects of sildenafil also caused by inhibition of diamine oxidase? *Urol Int* 2001;67:59–61.
- Sattler J, Hesterberg R, Schmidt U, Crombach M, Lorenz W. Inhibition of intestinal diamine oxidase by detergents: a problem for drug formulations with water insoluble agents applied by the intravenous route? *Agents Actions* 1987;20:270–3.
- Jarisch R, ed. Histamin-Intoleranz. Histamin und Seekrankheit. (Histamine intolerance. Histamine and motion sickness.) Stuttgart, Germany: Georg Thieme Verlag KG, 2004 (in German).
- Jarisch R, Wantke F. Wine and headache. *Int Arch Allergy Immunol* 1996;110:7–12.
- Wohrl S, Hemmer W, Focke M, Rappersberger K, Jarisch R. Histamine intolerance-like symptoms in healthy volunteers after oral provocation with liquid histamine. *Allergy Asthma Proc* 2004;25:305–11.
- Pollock I, Murdoch RD, Lessof MH. Plasma histamine and clinical tolerance to infused histamine in normal, atopic and urticarial subjects. *Agents Actions* 1991;32:359–65.
- Schmidt WU, Sattler J, Hesterberg R, et al. Human intestinal diamine oxidase (DAO) activity in Crohn's disease: a new marker for disease assessment? *Agents Actions* 1990;30:267–70.
- Missbichler A. Diagnostischer Nachweis der Aktivität von Diaminoxidase in Serum oder Plasma. (Diagnostic proof of the DAO activity in serum and plasma.) In: Jarisch R, ed. Histamin-Intoleranz. Histamin und Seekrankheit. (Histamine intolerance. Histamine and motion sickness.) Stuttgart, Germany: Georg Thieme Verlag KG, 2004:8–17 (in German).
- Jansen SC, van DM, Bottema KC, Dubois AE. Intolerance to dietary biogenic amines: a review. *Ann Allergy Asthma Immunol* 2003;91:233–40.
- Dale HD, Laidlaw PD. The physiological action of β -iminazolyethylamine. *J Physiol (Lond)* 1910;41:318–44.
- Steinhoff M, Griffiths C, Church M, Luger TA. Histamine. In: Burns T, Breathnach S, Cox N, Griffiths C, eds. *Rook's textbook of dermatology*. Oxford, United Kingdom: Blackwell Science, 2004:9.50–2.
- Vlieg-Boerstra BJ, van der HS, Oude Elberink JN, Kluin-Nelemans JC, Dubois AE. Mastocytosis and adverse reactions to biogenic amines and histamine-releasing foods: what is the evidence? *Neth J Med* 2005;63:244–9.
- Ring J. *Angewandte Allergologie*. (Implemented allergology.) Munich, Germany: Urban & Vogel, 2004 (in German).
- Raithel M, Ulrich P, Hochberger J, Hahn EG. Measurement of gut diamine oxidase activity. Diamine oxidase as a new biologic marker of colorectal proliferation? *Ann N Y Acad Sci* 1998;859:262–6.
- Kusche J, Bieganski T, Hesterberg R, et al. The influence of carcinoma

- growth on diamine oxidase activity in human gastrointestinal tract. *Agents Actions* 1980;10:110–3.
26. Kalchmair B, Klocker J, Perkmann R, et al. Alterations in plasma amine oxidase activities in a compartment syndrome model. *Inflamm Res* 2003;52(suppl):S67–8.
 27. Schwelberger HG. Diamine oxidase (DAO) enzyme and gene. In: Falus A, ed. *Histamine: biology and medical aspects*. Budapest, Hungary: SpringMed Publishing, 2004:43–52.
 28. Schwelberger HG, Hittmair A, Kohlwein SD. Analysis of tissue and subcellular localization of mammalian diamine oxidase by confocal laser scanning fluorescence microscopy. *Inflamm Res* 1998;47(suppl):S60–1.
 29. Schwelberger HG, Bodner E. Purification and characterization of diamine oxidase from porcine kidney and intestine. *Biochim Biophys Acta* 1997;1340:152–64.
 30. Brown DD, Tomchick R, Axelrod J. The distribution and properties of a histamine-methylating enzyme. *J Biol Chem* 1959;234:2948–50.
 31. Klocker J, Matzler SA, Huetz GN, Drasche A, Kolbitsch C, Schwelberger HG. Expression of histamine degrading enzymes in porcine tissues. *Inflamm Res* 2005;54(suppl):S54–7.
 32. Kufner MA, Ulrich P, Raithel M, Schwelberger HG. Determination of histamine degradation capacity in extremely small human colon samples. *Inflamm Res* 2001;50(suppl):S96–7.
 33. Raithel M, Kufner M, Ulrich P, Hahn EG. The involvement of the histamine degradation pathway by diamine oxidase in manifest gastrointestinal allergies. *Inflamm Res* 1999;48(suppl):S75–6.
 34. Backhaus B, Raithel M, Hahn EG. Nicht-immunologisch induzierte Histaminfreisetzung an vitalen menschlichen Darmschleimhautbiopsien durch Stimulation mit Polyaminen. (Nonimmunologically induced histamine release of biopsies of vital human intestinal mucosa after stimulation with polyamines.) *Allergo J* 2005;14:41 (abstr) (in German).
 35. Tsujikawa T, Uda K, Ihara T, Andoh A, Fujiyama Y, Bamba T. Changes in serum diamine oxidase activity during chemotherapy in patients with hematological malignancies. *Cancer Lett* 1999;147:195–8.
 36. Schwelberger HG. Histamine *N*-methyltransferase (HNMT) enzyme and gene. In: Falus A, ed. *Histamine: biology and medical aspects*. Budapest, Hungary: SpringMed Publishing, 2004:53–9.
 37. Yamauchi K, Sekizawa K, Suzuki H, et al. Structure and function of human histamine *N*-methyltransferase: critical enzyme in histamine metabolism in airway. *Am J Physiol* 1994;267:L342–9.
 38. Raithel M. Durchfälle und weicher Stuhl. In: Jarisch R, ed. *Histamin-Intoleranz. Histamin und Seekrankheit. (Histamine intolerance. Histamine and motion sickness.)* Stuttgart, Germany: Georg Thieme Verlag KG, 2004:77–110 (in German).
 39. Raithel M, Matek M, Baenkler HW, Jorde W, Hahn EG. Mucosal histamine content and histamine secretion in Crohn's disease, ulcerative colitis and allergic enteropathy. *Int Arch Allergy Immunol* 1995;108:127–33.
 40. Sattler J, Hesterberg R, Lorenz W, Schmidt U, Crombach M, Stahlknecht CD. Inhibition of human and canine diamine oxidase by drugs used in an intensive care unit: relevance for clinical side effects? *Agents Actions* 1985;16:91–4.
 41. Ahrens F, Gabel G, Garz B, Aschenbach JR. Release and permeation of histamine are affected by diamine oxidase in the pig large intestine. *Inflamm Res* 2002;51(suppl):S83–4.
 42. Aschenbach JR, Oswald R, Gäbel G. Gastrointestinal epithelia as barriers to luminal histamine of microbial origin. *Z Gastroenterol* 1998;36:12–7.
 43. Sattler J, Lorenz W, Kubo K, Schmal A, Sauer S, Luben L. Food-induced histaminosis under diamine oxidase (DAO) blockade in pigs: further evidence of the key role of elevated plasma histamine levels as demonstrated by successful prophylaxis with antihistamines. *Agents Actions* 1989;27:212–4.
 44. Petersen J, Raithel M, Schwelberger HG. Characterisation of functional polymorphisms of the human diamine oxidase gene. *Inflamm Res* 2005;54(suppl):S58–9.
 45. Petersen J, Drasche A, Raithel M, Schwelberger HG. Analysis of genetic polymorphisms of enzymes involved in histamine metabolism. *Inflamm Res* 2003;52(suppl):S69–70.
 46. Schwelberger HG, Drasche A, Petersen J, Raithel M. Genetic polymorphisms of histamine degrading enzymes: from small-scale screening to high-throughput routine testing. *Inflamm Res* 2003;52(suppl):S71–3.
 47. Petersen J, Raithel M, Schwelberger HG. Histamine *N*-methyltransferase and diamine oxidase gene polymorphisms in patients with inflammatory and neoplastic intestinal diseases. *Inflamm Res* 2002;51(suppl):S91–2.
 48. Yan L, Galinsky RE, Bernstein JA, Liggett SB, Weinshilboum RM. Histamine *N*-methyltransferase pharmacogenetics: association of a common functional polymorphism with asthma. *Pharmacogenetics* 2000;10:261–6.
 49. Sasaki Y, Ihara K, Ahmed S, et al. Lack of association between atopic asthma and polymorphisms of the histamine H1 receptor, histamine H2 receptor, and histamine *N*-methyltransferase genes. *Immunogenetics* 2005;51:238–40.
 50. Deindl P, Peri-Jerkan S, Deichmann K, et al. No association of histamine-*N*-methyltransferase polymorphism with asthma or bronchial hyperresponsiveness in two German pediatric populations. *Pediatr Allergy Immunol* 2005;16:40–2.
 51. Sharma S, Mann D, Singh TP, Ghosh B. Lack of association of histamine-*N*-methyltransferase (HNMT) polymorphisms with asthma in the Indian population. *J Hum Genet* 2005;50:611–7.
 52. Dyer J, Warren K, Merlin S, Metcalfe DD, Kaliner M. Measurement of plasma histamine: description of an improved method and normal values. *J Allergy Clin Immunol* 1982;70:82–7.
 53. Kaliner M, Shelhamer JH, Ottesen EA. Effects of infused histamine: correlation of plasma histamine levels and symptoms. *J Allergy Clin Immunol* 1982;69:283–9.
 54. Ind PW, Brown MJ, Lhoste FJ, Macquin I, Dollery CT. Concentration effect relationships of infused histamine in normal volunteers. *Agents Actions* 1982;12:12–6.
 55. Morrow JD, Margolies GR, Rowland J, Roberts LJ. Evidence that histamine is the causative toxin of scombroid-fish poisoning. *N Engl J Med* 1991;324:716–20.
 56. Hershko AY, Dranitzki Z, Ulmanski R, Levi-Schaffer F, Naparstek Y. Constitutive hyperhistaminaemia: a possible mechanism for recurrent anaphylaxis. *Scand J Clin Lab Invest* 2001;61:449–52.
 57. Steinbrecher I, Jarisch R. Histamin und Kopfschmerz. (Histamine and headache.) *Allergologie* 2005;28:84–91 (in German).
 58. Curtis MJ, Pugsley MK, Walker MJ. Endogenous chemical mediators of ventricular arrhythmias in ischaemic heart disease. *Cardiovasc Res* 1993;27:703–19.
 59. Endou M, Levi R. Histamine in the heart. *Eur J Clin Invest* 1995;25(suppl):5–11.
 60. Lessof MH, Gant V, Hinuma K, Murphy GM, Dowling RH. Recurrent urticaria and reduced diamine oxidase activity. *Clin Exp Allergy* 1990;20:373–6.
 61. Lassen LH, Heinig JH, Oestergaard S, Olesen J. Histamine inhalation is a specific but insensitive laboratory test for migraine. *Cephalalgia* 1996;16:550–3.
 62. Thomsen LL, Olesen J. Nitric oxide in primary headaches. *Curr Opin Neurol* 2001;14:315–21.
 63. Thomsen LL. Investigations into the role of nitric oxide and the large intracranial arteries in migraine headache. *Cephalalgia* 1997;17:873–95.
 64. Huszti Z. Histamine in CNS-resident non-neuronal cells. In: Falus A, Grosman N, Darvas Z, eds. *Histamine: biology and medical aspects*. Budapest, Hungary: SpringMed Publishing, 2004:272–80.
 65. Wantke F, Gotz M, Jarisch R. Histamine-free diet: treatment of choice for histamine-induced food intolerance and supporting treatment for chronic headaches. *Clin Exp Allergy* 1993;23:982–5.
 66. Krabbe AA, Olesen J. Headache provocation by continuous intravenous infusion of histamine. Clinical results and receptor mechanisms. *Pain* 1980;8:253–9.
 67. Mennigen R, Kusche J, Streffer C, Krakamp B. Diamine oxidase activities in the large bowel mucosa of ulcerative colitis patients. *Agents Actions* 1990;30:264–6.
 68. Raithel M, Ulrich P, Keymling J, Hahn EG. Analysis and topographical distribution of gut diamine oxidase activity in patients with food allergy. *Ann N Y Acad Sci* 1998;859:258–61.
 69. Kufner MA, Schwelberger HG, Ulrich P, Hahn EG, Raithel M. Total histamine degradation capacity (THDC) as an important biological

- marker of histamine metabolism in human colonic mucosa. *Inflamm Res* 2002;51(suppl):S87–8.
70. Kuefner MA, Schwelberger HG, Weidenhiller M, Hahn EG, Raithe M. Both catabolic pathways of histamine via histamine-*N*-methyltransferase and diamine oxidase are diminished in the colonic mucosa of patients with food allergy. *Inflamm Res* 2004;53(suppl):S31–2.
 71. Preuss CV, Wood TC, Szumlanski CL, et al. Human histamine *N*-methyltransferase pharmacogenetics: common genetic polymorphisms that alter activity. *Mol Pharmacol* 1998;53:708–17.
 72. Bodmer S, Imark C, Kneubuhl M. Biogenic amines in foods: histamine and food processing. *Inflamm Res* 1999;48:296–300.
 73. Sarkadi L. Histamine in food. In: Falus A, Grosman N, Darvas Z, eds. *Histamine: biology and medical aspects*. Budapest, Hungary: Springer-Med Publishing, 2004:176–85.
 74. Bover-Cid S, Holzapfel W. Biogenic amine production by bacteria. In: Morgan D, White A, Sánchez-Jiménez F, Bardóc S, eds. *Biogenically active amines in food*. Luxembourg City, Luxembourg: EC Publication, 2000:20–9.
 75. Beutling DM. Biogene Amine in der Ernährung. (Biogenic amines in nutrition.) Berlin, Germany: Springer, 1996 (in German).
 76. Pechanek U, Pfannhauser W, Woidich H. [Content of biogenic amines in four food groups of the Austrian marketplace]. *Z Lebensm Unters Forsch* 1983;176:335–40 (in German).
 77. Halász A, Baráth, Á, Simon-Sarkadi L, Holzapfel WH. Biogenic amines and their production by microorganisms in food. *Trends Food Sci Technol* 1994;5:42–9.
 78. Nordic Council of Ministers. Present status of biogenic amines in foods in Nordic countries. Tema Nord 2002:524 (ISBN: 92-893-0773-0). Cited by: Sarkadi L. Histamine in food. In: Falus A, Grosman N, Darvas Z, eds. *Histamine: biology and medical aspects*. Budapest, Hungary: Springer-Med Publishing, 2004:176–85.
 79. Bieck PR, Antonin KH. Oral tyramine pressor test and the safety of monoamine oxidase inhibitor drugs: comparison of brofaromine and tranlycypromine in healthy subjects. *J Clin Psychopharmacol* 1988;8:237–45.
 80. Littlewood JT, Gibb C, Glover V, Sandler M, Davies PT, Rose FC. Red wine as a cause of migraine. *Lancet* 1988;1:558–9.
 81. Forsythe WI, Redmond A. Two controlled trials of tyramine in children with migraine. *Dev Med Child Neurol* 1974;16:794–9.
 82. Ziegler DK, Stewart R. Failure of tyramine to induce migraine. *Neurology* 1977;27:725–6.
 83. Moffett A, Swash M, Scott DF. Effect of tyramine in migraine: a double-blind study. *J Neurol Neurosurg Psychiatry* 1972;35:496–9.
 84. Ryan RE. A clinical study of tyramine as an etiological factor in migraine. *Headache* 1974;14:43–8.
 85. Moneret-Vautrin DA, de Korwin JD, Tisserant J, Grignon M, Claudot N. Ultrastructural study of the mast cells of the human duodenal mucosa. *Clin Allergy* 1984;14:471–81.
 86. Izquierdo-Pulido, M. Biogenic amines in European beers. *J Agric Food Chem* 1996;44:33159–63.
 87. Jarisch R, Pirker C, Möslinger T, Götz M. The role of histamine in wine intolerance. *J Allergy Clin Immunol* 1992;91:197 (abstr).
 88. Wantke F, Hemmer W, Gotz M, Jarisch R. Adverse reactions to alcoholic beverages: a diagnostic guideline. *Clin Exp Allergy* 1997;27:343 (abstr).
 89. Dahl R, Henriksen JM, Harving H. Red wine asthma: a controlled challenge study. *J Allergy Clin Immunol* 1986;78:1126–9.
 90. Gershwin ME, Ough C, Bock A, Fletcher MP, Nagy SM, Tuft DS. Grand rounds: adverse reactions to wine. *J Allergy Clin Immunol* 1985;75:411–20.
 91. Kanny G, Bauza T, Fremont S, et al. Histamine content does not influence the tolerance of wine in normal subjects. *Allerg Immunol (Paris)* 1999;31:45–8.
 92. Kanny G, Gerbaux V, Olszewski A, et al. No correlation between wine intolerance and histamine content of wine. *J Allergy Clin Immunol* 2001;107:375–8.
 93. Yang WH, Purchase EC. Adverse reactions to sulfites. *CMAJ* 1985;133:865–7, 880.
 94. Gunnison AF, Jacobsen DW. Sulfite hypersensitivity. A critical review. *CRC Crit Rev Toxicol* 1987;17:185–214.
 95. Przybilla B, Ring J. [Sulfite hypersensitivity]. *Hautarzt* 1987;38:445–8 (in German).
 96. Brink B, Damink C., Joosten HM, Huis in 't Veld JH. Occurrence and formation of biologically active amines in foods *Int J Food Microbiol* 1990;11:73–84.
 97. Wantke F, Proud D, Siekierski E, Kagey-Sobotka A. Daily variations of serum diamine oxidase and the influence of H1 and H2 blockers: a critical approach to routine diamine oxidase assessment. *Inflamm Res* 1998;47:396–400.
 98. Novotny WF, Chassande O, Baker M, Lazdunski M, Barbry P. Diamine oxidase is the amiloride-binding protein and is inhibited by amiloride analogues. *J Biol Chem* 1994;269:9921–5.
 99. Stein J, Scheuermann EH, Yazdi R, Lembcke B, Caspary WF. Reduced postheparin plasma diamine oxidase activity in patients with chronic renal failure. *Z Gastroenterol* 1994;32:236–9.
 100. Gang V, Berneburg H, Hennemann H, Hevendehl G. Diamine oxidase (histaminase) in chronic renal disease and its inhibition in vitro by methylguanidine. *Clin Nephrol* 1976;3:171–7.
 101. Gang V, Stanjek J, Gaubitz W. [Diaminoxidase (histaminase) in liver diseases and experimental liver lesions]. *Verh Dtsch Ges Inn Med* 1976;82:434–6 (in German).
 102. Ruan P, Gong ZJ, Zhang QR. Changes of plasma D(-)-lactate, diamine oxidase and endotoxin in patients with liver cirrhosis. *Hepatobiliary Pancreat Dis Int* 2004;3:58–61.
 103. Guida B, De Martino CD, De Martino SD, et al. Histamine plasma levels and elimination diet in chronic idiopathic urticaria. *Eur J Clin Nutr* 2000;54:155–8.
 104. Ionescu G, Kiehl, R. Monoamine and diamine oxidase activities in atopic eczema. *Allergy* 1988;43:318–9.
 105. Ring, J. Plasma histamine concentrations in atopic eczema. *Clin Allergy* 1983;13:545–52.
 106. Ring J, Sedlmeier F, Dorsch W, Hermann K. In vitro IgE elution and histamine releasability from peripheral leukocytes of atopics and normals. *J Dermatol Sci* 1991;2:413–21.
 107. Ring J, O'Connor R. In vitro histamine and serotonin release studies in atopic dermatitis. *Int Arch Allergy Appl Immunol* 1979;58:322–30.
 108. Ring J, Thomas P. Histamine and atopic eczema. *Acta Derm Venereol Suppl (Stockh)* 1989;144:70–7.
 109. Sampson HA, Jolie P. L. Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med* 1984;311:372–6.
 110. Kiehl R, Ionescu G. [Histamine-degrading enzymes in atopic eczema]. *Z Hautkr* 1989;64:1121–3 (in German).
 111. Maintz L, Benfadal S, Allam JP, Hagemann T, Fimmers R, Novak N. Evidence for a reduced histamine degradation capacity in a subgroup of patients with atopic eczema. *J Allergy Clin Immunol* 2006;117:1106–12.
 112. Fiedler EM, Pelchrim R, Focke M, Zuberbier T, Worm M. Bedeutung von exogen zugeführtem Histamin bei Patienten mit atopischer Dermatitis. (Histamine intolerance. Effect of ingested histamine on the skin status of atopic patients.) *Allergo J* 2004;13:S49–50 (abstr) (in German).
 113. Bieganski T, Osinska Z, Maslinski C. Inhibition of plant and mammalian diamine oxidase by substrate analogues. *Agents Actions* 1982;12:41–6.
 114. Herman JJ, Brenner JK, Colten HR. Inhibition of histaminase release from human granulocytes by products of histaminase activity. *Science* 1979;206:77–8.
 115. Elmore BO, Bollinger JA, Dooley DM. Human kidney diamine oxidase: heterologous expression, purification, and characterization. *J Biol Inorg Chem* 2002;7:565–79.
 116. Ignesti G. Equations of substrate-inhibition kinetics applied to pig kidney diamine oxidase (DAO, E.C. 1.4.3.6). *J Enzyme Inhib Med Chem* 2003;18:463–73.
 117. Bodis J, Tinneberg HR, Schwarz H, Papenfuss F, Torok A, Hanf V. The effect of histamine on progesterone and estradiol secretion of human granulosa cells in serum-free culture. *Gynecol Endocrinol* 1993;7:235–9.
 118. Kalogeromitros D, Katsarou A, Armenaka M, Rigopoulos D, Zapanti M, Stratigos I. Influence of the menstrual cycle on skin-prick test reactions to histamine, morphine and allergen. *Clin Exp Allergy* 1995;25:461–6.
 119. Sabbah A, Heulin MG, Drouet M, Bonneau JC, Sellin JL, Bouquin D. [Antihistaminic or antidegranulating activity of pregnancy serum]. *Allerg Immunol (Paris)* 1988;20:236–40 (in French).
 120. Morel F, Surla A, Vignais PV. Purification of human placenta diamine oxidase. *Biochem Biophys Res Commun* 1992;187:178–86.
 121. Lindberg S. 14-C-histamine elimination from the blood of pregnant and non-pregnant women with special reference to the uterus. *Acta Obstet Gynecol Scand* 1963;42(suppl):3–25.

122. Jarisch R. Histamin-Intoleranz. (Histamine intolerance.) *Aerztemagazin* 2004;8:1–4 (in German).
123. Tufvesson G, Tryding N. Determination of diamine oxidase activity in normal human blood serum. *Scand J Clin Lab Invest* 1969;24:163–8.
124. Okuyama T, Kobayashi Y. Determination of diamine oxidase activity by liquid scintillation counting. *Arch Biochem Biophys* 1961;95:242–50.
125. Schwelberger HG, Klocker J, Sattler J, Bodner E. Determination of the activity of diamine oxidase in extremely small tissue samples. *Inflamm Res* 1995;44(suppl):S94–5.
126. Pacifici GM, Donatelli P, Giuliani L. Histamine *N*-methyl transferase: inhibition by drugs. *Br J Clin Pharmacol* 1992;34:322–7.
127. Hansson R, Holmberg CG, Tibbling G, Tryding N, Westling H, Wetterqvist H. Heparin-induced diamine oxidase increase in human blood plasma. *Acta Med Scand* 1966;180:533–6.
128. Klocker J, Perkmann R, Klein-Weigel P, et al. Continuous administration of heparin in patients with deep vein thrombosis can increase plasma levels of diamine oxidase. *Vascul Pharmacol* 2004;40:293–300.
129. Biebl M, Klocker J, Perkmann R, et al. Effects of unfractionated and low molecular weight heparins on diamine oxidase release. *Inflamm Res* 2003;52(suppl):S63–4.
130. Biebl M, Klocker J, Perkmann R, et al. Heparin-induced diamine oxidase release into the circulation in pigs. *Inflamm Res* 2002;51(suppl):S93–4.
131. Mayer I, Missbichler A, Wantke F, et al. Optimierter Radioextraktionsassay zur quantitativen Bestimmung der Aktivität von Diaminoxidase (DAO) in humanem Serum und Plasma. (Optimized radio-extraction assay for the quantitative measurement of the activity of diamine oxidase (DAO) in human serum and plasma.) *Allergologie* 2005;28:1–8 (in German).
132. Hermann K, Hertenberger B, Ring J. Measurement and characterization of histamine and methylhistamine in human urine under histamine-rich and histamine-poor diets. *Int Arch Allergy Immunol* 1993;101:13–9.
133. Johnston CS. The antihistamine action of ascorbic acid. *Subcell Biochem* 1996;25:189–213.
134. Wantke F, Gotz M, Jarisch R. [The histamine-free diet]. *Hautarzt* 1993;44:512–6 (in German).
135. Martner-Hewes PM, Hunt IF, Murphy NJ, Swendseid ME, Settlege RH. Vitamin B-6 nutriture and plasma diamine oxidase activity in pregnant Hispanic teenagers. *Am J Clin Nutr* 1986;44:907–13.
136. Raithel M, Konturek PC, Wildner S, et al. Evaluation der immunologischen Effekte von Bauchspeicheldrüsenenzymen bei gastrointestinal vermittelten Allergien (GMA) mittels doppel-blinder, placebokontrollierter Provokationstestung, ex vivo Mukosa-oxygenation und der in vitro Allergendegradation. (Evaluation of immunologic effects of pancreas enzymes in gastrointestinally mediated allergies (GMA) with the help of double-blind placebo-controlled provocation, ex vivo mucosa oxygenation, and in vitro allergen degradation.) *Allergo J* 2005;14:41 (abstr) (in German).
137. Lorenz W, Ennis M, Doenicke A, Dick W. Perioperative uses of histamine antagonists. *J Clin Anesth* 1990;2:345–60.