# Histamine and histamine intolerance

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Laura Maintz
University of Bonn
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**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 $\mu$mol/L<br>Putrescine, 350 $\mu$mol/L<br>Spermidine, 3 mmol/L | Histamine, 6–13 $\mu$mol/L<br>*S*-adenosyl-L-methionine, 6–10 $\mu$mmol/L |
| Optimum pH | 7.2 | 7.5–9.0 |
| Inhibititors | Copper-chelating agents, eg cyanide<br>Carbonylgroup reagents, eg, aminoguanidine, semibarbacide | Reaction products: *N*-methylhistamine, *S*-adenosyl-L-homocysteine<br>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