Histamine in food: is there anything to worry about?

W.A. Fogel*, A. Lewinski† and J. Jochem‡

*Department of Hormone Biochemistry, Medical University of Lodz, 7/9 Zeligowskiego, 90-752 Lodz, Poland, †Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, 281/289 Rzgowska, 93-338 Lodz, Poland, and ‡Department of Physiology, Medical University of Silesia, 19, H. Jordana 41-808 Zabrze, Poland

Abstract

Biogenic mono-, di- and poly-amines are widely distributed among living organisms. The amines fulfill many important functions in the human body both in the periphery and brain. Some authors suggest that foods rich in biogenic amines, especially histamine, present high health hazards for consumers. However, this is conditional on a range of other factors. The alimentary tract is well equipped with enzymes that inactivate amines and the blood–brain barrier prevents them entering the brain from the circulation. Oxidative deamination, methylation, acetylation and transglutamylation are the degradation pathways which operate efficiently in the stomach, intestines and liver. Particularly important is oxidative deamination. Food histamine poisoning or cheese reaction, manifested itself in patients treated with drugs that inhibit amine oxidases or in patients showing an enterocytic diamine oxidase deficit. It is rather food allergy, which should worry us more, as endogenous histamine release from mast cells is more dangerous. Preventive measures should be undertaken against increases in food allergies.

Introduction

Biogenic amines belong to a family of low-molecular-mass compounds not exceeding 200 Da and possessing the active amino group(s). The first monograph on biogenic amines was published in 1920 [1], and its author, Markus Guggenheim, a physiologist from Switzerland, summarized all structural and functional features pertinent to the group. Methyl-, di- and trimethyl-amines, and di- and poly-amines, i.e. putrescine, spermidine and spermine, acetylcholine, choline, dopamine, noradrenaline, adrenaline, histamine, serotonin and guanidines are among the members. Usually, however, when we hear the term biogenic amines, we mean acetylcholine, catecholamines, serotonin and histamine, i.e. the neurotransmitters.

Amine function and metabolism

Biogenic amines are universal regulators that are involved in control of body homoeostasis, influencing all vital body functions. Not only do they serve as transmitters for the central and peripheral nervous systems, but also, being mostly potent vasoactive agents, they influence blood supply to the organs, act as hormones (adrenaline and noradrenaline), influence gastric and intestinal ion secretion and intestinal motility (histamine and serotonin). Histamine is a mediator of acute anaphylaxis and vascular permeability and strongly influences immune responses [2,3], while the polyamines spermidine and spermine and their precursor putrescine are absolutely required for cell growth and differentiation [4,5].

Biogenic amines are formed from their amino acid precursors by decarboxylation. In some neural, neuroendocrine and exocrine cells, the amines are stored in high quantities to ensure their immediate supply upon demand. Neurons, enterochromaffin and enterochromaffin-like cells, blood platelets, mast cells and basophils act as endogenous depots. The amines are located there in secretory vesicles and their secretion from cells is a highly controlled event [2]. Transport and storage in secretory vesicles is accomplished by VMATs (vesicular monoamine transporters): VMAT1 and VMAT2 carry biogenic amines, whereas VAchT (vesicular acetylcholine transporter) transports acetylcholine, a quaternary amine. In the central nervous system, serotoninergic, dopaminergic, noradrenergic, adrenergic and histaminergic neurons, use VMAT2 exclusively. At the periphery, all the amines, except histamine, are transported by VMAT1. Accordingly, in histamine-storing enterochromaffin-like cells, mast cells and basophils, VMAT2 is present [6].

The action of amines on their targets is mediated by appropriate membrane receptors, members of superfamily G receptors [7], and is terminated by rapid amine removal to render the receptors vulnerable to new messages. Reuptake systems and catabolic enzymes play important roles here.

The oxidative deamination and ring methylation are two major degradation pathways for monoamines and histamine [2,8]; direct oxidative deamination or oxidative deamination with prior acetylation concerns polyamines [4,5], while transglutamylation involves all of them, i.e. mono-, di- and poly-amines [9].

Key words: allergy, amine oxidase, food, gastrointestinal system, histamine.

Abbreviations used: ABP1, amiloride-binding protein 1; DAO, diamine oxidase; HNMT, histamine N-methyltransferase; MAO, monoamine oxidase; PAO, polyamine oxidase; SNP, single nucleotide polymorphism; VMAT, vesicular monoamine transporter.

* To whom correspondence should be addressed (email wafogel@mazurek.man.lodz.pl).
Monamine-degrading enzymes

The key enzymes, MAO (monoamine oxidase) A and B (EC 1.4.3.4), are FAD-dependent isoenzymes associated with the outer mitochondrial membrane, encoded by two different genes that are found at chromosome locus Xp11.23. The enzymes differ in substrate specificity and sensitivity to acetylenic inhibitors. MAO A, which is sensitive to clorgyline, preferentially oxidizes serotonin, MAO B prefers phenylethylamine and is inhibited by deprenyl. Dopamine, noradrenaline, adrenaline, tryptamine and tyramine are oxidized by both MAO forms, and Methylhistamine is an MAO B substrate. Isoenzyme distribution is cell- and tissue-specific: placenta and fibroblasts contain MAO A, blood platelets and lymphocytes exclusively contain MAO B. MAO A prevails in the intestine. In the brain, MAO A is expressed in catecholaminergic neurons, while MAO B is expressed in serotoninergic and histaminergic counterparts, and in astrocytes. MAO enzymes are implicated in neurodegenerative diseases, psychiatric disorders and addictions [10]. The participation of MAO in metabolism of endogenous, food-derived sympathomimetic amines was recognized due to “cheese reaction”. Many of the first-generation MAO inhibitors that were introduced for clinical use against depressive disorders had to be withdrawn due to life-threatening hypertensive crises that they evoked in some patients. Studies have shown that the culprit was tyramine, present in ingested cheese or fermented products. Under MAO enzyme blockade, tyramine survived metabolism in the intestine and liver, entered the circulation and induced noradrenaline release from adrenergic neurons at the periphery [11], as no biogenic amine can penetrate the blood–brain barrier. This is formed by brain endothelial cells, lining the cerebral microvasculature, and is an important mechanism protecting the brain from fluctuations in plasma composition and from circulating agents such as neurotransmitters and xenobiotics, which are capable of disturbing neural function [12]. The recognition of cheese reaction mechanism led scientists and clinicians to pay attention to the intestinal oxidative barrier and to design and develop drugs that do not interfere with it.

Methylation of catechol- and indole-amines is catalysed by cytosolic COMT (catechol O-methyltransferase) (EC 2.1.1.6) and HIOMT (hydroxyindole O-methyltransferase) (EC 2.1.1.4), respectively with S-adenosyl-L-methionine serving as a methyl group donor [2].

Histamine-degrading enzymes

Two major histamine-degrading enzymes are DAO (diamine oxidase) [EC 1.4.3.6, also known as histaminate or ABP1 (amiloride-binding protein 1)] and HNMT (histamine N-methyltransferase) (EC 2.1.1.8) [8]. In the brain, lacking DAO, N-methylation is the major process regulating histamine metabolism and function [13]; likewise in the airways and stomach [8,14]. DAO is critical in the intestinal tract, where it serves to eliminate ingested histamine, thus protecting against histaminosis. The genes coding for DAO and HMT enzymes are polymorphic and diverse SNPs (single nucleotide polymorphisms) have been described on these genes. The HNMT gene, on chromosome locus 1p32, shows eight SNPs, of which one has importance, causing amino acid substitution T105I [15]. The variant expresses lower enzyme activity and less immunoreactive protein and is more frequently found among asthmatics [16]. Four SNPs have been mapped to the DAO ABP1 gene, found at chromosome locus 7q34–36 [17]. Among these, the SNP located in exon 3 C2029G codes for an altered protein with the amino acid substitution H645D. Recently, the association of the H645D polymorphism with the severity of ulcerative colitis has been indicated [18].

Polyamine-degrading enzymes

Similarly to histamine, putrescine is a substrate of DAO [2,8], whereas polyamines are oxidatively deaminated by FAD-dependent PAOs (polyamine oxidases), either directly by inducible enzyme PAO-h1 (human PAO 1)/SMO (spermine oxidase) [19] or by a constitutive PAO in a step subsequent to N-acetylation, carried out by spermidine/spermine N\(^1\)-acyltransferase [3,4].

Metabolism of dietary amines

Heterocyclic amines and aliphatic mono- di- and polyamines are normal food constituents. The daily consumption depends on the type of ingested food. Vegetable-derived foods contain, for example, a lot of putrescine, but significantly lower amounts of histamine, spermidine and spermine than animal-derived foods. Normally, dietary amines are processed rapidly. Amines cross the intestinal epithelial barrier passively and are metabolized in situ [20]. The intestinal mucosa contains MAO, DAO and PAO activities which form an efficient barrier, limiting free amine access to the sites of their action and to the systemic circulation. The enzyme distribution patterns are not uniform along either the digestive tract or across the mucosa from the crypt base to the villus tip [21]. Ingested histamine is catabolized not only by DAO but also by HNMT, as both are present in the small and large bowel [2,8,21–23]. Several results suggest that DAO is a secretory protein, which operates in microvascular endothelium and is responsible for scavenging extracellular histamine [21–25], whereas HNMT is a cytosolic enzyme, metabolizing histamine in the intracellular space [2,8,13,14]. Although plasma membrane transporters for scavenging and recycling dopamine, noradrenaline, adrenaline and serotonin from the extracellular space (abbreviated DAT, NAT and SERT respectively) are well known and characterized [26], only recently have organic cation transporters OCT-2 and OCT-3 been suggested to facilitate the intracellular metabolism of histamine by HNMT [27]. Alternatively, histamine is metabolized in the plasma membrane after receptor-stimulated HNMT translocation from cytoplasm [27].

Food-derived histamine is associated with non-allergic food hypersensitivity, whereas endogenous histamine stored in histaminocytes is responsible for food allergy reactions.
Non-allergic food hypersensitivity (food intolerance)

Food intolerances do not involve the immune system, although the symptoms that they induce are similar to those observed in classical IgE-mediated allergy [28]. However, they are milder and shorter in duration. They can be caused by adverse reaction to irritants, enzymatic or pharmacological causes: the concurrent presence of more than one of the causative factors may enhance the severity of histamine intoxication [29–34]. There is an increased risk of histamine-induced adverse reactions in humans with decreased amine oxidase activity and/or increased gut permeability, as in subjects with colitis ulcerosa or Crohn’s disease [25,32,33]. Reduced histamine degradation capacity was disclosed also in a subgroup of patients with atopic eczema [34]. Poor degradation of histamine by DAO is suggested to be the major reason for non-immunological histamine intolerance [31,35]. The role of histamine in the provocation of symptoms is clear, since they can be eliminated by treatment with H1 histamine receptor antagonists [30]. A sustained high histamine level was suggested to underlay syndrome characterized by eosinophilia with myalgia. Excessive intakes of tryptophan supplements cause, among other relevant side effects, an increased formation of formate and indolyl metabolites, several of which inhibit the degradation of histamine [35]. It should be recalled at this point that pharmacological effects of histamine are mediated by four subtypes, H1–H4, of histamine receptors [36,37]. Whereas H1 receptors mediate smooth muscle and endothelial cell contractions, increased vascular permeability and antibody production, H2 and H4 receptors are involved in the modulation of cytokine production and various immunomodulatory effects including eosinophil and mast cell chemotaxis and calcium influx in these cells, also neutrophil chemotaxis, which all affect inflammatory responses. H3 receptors control neurotransmitter release. H1, H2 and H3, but not H4, receptors are expressed in the human digestive tract, and, interestingly enough, there is up-regulation of H1 and H2 receptors in patients with food allergy or irritable bowel syndrome [37].

Food allergy

Food allergy is defined as an immune-mediated hypersensitivity to ingested allergens. It affects as much as ~6% of infants below 3 years and ~2% of the general population [28], although self-reported prevalence is much higher [38,39]. It is divided into three groups: IgE-mediated food allergy (type I), mixed IgE-mediated food allergy (type II) and non-IgE-mediated food allergy (type III) [40]. Coeliac disease (coeliac sprue) or gluten-sensitive enteropathy is characterized by malabsorption, which results from IgA- and cytolytic T-cell-mediated damage of the absorptive epithelial cells of the small intestine. The damage occurs in susceptible individuals after consumption of the gliadin fraction of wheat and the prolamin fractions of barley and rye protein [41].

IgE-mediated response occurs most frequently and is most dangerous. Antigen uptake from the intestinal surface initiates the production of food-specific IgE antibodies. These are linked to high-affinity membrane receptors on mast cells. The exposure to the antigen triggers mast cell degranulation and release of several mediators, including histamine, platelet-activating factor, leukotrienes and prostaglandins, which evoke allergic reactions [40]. The foods which most commonly elicit anaphylactic reactions are cow’s milk, hen’s eggs, nuts, fish, seafood and pollen-related fresh fruits and vegetables [28,38,39]. Clinical manifestations of food allergies include gastrointestinal symptoms, such as nausea, vomiting, abdominal pain and diarrhoea, and general symptoms, such as rhinitis, asthma, oedema, hypotension, itching, urticaria (hives), dermatitis/eczema, bronchospasm and, in severe cases, anaphylactic shock [39,40,41]. Released histamine and other mast cell mediators are responsible for the severity and duration of intestinal and extra-intestinal symptoms. The decreased intestinal DAO activities found in patients with food allergy [42] may add further to the deleterious effect of the massive mast cell degranulation. Since a variety of drugs, such as metoclopramide, d-tubocurarine, pancuronium and many antibiotics, are able to inhibit DAO activity [29], they may intensify food allergy symptoms.

Experimental data suggest that intestinal inflammation, by increasing gut permeability, enhances the sensitization process [43]. Indeed, serum levels of IgG and IgM in response to cow’s milk proteins are higher in patients with ulcerative colitis or Crohn’s disease [44,45]. High alcohol consumption is associated with increased total serum IgE levels and pollen sensitization prevalence [46]. Evidence has been provided [47] that IgE-mediated food hypersensitivity may develop as a consequence of prolonged suppression of gastric acid during H2 receptor antagonist or proton pump inhibitor medication against duodenal and gastric ulcers, gastro-oesophageal reflux or gastritis. After 3 months of antacid therapy, de novo formation of IgE-antibodies towards food components occurred in 15% of patients and persisted for 5 months after therapy in 6% of patients, indicating that, owing to an increase in the pH of gastric juice, digestion labile food allergens escape degradation [47]. This is an important finding, as it shows that the free use of some drugs sold over the counter can be risky. In this particular case, it can lead to unpredicted increase of population hypersensitive to food.

According to the recent hypothesis by Berstad et al. [48], poor quality of life and many abdominal and extra-abdominal complains in patients with food hypersensitivity and subjective food hypersensitivity can be explained by extensive activation of cognitive networks triggered by peripheral sensory mechanisms. This central cognitive-emotional sensitization at the brain level could be an important pathogenetic mechanism of the generation of food intolerance-associated symptoms [48]. The possible role of histamine in this process should be discussed, since there are close anatomical and functional connections between the enteric part of the autonomic nervous system and the mucosal mast cells. Clinical studies by Santos et al. [49] demonstrate clearly the release of histamine and tryptase from enteric mucosal mast cells in response to stress (repeated insertion
of one hand in ice-cold water), accompanied by mucosal hyperaemia, oedema and increased mucosal permeability. Released histamine may activate also enteric sensory endings and, in this way, initiate firing in afferent fibres. Therefore it seems reasonable to accept that histamine intolerance may belong, at least in some patients, to a group of sensitization diseases at brain level, called cognitive-emotional sensitizations [48].

**Conclusions**

Owing to strict technological regimens, the incidence of histamine food poisoning related to high amine content arising from bacterial contamination, is sporadic. Jansen et al. [50], who evaluated clinical data published during the last 35 years on the relationship between the adverse effects and amine contents of food, found no scientific basis for dietary recommendation concerning amines. Food allergy, on the other hand, affects at least 2–6% of the population [28], with 25% believing they suffer from it [38]. It can be primary food hypersensitivity or caused by primary sensitization to airborne allergens resulting in cross-reactive IgE antibodies to certain foods. Food hypersensitivity, including the belief that one suffers from it, strongly affects quality of life. Alcohol, antacid medication and stress are among the factors that have an important role in inducing food hypersensitivity. Insufficiency of oxidative deamination enzymes and histamine receptor up-regulation will potentiate symptoms. Preventive measures should be undertaken against food allergy increase.

**References**

1 Guggenheim, M. (1920) Die biogenen Amine und ihre Bedeutung für die Physiologie und Pathologie des pflanzlichen und tierischen Stoffwechsels, Springer, Berlin
29 Kubler, R., Zeller, R., Tschudi, D., Fehr, M., Kojic, K., Tschopp, M. et al. (2005) Allergy 60, 813-824
34 Milovic, V., Turchanova, L., Ulrich, P. and Hahn, E.G. (1999) Inflamm. Res. 48 (Suppl. 1), S57-S56