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Biogenic amines in food as a public health concern
An outline of histamine food poisoning

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Food-borne diseases have an important impact on public health. In recent years, epidemiological recording of diseases is ongoing, but more data are required for the assessment of food poisoning from biogenic amines. This article presents an outline of the consequences of biogenic amines in food, with an emphasis on histamine food poisoning and the foods which are most likely to pose a health risk from biogenic amines in high levels. Scombroid food poisoning (SFP) is a global food safety problem. Histamine intoxication is the form of food poisoning which is the most toxic and the most frequently observed. The toxic effects of food-borne histamine can present with a variety of symptoms, including anaphylaxis, irritation and nausea. The current legal limits for food content are presented, along with the preventive measures that businesses should take for the avoidance of accumulation of biogenic amines in foods at levels unsafe for consumer health.

Η παρουσία των βιογενών αμινών στα τρόφιμα ως κίνδυνος για τη δημόσια υγεία. Μια περιγραφή με έμφαση στην ισταμινική τροφική δηλητηρίαση

Περίληψη στο τέλος του άρθρου

Key words

Biogenic amines
Food-borne intoxication
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1. INTRODUCTION

The biogenic amines are organic nitrogen bases of low molecular weight and a variety of structures: aliphatic (e.g., spermine, spermidine, putrescine, cadaverine), aromatic (e.g., tryptamine, histamine) and heterocyclic (e.g., tyramine), which have biological activity.[1,2] They are naturally present in living organisms and foods.[3] Several of these play a significant role in many human physiological functions. The presence of biogenic amines in food is also used as an indicator of spoilage of food. The consumption of foods that contain high levels of these compounds can provoke toxic effects in susceptible people.[4]

Biogenic amines are produced by decarboxylation of free amino acids mediated by amino acid decarboxylase enzymes in a wide range of foods (tab. 1).[3] Their presence in raw foods is a result of the activity of bacterial enzymes that cause decarboxylation. The process of decarboxylation can be accomplished through both the endogenous and the exogenous generation of amines.[5] The first is due to the decarboxylation enzymes which occur naturally in various foods and the second to the exogenous enzymes released by various microorganisms that may be found in food. The second pathway of biogenic amine generation, especially diamines, is the most common.[5,6]

The presence of biogenic amines is an important in-

Table 1. Examples of biogenic amines in foods due to specific amino acid presence.

Amine	Amino acid
Choline	Serine
Putrescine	Ornithine
Cadaverine	Lysine
Histamine	Histidine
Tryptamine	Tryptophane
Serotonine	5-hydroxytryptophan

Source: Mayer et al[34]

dicator of the freshness, spoilage, and quality of food.[2–4] They may be present in different types of foods, but they are usually found in fish and fish products (giving rise to scombroid histamine poisoning),[7] cheeses, meat and fermented products.[8] The conditions for the accumulation of biogenic amines in cheese (mainly tyramine, histamine, cadaverine, putrescine, and tryptamine) are the availability of free amino acids, the presence of bacteria that contain decarboxylase and the environmental conditions that allow bacterial growth and enzymatic activity.[9] Biogenic amines may be endogenous in low concentrations even in non-fermented foods such as fruit and vegetables.[1]

2. FOOD POISONING FROM BIOGENIC AMINES

The consumption of high amounts of biogenic amines with foods can lead to food poisoning.[10] In terms of public health, amines are an important factor because they have been involved in various incidents of food poisoning.[11] They are also considered to be carcinogenic because of their ability to react with nitrite salts, resulting in the formation of nitrosamines (e.g. putrescine, cadaverine) which have a carcinogenic effect.[12,13] Poisoning from biogenic amine consumption has been reported in the United States of America (USA), Canada, Japan and other countries where fish consumption is the most common source (tab. 2). After fish, cheese is food next most commonly implicated in histamine poisoning.[4] Outbreaks of histamine poisoning have been reported after consumption of different types of cheese. Several histamine outbreaks were caused by consumption of Swiss and Cheddar cheese, which may contain high amounts of histamine.[14,15]

Another amine poisoning phenomenon is the "cheese reaction", which is triggered by high tyramine levels in cheese.[11,12] "Cheese reaction" has been observed after ingestion of foods rich in tyramine, presenting as a hypertensive crisis, usually accompanied by severe headache.[16]

Table 2. Reported sources of food poisoning from biogenic amines in various countries worldwide.

Country	Incriminated food
Canada	Fish, Cheddar cheese
Denmark	Fish
France	Fish, Swiss cheese, Cheshire cheese, Gruyere cheese, ham, fish
Germany	Fish, Gouda cheese, sauerkraut
Great Britain	Fish
Japan	Fish, chicken
Netherlands	Gouda cheese
New Zealand	Fish
United States	Fish, Swiss cheese

Source: Shalaby[13]

Some of the amines have been studied more thoroughly because they are associated with an increased risk for human health. With regard to food safety, histamine and tyramine are the main causes of food-borne poisoning from biogenic amines.[17]

3. BIOGENIC AMINES TOXICITY

The consumption of foods that contain certain biogenic amines may cause serious toxic reactions.[12] The toxic effects of biogenic amines may be manifested by a variety of symptoms, including vomiting, headache, respiratory difficulties, a burning sensation in the mouth, arrhythmia, hypotensive episodes or hypertensive crisis.[18] These symptoms are particularly intense in the case of interaction with certain drugs, including antihistamines, antimalarials and other medications.[14] Reactions may be more pronounced in the presence of other types of amines, such as putrescine and cadaverine.[11]

The determination of the exact lower limit of toxicity of biogenic amines is particularly difficult, as the toxic dose is strongly dependent on the capacity of the detoxification mechanisms of each person. In general, the ingestion of a dose that is greater than 40 mg of biogenic amines per meal has been considered potentially toxic. Regarding cheese, one study showed that the total of tyramine, histamine, putrescine and cadaverine amines should not exceed the amount of 900 mg/kg of cheese.[19] Currently, no legal limit has been established for the presence of biogenic amines in cheese but a specific limit has been set for the presence of histamine in fish in the European legislation.[20]

As mentioned above, the toxic dose of amines shows individual variation. Clinical studies have documented that specific levels of certain biogenic amines provoke toxic effects which differ from person to person, depending on individual detoxification efficiency (by conversion to an aldehyde through the action of a monoamine oxidase [MAO] or a diamine oxidase [DAO]).[14] The use of certain medications which are monoamine and diamine oxidase inhibitory factors has been curtailed due to the observed frequency of amines in foods, especially cheeses. It is now known that the consumption of cheese in combination with specific drugs (MAO inhibitors) should be avoided because it could result in hypertensive crisis and even death from cerebral hemorrhage.[21]

Concerning the action pathway, differences have been found between the various amines. Histamine acts by binding to receptors on the cell membrane in the respiratory, cardiovascular, gastrointestinal, immune system and skin.[22] Histamine and tyramine act on the blood vessels, while others such as cadaverine act mainly by installing histamine detoxifying enzymes. Several studies have shown that cadaverine, putrescine and other diamines facilitate the transfer of histamine in the intestinal wall, thereby increasing histamine toxicity (tab. 3).[15–18]

4. PHYSIOLOGICAL EFFECTS AND RISKS OF HISTAMINE TOXICITY

Histamine has been reported to exert multiple effects on the human organism.[15] It is a compound that appears naturally in the human body and plays a significant role in human metabolism. It takes part in biological processes such as allergic reactions and acts as a neurotransmitter or chemical messenger in synaptic transmission. The concentration of histamine in the blood is strictly regulated. When its intake is through the oral route, histamine poisoning occurs only when the regulating mechanisms fail to react to the received dose, e.g., when challenged by high dose enzyme consumption which disturbs histamine metabolism. In small doses, it has a minimal effect, but toxic effects occur at higher doses. In addition to endogenous generation, histamine may be introduced into the body through exogenous sources and in particular by the consumption of foods which contain high levels, and it may become dangerous for human health if its levels reach a critical limit.[23]

Food poisoning from histamine occurs as a result of consumption of foods with high amine content.[24] Histamine can be found in foods that have ripened or are fermented. When associated with a high consumption of scombroid fish it is also referred to as scombroid fish poisoning (SFP), which constitutes a significant food-borne disease.[12]

In addition to fish and their products, other fermented foods (i.e., meat, dairy products, vegetables and alcoholic beverages such as beer and wine) may contain high levels of histamine.[25] Although usually connected with the consumption of scombroid fish, other foods, and in particular cheeses, have been associated with outbreaks of histamine poisoning.

During the process of risk analysis, the experts from the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) concluded that the dose of 50 mg histamine, which is the no observed adverse effect level (NOAEL) is an acceptable risk level. At this level, healthy people are not expected to suffer from the symptoms associated with histamine poisoning. There is no apparent cumulative effect of consecutive consumption of meals that contain fish, because histamine is usually discharged from the body within a few hours. In healthy people, histamine that is ingested in the diet is detoxified rapidly by aminoxidases, and only when large amount of histamine-rich foods are eaten consumers may develop toxic symptoms.[23] Smoking and alcohol consumption may also increase susceptibility to biogenic amines by reducing their degradability by the body.[24]

4.1. Epidemiological data on food-borne histamine poisoning

SFP is a global food safety problem.[24] Histamine poi-

Table 3. Pathophysiological and toxicological effects of amines in food.

Amine	Effect	Toxic level
Tyramine	Effects on blood vessels, headache, fever, hypertension, vomiting, sweating	10–80 mg
Histamine	Capillary dilation, hypotension, nausea, vomiting, face redness, stomach disturbances, lip swelling, intense headache, thirst, anaphylaxis	70–1.000 mg
Putrescine and cadaverine	Increased cardiac output, tachycardia, hypotension, carcinogenic effects	29.5–35.6 mg
Tryptamine	Effects on blood vessels, headache, fever, hypertension, vomiting, sweating	–

Sources: Rauscher-Gabernig et al,[18] Edwards and Sandine[21] soning is the most toxic form observed, and the most common.[12] The toxic effects of histamine present with a variety of symptoms (tab. 4), including anaphylaxis, irritation and nausea. The incubation time is very short and the duration of disease is also short.[25] After the consumption of food that contains large amounts of histamine, the symptoms may develop within a few minutes or a few hours. They are often mild and medical supervision may not be required. The significance of histamine and biogenic amines in fermented foods would be developed more objectively if a different outbreak management policy was exercised.[14]

As many countries do not keep official statistics on histamine poisoning, there are no comprehensive global data.[12] The number of outbreaks globally due to histamine food poisoning is unclear, because most countries have not established limits on permissible levels of histamine in foods, and outbreak reporting is not required. Because the symptoms may resemble allergic reactions that occur after consumption of certain foods, misdiagnosis is common. Regarding cheeses, although the evaluation of morbidity connected with cheese consumption is inaccurate, new outbreaks are often reported in the literature.[15]

According to the European Centre for Disease Prevention and Control (ECDC) of the European Union (EU), in 2015, 80 outbreaks of histamine food poisoning were reported by 7 EU member states, involving 437 cases of which 43 individuals were hospitalized. The percentage of cases for which hospitalization was required was low (9.8%). The number of epidemic outbreaks reported in 2015 represents an increase from 2014, with 75 epidemic outbreaks.[23]

The reported data cite foods as the transmission vehicle for 23 of 80 epidemiological outbreaks, involving 193 people and 11 hospitalizations, but no deaths in 2015 due to histamine poisoning. In all the epidemic outbreaks, the data refer to the detection of a causative factor in foods or food components as a transmission vehicle, or the detection of a causative factor in the food chain or the environment, together with the occurrence of disease symptoms. Epidemic outbreaks are recorded using descriptive epidemiological data.[23]

Table 4. Common symptoms of scombroid fish poisoning (SFP).

Type	Symptoms
Cardiovascular	Flushing, rash (urticaria), hypotension, headache, tachycardia
Gastrointestinal	Abdominal cramps, diarrhea, vomiting
Neurological	Pain, itching

Source: Food and Agriculture Organization of the United Nations[24]

The above outbreaks were related to the consumption of fish and fish products (20 epidemic outbreaks), cheese (2 epidemic outbreaks), and composite foods (1 epidemic outbreak). Tuna was identified as the specific food-line for 5 epidemic outbreaks (tuna in oil in 1 case and tuna in salad in 2 cases). Information was not provided about one epidemic outbreak. The food businesses where the occurrences presented are reported as follows: Restaurant or café or bar or hotel or catering services in 13 cases, school or kindergarten in 4 cases, canteen or work catering in 2 cases, and 3 outbreaks at the household consumption level.

During the period 2010–2014, 306 outbreaks of food-borne occurrences connected to histamine were reported by 12 EU member states. For 168 of these epidemics the evidence identified foods as the transmission vehicle. During this 5-year period, the most commonly reported foods were: Fish and fish products (156 outbreaks), composite foods (5 outbreaks), cheese, meal in buffet, crabs, shellfish, mollusks and their products, dairy products other than cheeses, vegetables, juices and other products (1 outbreak each).

Two of the above outbreaks were attributed to "other foods". None of the epidemiological data available record any deaths from food histamine poisoning. It is of note that there have been no official reports of outbreaks of food histamine poisoning in Greece.[23]

4.2. Toxicity from histamine production in foods

Generally, production of histamine takes place in temperatures higher than 25 °C and over a period of time longer than 6 hours, and needs longer periods at lower temperatures.[24] The relevent enzyme requires temperatures of over 15 °C, with an optimum temperature of 30 °C for the production of histamine. Even if the temperature is lowered to 0 ° C to 5 °C (cooling temperature) and bacterial growth is inhibited, the enzyme activity may continue, resulting in further amine production.[26] Microorganisms that produce the decarboxylation enzyme that converts histidine to histamine are responsible for the formation of histamine in foods (tab. 5).[27]

Histamine poisoning appears to be enhanced by the presence of other biogenic amines (diamines) found in foods, which can inhibit the metabolism of enzymes in the small intestine. Also, it has been reported that certain bacterial endotoxins which are widespread help the histamine action.[15]

Table 5. Amine producing microorganisms found in foods.

Food	Biogenic amine	Bacteria
Fish	Histamine	*Enterobacter* spp, *Clostridium* sp, *Pseudomonas* spp, *Aeromonas* spp, *Pleisomonas shigelloides, Photobacterium* spp
Cheese	Putrescine	*Enterobacteriaceae, Lactobacillus* spp
Cheese	Histamine	Oenococcusoeni, *Lactobacillus hilgardii, Pediococcus parvulus*
Cheese	Tyramine	*Enterococcus* spp, *Lactobacillus* spp
Wine	Cadaverine	*Enterobacteriaceae*
Wine	Histamine	*Enterobacteriaceae, Staphylococcus capitis*
Wine	Tyramine	*Staphylococcus* spp
		Lactobacillus spp, *Carnobacterium* spp
Wine	Putrescine	*Enterobacteriaceae, Pseudomonas, Enterococcus*
Fermented meat	Histamine	*Enterobacteriaceae, Staphylococcus capitis*
Fermented meat	Cadaverine	*Enterobacteriaceae*
Fermented meat	Putrescine	*Enterobacteriaceae, Pseudomonas* spp, *Enterococcus* spp

Source: Ladero et al[27]

Because food poisoning from histamine is dependent on the presence of other biogenic amines, the determination of lower limits is difficult. Intake of approximately up to 70 mg of histamine causes no symptoms in healthy people. Information from reported cases of food poisoning indicates that a level of 500 to 1,000 mg/kg in food is potentially dangerous for human health.[28]

Lenistea has shown that according to the quantity which is consumed with foods, different toxicity phenomena can be provoked,[29] which can classified as follows: 8–40 mg/meal provokes mild toxicity, 70/1,000 mg/meal causes moderate intensity dysfunction and 1,500–4,000 mg/meal causes intense manifestation.

With the publication of regulation 1019/2013 that changes regulation 2073/2005 for microbiological criteria in foods, the EU established the permitted limits for safety criteria for foods as follows: Fishery products from fish species associated with high amounts of histidine, 100–200 mg/kg, fishery products which have undergone enzymatic maturation in brine, prepared from fish species associated with high amounts of histidine, 200–400 mg/kg, fish sauce that is made by fermentation of fish products, up to 400 mg/kg of food.[20]

5. TOXICITY INFORMATION ON OTHER BIOGENIC AMINES

5.1. Tyramine

Tyramine belongs to the alkaloids and is an aromatic type amine. Like histamine, it has been incriminated in unfavorable reactions, such as hypertensive episodes and headache, particularly in patients who are taking medication in the form of MAO.[15] Tyramine and histamine exert a synergistic cytotoxic effect in an *in vitro* model of human intestinal epithelium.[30]

5.2. Tryptamine, putrescine, cadaverine

Although tryptamine has a pharmacological action similar to that of tyramine, hypertensive episodes are not often reported. In 1965 Blackwell and Mabbit reported that 6 mg of tryptamine ingested by mouth provoked hypertensive episodes in some patients.[15]

It has been documented that putrescine and cadaverine operate as inhibitors of two histamine detoxifying enzymes, DAO and histamine N-methyltransferase (HTM). Taylor and Summer reported that many bacteria, and particularly *Enterobacteriaceae* spp, are able to produce these amines because they contain ornithine and lysine decarboxylases.[14] The toxicity mechanism of histamine is thought to be configured by bacteria other than those responsible for its production, since few bacteria contain the histidine decarboxylation enzyme from which histamine is produced. Also, tyramine, tryptamine and B-phenylalamine have an effective inhibitory action; as noted above, tyramine inhibits MAO, tryptamine blocks DAO and B-phenylalamine inhibits DAO and HTM.[15]

6. CONCLUSIONS

The presence of biogenic amines in food is a public health concern, being responsible for serious incidents of food poisoning.[31] In general, they are not considered a serious hazard for the consumer health, so long as their level in foods is low and their metabolism is not inhibited or genetically altered,[9] but the consumption of high amounts of biogenic amines can lead to toxic effects (e.g., headache, nausea, hypoglycemia or hypertension, palpitations, weakness).

Biogenic amines are very frequently involved in human food poisoning worldwide.[3] Histamine formation and the consequent appearance of histamine poisoning can be easily controlled. The risk of disease is moderated by application of good practices and a food safety management system based on Hazard Analysis and Critical Control Points (HACCP) principles where possible.[24] A combination of factors, including people who show symptoms but do not seek medical care, misdiagnosis and inadequate reporting of incidents to the responsible authorities, leads to the fact that the real incidence of the disease remains unknown.[32]

Several fields have been identified where further research is required, including further clarification of the critical role that histamine and other biogenic amines play in the pathogenesis of histamine food poisoning.[24] More epidemiological information needs to be collected on histamine food poisoning incidents on a global basis. WHO concluded that further epidemiological research is required to provide additional information necessary for the development of regulatory limits of histamine in foods.[33] Current EU legislation for foods recommends ceilings for histamine content in fish products[20] produced from fish species associated with high amounts of histidine and fish sauce which are made by fermentation of fish products. Foods frequently involved in amine poisoning should be identified through epidemiological research on global basis so that effective procedures and regulations can be developed for their control.[23] Attention should be focused on the identification of bacteria responsible for the histamine production in fermented foods such as fish and dairy products. Several measures need to be applied by relevant food businesses, including appropriate sampling and testing for histamine detection, HACCP system validation, verification of the effectiveness of control measures, and detection of system failure resulting in the presence of high levels of biogenic amines in foods.[24]

ΠΕΡΙΛΗΨΗ

Η παρουσία των βιογενών αμινών στα τρόφιμα ως κίνδυνος για τη δημόσια υγεία. Μια περιγραφή με έμφαση στην ισταμινική τροφική δηλητηρίαση

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Τα τροφιμογενή νοσήματα έχουν μεγάλο αντίκτυπο στη δημόσια υγεία. Τα τελευταία έτη, η επιδημιολογική καταγραφή των νοσημάτων είναι διαρκής. Ωστόσο, απαιτούνται περισσότερα αξιόλογα δεδομένα για την εκτίμηση των εμφανιζόμενων τροφιμογενών τοξινώσεων από βιογενείς αμίνες. Στόχος του άρθρου είναι η ανάδειξη της εξέλιξης των νοσημάτων με έμφαση στην ισταμινική τοξίνωση (SFP), καθώς και των τροφίμων που εμπλέκονται πιο συχνά με την πρόκληση νοσημάτων από την παρουσία βιογενών αμινών σε υψηλά επίπεδα. Η σκομβροειδής δηλητηρίαση των τροφίμων αποτελεί ένα παγκόσμιο πρόβλημα ασφάλειας αυτών. Η δηλητηρίαση από ισταμίνη είναι η πλέον τοξική και συχνή μορφή που παρατηρείται. Το τοξικό αποτέλεσμα της ισταμίνης μπορεί να εκδηλωθεί με μια ποικιλία συμπτωμάτων, όπως αναφυλαξία, ερεθισμός, ναυτία κ.λπ. Τέλος, αναδεικνύονται τα πρόσφατα νομοθετικά όρια καθώς και τα μέτρα πρόληψης που οφείλουν να λαμβάνουν οι επιχειρήσεις των τροφίμων για την αποτροπή της ανάπτυξης των βιογενών αμινών στα τρόφιμα σε μη ασφαλή για την υγεία των καταναλωτών επίπεδα.

Λέξεις ευρετηρίου: Ασφάλεια τροφίμων, Βιογενείς αμίνες, Δηλητηρίαση, Δημόσια υγεία, Ισταμίνη, Σκομβροειδής τοξίνωση, Τοξικολογική επίδραση, Τροφιμογενείς επιδημίες

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