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Biogenic Amines as Risk Factors of Food Chain

Juraj Čuboň^{a*}, Peter Haščík^a, Lukáš Hleba^b, Petronela Cviková^a, Jana Tkáčová^a, Ľubomír Lopašovský^c, Adriana Pavelková^a

^a Department of Evaluation and Processing of Animal Products, Slovak University of Agriculture in Nitra, Tr. A. Hlinku 2, 949 76 Nitra, Slovak Republic

^b Department of Microbiology, Slovak University of Agriculture in Nitra, Tr. A. Hlinku 2, 949 76 Nitra, Slovak Republic

^c Department of Food Hygiene and Safety, Slovak University of Agriculture in Nitra, Tr. A. Hlinku 2, 949 76 Nitra, Slovak Republic

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Abstract

Biogenic amines at higher doses have negative effects on the human organism. Some biogenic amines (e.g. putrescine, spermine, spermidine, cadaverine, histamine) are an essential component of living cells because they are involved in the regulation of nucleic acid and protein synthesis and membrane stabilization. Amines are produced by the decarboxylation of natural free amino acids. Decarboxylases are not common in bacteria but occur in species of many genera, particularly in *Bacillus*, *Citrobacter*, *Clostridium*, *Escherichia*, *Klebsiella*, *Photobacterium*, *Proteus*, *Pseudomonas*, *Salmonella*, *Shigella* and lactic bacteria of the *Lactobacillus* genera, *Pediococcus* and *Streptococcus*. Main factors influencing the biogenic amines formation are pH, water activity, storage time, temperature and salt content. Typical levels of biogenic amines in foods range from 10 mg/kg to 100 mg/kg. Occasionally, the amount of biogenic amines in food can exceed 1000 mg/kg.

1. Introduction

Biogenic amines (BA) are low molecular weight aliphatic organic compounds derived from amino acids that commonly participate in metabolic processes in living tissues with different biological, pharmacological and physiological effects. At higher doses they have negative effect on the human organism (Komprda, 2005; Ordóñez *et al.*, 2016).

Amines are produced by natural free amino acids decarboxylation by the action of living organisms, or amination and transamination of aldehydes and ketones are referred to as biogenic amines (Kohajdová and Karovičová, 2001).

According to the chemical structure, biogenic amines are divided into aromatic (tyramine, phenylethylamine), heterocyclic (histamine, tryptamine), aliphatic (putrescine, cadaverine) and polyamines (spermidine, spermine, or agmatine). Diamines can be also classified as polyamines, while the heterocyclic amines are assigned to a group of aromatic amines (Velíšek, 2002; Čuboň *et al.*, 2017).

Some biogenic amines (e.g. putrescine, spermine, spermidine, cadaverine, histamine) are an essential component of living cells because they are involved in the regulation of nucleic acid and protein synthesis and membrane stabilization (Halász *et al.*, 1994).

1.1 Amine production in food

The basic condition for biogenic amines formation is the presence of free amino acids in substrate, presence of

microorganisms with decarboxylase activity and conditions for growth and multiplication of microorganisms. The process of forming biogenic amines is catalysed by microbiological enzymes (carboxylase, transaminases). Formation of these substances proceeds from proteins through peptides to amino acids that are decarboxylated. Other enzymes such as oxygenase or methyltransferase may be applied to their transformation into other biologically active products (Halász *et al.*, 1994).

Histamine is the product of histidine decarboxylation in the presence of histidine decarboxylase (Figure 1). From lysine, the carboxyl group is cleaved by lysine decarboxylase and amine cadaverine is formed. Putrescine may be created by several biochemical pathways. By decarboxylation of arginine by arginine decarboxylase, agmatine and then putrescine is produced. Putrescine can also be formed by direct decarboxylation of ornithine by ornithine decarboxylase. Putrescine can be methylated by S-adenosylmethionine produced spermidine and further spermine. The tryptophan decarboxylation product by tryptophan decarboxylase activity is tryptamine, and by tyrosine decarboxylase activity is produced tyramine. Decarboxylation of phenylalanine with phenylalanine decarboxylase gives 2-phenylethylamine (Velíšek *et al.*, 1999; Buňka *et al.*, 2012; Pachlová *et al.*, 2015).

Some conditions must be met for the formation of biogenic amines in food. It is the amino acid content, the presence of microorganisms with decarboxylase activity and the appropriate conditions. Most commonly, biogenic amines are formed in fermentation processes (Miliotis *et al.*, 2003; Buňková *et al.*, 2013).

*Corresponding author: juraj.cubon@uniag.sk

Figure 1. The formation of biogenic amines (according to <http://www.vetweb.cz>).

1.2 Factors influencing biogenic amines formation

Many factors influence the biogenic amines formation, such as pH, water activity, storage time, temperature and salt content (Loizzo *et al.*, 2013). An optimal pH for decarboxylation of amino acids ranges from 2.5 to 6.5. Growth of bacteria in the acid foods stimulates the formation of decarboxylase enzymes.

Temperature is the most important factor that prevents the formation of biogenic amines. It significantly affects the enzymatic activity of microorganisms, and thus the formation of biogenic amines. Their production is related with temperature and storage time. Biogenic amines are thermostable, therefore heat treatment has a little influence on their contents (Lorencová *et al.*, 2012; Benkerroum, 2016; Ladero *et al.*, 2017).

Salts generally have an inhibitory effect on biogenic amines formation. However, it depends on the salt mixture used. It was found that the addition of nitrite salt mixture decreases growth of biogenic amines more than the same amount of standard salt (Buňková, 2010).

Of course, there are other factors influencing the formation of biogenic amines, such as starter cultures use, production hygiene, additives, and others.

Biogenic amines can also be produced by strains of LAB (lactic acid bacteria) which are commonly used for technological purposes (starter cultures) and therefore it is appropriate to test these strains for decarboxylase activity prior to use in the dairy industry. It would also be appropriate for the technological purposes to test the kinetics of biogenic amines production under similar environmental conditions that may occur during the technological process of producing fermented dairy products (Pachlová *et al.*, 2018).

1.3 Microorganisms producing biogenic amines

Decarboxylases are not common in bacteria but occur in species of many genera (Lorencová *et al.*, 2012), particularly in *Bacillus*, *Citrobacter*, *Clostridium*, *Escherichia*, *Klebsiella*,

Photobacterium, *Proteus*, *Pseudomonas*, *Salmonella*, *Shigella* and lactic bacteria of *Lactobacillus* genera, *Pediococcus* and *Streptococcus*. Some bacteria producing biogenic amines are listed in Tab. 1 (Kohajdová and Karovičová, 2001).

Another group of bacteria that is capable of producing larger amounts of biogenic amines is a group of enterococci. Enterococci have been isolated from foods that have caused poisoning by the action of biogenic amines (mainly tyramine) at high concentrations and are therefore considered to be the origin of their formation (Suková, 2003).

Table 1. Some bacteria producing biogenic amines (according to Kohajdová and Karovičová, 2001)

Food	Bacteria	Produced BA
fish	<i>Morganella morganii</i> , <i>Klebsiella pneumoniae</i> , <i>Hafnia alvei</i> , <i>Proteus mirabilis</i> , <i>P. vulgaris</i> , <i>Clostridium perfringens</i> , <i>Enterobacter aerogenes</i> , <i>Bacillus</i> spp., <i>Staphylococcus xylosus</i>	histamine, tyramine, cadaverine, putrescine, agmatine, spermidine, spermine
cheese	<i>Lactobacillus buchneri</i> , <i>L. bulgaricus</i> , <i>L. plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>Streptococcus faecium</i> , <i>S. mitis</i> , <i>Bacillus macerans</i> , <i>Propionibacterium</i> spp.	histamine, cadaverine, putrescine, tyramine, 2-phenylethylamine, tryptamine
meat and meat products	<i>Pediococcus</i> , <i>Lactobacillus</i> , <i>Pseudomonas</i> , <i>Streptococcus</i> , <i>Micrococcus</i> , <i>Enterobacteriaceae</i>	histamine, cadaverine, putrescine, tyramine, 2-phenylethylamine, tryptamine
fermented vegetables	<i>Lactobacillus plantarum</i> , <i>Leuconostoc mesenteroides</i> , <i>Pediococcus</i> spp.	histamine, cadaverine, putrescine, tyramine, tryptamine

1.4 Content of biogenic amines in cheese

Content of biogenic amines in certain foods may be very different. Typical levels of biogenic amines in foods range from 10 mg/kg to 100 mg/kg. Occasionally, the amount of biogenic amines in food can exceed 1000 mg/kg. It is very difficult to remove already formed biogenic amines from food. However, the most suitable way of producing food containing small amounts of biogenic amines is to adhere to such technological processes and hygienic conditions of production that prevent their creating (Buňková, 2010).

Natural cheeses also belong to frequent sources of biogenic amines, in particular histamine, tyramine, putrescine and cadaverine. Starter cultures, non-starter lactic acid bacteria, or other spontaneous microflora may be the source of decarboxylase (Halász *et al.*, 1994; Buňková *et al.*, 2013).

The BA (biogenic amines) concentration in fresh milk is less than 1 mg/kg. These are histamine and tyramine primarily. The histamine content in milk is 0.5 to 0.8 mg/kg, the histamine content in dried milk is 131 mg/kg, tyramine content 42 mg/kg. The BA content in cheese may be higher than 10 g/kg (Greif and Greifová, 2006).

In cheese production technology, BA can be formed in several technological operations. The quality of milk determines their presence in the cheese. Milk with a high content of decarboxylation bacteria contains a larger amount of BA. This can be avoided by heat treatment of milk.

During cheese maturation, the proteins are enzymatically degraded to free amino acids. These may be precursors to the formation of BA. Current technologies use starter cultures that do not produce BA. Non-starter bacterial contaminants are a potential risk for their formation. These are for example, heterofermentative lactobacilli, *Enterobacteriaceae*, *Hafnia alvei* and others (Benkerroum, 2016; Ladero et al., 2017). During maturation process the BA content of all cheeses increases. Their kinetics also depend on the type of cheese and the technology used. Hard cheeses contain less BA than soft cheeses.

Fresh unfermented cheeses also undergo proteolysis during storage. The production of BA is affected mainly by content of salt, protein and pH value. The content of different BA in cheese is different, each cheese has a characteristic spectrum of BA. The most occurring BA are tyramine (up to 146 mg/kg) and histamine up to 85 mg/kg. Tryptamine, phenylethylamine, putrescine, cadaverine, spermine, spermidine, adrenaline and noradrenaline were also identified in the cheeses (Kolesarova, 1995).

1.5 Effects of biogenic amines

Biogenic amines are natural antinutrients and are important in food hygiene. They have been indicated as one of the causes of many food poisons. They are able to initiate various undesirable biochemical reactions. Analyses of biogenic amines are particularly important for their use as indicators of freshness degree or food degradation (Önal, 2007).

Symptoms of high dose consumption of biogenic amines are vomiting, breathing difficulties, sweating, heart failure, hypo- or hypertension (histamine), and migraine (phenylethylamine, tyramine).

The major enzymes that degrade biogenic amines are monoamine oxidase and diaminoxidase. The activity of these enzymes is strongly influenced by the toxic effect of biogenic amines (Velíšek, 2002).

In practice, all biogenic amines are not specified, but mostly histamine is determined and limited in food. Histamine values at which signs of poisoning begin to show are above 100 mg per 100 g of food. It should be noted that there is an individual sensitivity to biogenic amines, other factors such as the amount of food consumed, the presence of other toxic substances, and so on. Therefore, it is very difficult to determine the level of toxicity of biogenic amines.

The food legislative of the Slovak Republic sets maximum limits for two biogenic amines. These are histamine (20 mg/kg in beer and 200 mg/kg in fish and fish products) and tyramine (200 mg/kg in hard cheeses).

1.6 Histamine and its effects

Under normal conditions, histamine that gets into the human gut is inactivated and does not produce any clinical signs of the disease. When large amounts of histamine are ingested, the inactivation mechanisms are broken down and histamine goes out of the digestive tract. There are two major enzymes known to metabolize histamine. It is histaminase and histamine-N-methyltransferase. The presence of other biogenic amines or the use of some drugs may inhibit the effect of these enzymes and potentiate the effect of biogenic amines. The effect of consumed biogenic amines is determined by their quantity but also by other factors (Maintz and Novak, 2007; Buňková, 2010).

Some people are hypersensitive to biogenic amines and have histamine intolerance. Histamine intolerance is manifested in individuals lacking the diaminoxidase enzyme which degrades histamine and other biogenic amines. Poisoning occurs within a few minutes to three hours after ingestion of a contaminated diet. Symptoms include headache, nausea, stomach cramps, skin

reddening, feeling sick, breathing difficulties, blood flow and seizures, feelings of hot flushes, general discomfort (Buňková, 2010; Alvarez and Moreno-Arribas, 2014).

1.7 Tyramine and its effects

Tyramine is a local tissue hormone and acts as a dopamine precursor. It causes severe headaches accompanied by frequent vomiting and elevated temperature. It rapidly increases blood pressure and acts irritant to the smooth muscles (Velíšek et al., 1999; Alvarez and Moreno-Arribas, 2014).

1.8 Putrescine and its effects

Putrescine is formed by the decarboxylation of the amino acid lysine or the amino acid ornithine. It also occurs during the proteolysis of meat. It is therefore a degradation product of proteins and its toxic effects are almost the same as for ammonia. This effect is cumulative with other amines and ptomaine. The major functions of putrescine include stabilizing macromolecules (nucleic acids), subcellular structures (ribosomes), and stimulating cell differentiation. Putrescine synergistically enhances the effect of histamine and tyramine (Buňková, 2010; Ruiz-Capillas and Herrero, 2019).

1.9 Cadaverine and its effects

Similarly to putrescine, cadaverine originates in decarboxylation of the amino acids lysine and ornithine, and by meat degradation. Its toxic effects are similar to those of ammonia. Cadaverine belongs to the group of polyamines (like spermine, spermidine and putrescine). Their biological functions include participation in cell growth and proliferation. Polyamines are also considered as potential precursors of carcinogenic N-nitrosocompounds and aromatic heterocycles (Buňková, 2010; Ruiz-Capillas and Herrero, 2019).

2. Conclusion

Biogenic amines are low molecular weight aliphatic organic compounds derived from amino acids that are commonly involved in metabolic processes in living tissues and exhibit different biological, pharmacological and physiological effects. Amines are produced by the decarboxylation of natural amino acids by the action of living organisms. At higher doses they have a negative effect on the human organism. Some biogenic amines are an essential component of living cells because they are involved in the regulation of nucleic acid and protein synthesis as well as in membrane stabilization.

The content of biogenic amines in food can vary greatly. Commonly, biogenic amines in food are in tens of milligrams per kilogram. Values in hundreds of mg/kg are considered to be high.

Under normal circumstances, biogenic amines in the digestive system are inactivated and there are no clinical signs of the disease. In the case of large intake of biogenic amines the inactivation mechanisms are broken, they get out of the digestive system. The presence of higher levels of multiple biogenic amines or the use of certain drugs may inhibit the effect of enzymes and potentiate the effect of biogenic amines. The effect of biogenic amines is determined by their quantity but also by other factors. Under normal conditions, with common consumption of foods, the concentration of biogenic amines is low and does not result into allergic reactions.

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Declaration of interest

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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