Biogenic amines formation and their importance in fermented foods

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Abstract. Biogenic amines (BAs) are low molecular weight organic bases with an aliphatic, aromatic, or heterocyclic structure which have been found in many foods. biogenic amines have been related with several outbreaks of food-borne intoxication and are very important in public health concern because of their potential toxic effects. The accumulation of biogenic amines in foods is mainly due to the presence of bacteria able to decarboxylate certain amino acids. Biogenic amines are formed when the alpha carboxvl group breaks away from free amino acid precursors. They are colled after the amino acid they originated from. The main biogenic amines producers in foods are Gram positive bacteria and cheese is among the most commonly implicated foods associated with biogenic amines poisoning. The consumption of foods containing high concentrations of biogenic amines has been associated with health hazards and they are used as a quality indicator that shows the degree of spoilage, use of non-hygienic raw material and poor manufacturing practice. Biogenic amines may also be considered as carcinogens because they are able to react with nitrites to form potentially carcinogenic nitrosamines. Generally, biogenic amines in foods can be controlled by strict use of good hygiene in both raw material and manufacturing environments with corresponding inhibition of spoiling microorganisms. The aim of this review was to give some information about biogenic amines in foods.

1 Introduction

Biogenic amines (BAs) are organic bases with an aliphatic, aromatic, or heterocyclic structure which have been found in many foods, such as fishery products, cheese, wine, beer, and other fermented foods [1, 2]. The term ‘‘biogenic amines” defines decarboxylation products such as histamine, serotonin, tyramine, phenylethylamine, tryptamine, and also aliphatic polyamines and can be ubiquitously synthesised from their aminoacidic precursors [3].

In general, the name of biogenic amines is ascribed depend upon the name of their originating amino acids. For example, histamine is the biogenic amine formed from amino acid histidine decarboxylation, tyramine is that formed from tyrosine amino acid, tryptophan is decarboxylated to produce tryptamine, phenylethylamine is that synthesized from phenylalanine, cadaverine is produced from lysine, ornithine is decarboxylated to produce putrescine, and spermine also spermidine is formed from decarboxylation of arginine [4]. Microbial fermentation is one of the oldest and most practical technologies used in food processing and preservation. However, fermentation of protein-rich raw materials such as fish, meat, and soybean commonly provides abundant precursor amino acids of biogenic amines [5].

In general, the highest concentrations of these compounds have been found in fermented products, which show a significantly higher amount than nonfermented foods [6].

Biogenic amine plays an essential role in human body like; direction of body temperature and stomach pH, gastric acid secretions, metabolic disorder and immunological arrangement of gastrointestinal tract, are active in the nervous system and in the blood pressure control [7]. Biogenic amines may also be considered as carcinogens because they are able to react with nitrites to form potentially carcinogenic nitrosamines [8]. Nitrosable secondary amines (agmatine, spermine, spermidine) can form nitrosamines by reaction with nitrite and produce carcinogenic compounds [9].

Biogenic amines accumulation in foods usually results from the decarboxylation of amino acids by enzymes of bacterial origin, which is associated with food hygiene and technology. The accumulation of biogenic amines was attributed to the decarboxylase activity of fermenting microorganisms, their occurrence would be inevitable [1]. Bacterial strains known to be capable of biogenic amines production include *Escherichia*, *Enterobacter*, *Pseudomonads*, *Salmonella*, *Shigella*, *Clostridium perfringens*, *Streptococcus*, *Lactobacillus* and *Leuconostoc* [10, 11]. The detection of biogenic amines in foodstuffs is of great interest because of their potential toxicity and can be used as indicators for nourishment quality markers [12].

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2 Physicochemical characteristics of biogenic amines

According to their chemical structure biogenic amines can be classified as aliphatic (putrescine, cadaverine, spermine and spermidine), aromatic (tyramine and β-phenylethylamine), or heterocyclic (histamine, tryptamine) structures [4]. They have also been classified into monoamine (tyramine and β-phenylethylamine), diamine (histamine, serotonin, tryptamine, putrescine and cadaverine), and polyamine (agmatine, spermine and spermidine) according to their number amine groups [13].

3 Formation of biogenic amine in foods

Biogenic amines can be present in a variety of food products, low contents of biogenic amines are natural characteristics of different foods like fruits and vegetables. Generally, almost all foods that contain proteins or biochemical activity biogenic amines can be expected [4]. In nourishment and drinks, biogenic amines are formed by enzymes of raw material or are generated by microbial decarboxylation of amino acids during maturing and storage [13]. Biogenic amines are present almost in every food in daily diet but their concentrations change extensively between and even inside sustenance sorts [7]. Biogenic amines can aggregate as the after effect of uncontrolled microbial enzymatic action [9]. During food spoilage bacteria can form a large level of biogenic amines by decarboxylation the corresponding amino acids precursors [14]. Also, the production of amines has been related to the protective actions of bacteria against an acidic milieu. For instance, lactic acid bacteria produce biogenic amines to survive during fermentation of foods such as in cheese, sausage and fermented vegetables [13, 14]. Amino acid decarboxylation takes place by removal of the alpha-carboxyl group from amino acid precursor to give the corresponding amine [8].

Species of many genera, such as *Pseudomonas*, *Clostridium*, *Bacillus*, *Photobacterium* and furthermore in variety identified with *Enterobacteriaceae* family, for example, *Escherichia*, *Klebsiella*, *Citrobacter*, *Proteus*, *Shigella*, and *Salmonella* and *Micrococcaceae* family, for example, *Staphylococcus*, and *Micrococcus*. Additionally, a considerable measure of LAB having a place with the genera *Enterococcus*, *Lactobacillus*, *Carnobacterium*, *Pediococcus*, *Lactococcus*, and *Leuconostoc* can decarboxylate amino acids [4, 13].

4 Factors affecting biogenic amines in food products

Several extrinsic and intrinsic characteristics (for example, redox potential, pH, temperature, NaCl, water activity, etc.), sanitary conditions of manufacturing practices play a significant part in the creation of biogenic amines in foodstuffs [15–17]. Elevated temperatures, lofty pH qualities, and little salt substance can support the collection of free amino acids and in this manner animate the development of biogenic amines [18]. Storage temperature is the most significant reason influencing to biogenic amines formations [19]. Amine formation is minimized at reducing temperatures by the way of prevention of bacterial development and the diminishment of enzyme activity [17].

The best temperature for the production of biogenic amines by microorganism has mainly been recommended to be between 20 to 37 °C, while the formation of biogenic amines reduces beneath 5 °C or over 40 °C [14, 20]. Besides temperature control, other factors (for example pH, water activity, redox potential, oxygen supply, nature of the food, manufacturing practices, preservatives, and additives, etc.) may have a significant effect on the creation of BAs in fermented foods [15]. pH is the main factor affect amino acid decarboxylase activity [4]. In a reduce pH climate, microorganisms are more induced to generate decarboxylase as a part of their protective mechanism upon the acidity. Nevertheless, a quick, sharp and immediate decrease in pH is known to minimize the growth of the amine-positive microorganisms [13].

Oxygen supply seems to importantly affect the biosynthesis of biogenic amines. *Enterobacter cloacae* produce about a large portion of the amount of putrescine under anaerobic as contrasted to oxygen consuming, and *Klebsiella pneumoniae* incorporates fundamentally less cadaverine, however, gains the capacity to deliver putrescine under anaerobic settings [9]. The redox potential of the medium additionally impacts biogenic amines generations. Conditions bringing about a diminished redox potential fortify histamine creation, and histidine decarboxylase movement is by all accounts inactivated or crushed within the sight of oxygen [14].

5 Detoxification of biogenic amines

In the human body, there is a detoxification system that broken-down the biogenic amines to a physiologically less active amine. The enzymes diamine oxidase (DAO) and monoamine oxidase (MAO) play an essential role in system detoxification. Nevertheless, upon intake of a high content of biogenic amines in sustenance, this detoxification framework is deactivated and not able to eliminate of biogenic amines adequately [21]. Under normal circumstances, the human body possesses detoxification systems to take care of these biogenic amines, mainly in the intestine through the action of monoamine oxidase (MAO; CE 1.4.3.4), diamine oxidase (DAO; CE 1.4.3.6), and polyamine oxidase (PAO; CE 1.5.3.11). However, in certain cases this mechanism can be hindered by a variety of factors or circumstances, and biogenic amines could accumulate in the body and cause serious toxicological problems and a high risk of poisoning [20, 22, 23]. Factors that could alter the detoxification mechanism include the consumption of amine oxidase inhibitors (mono and diamine oxidase inhibitors (MAOI/DAOI)), alcohol, immune deficiency of the consumer, gastrointestinal

disorders, large amounts of biogenic amines, for example in the case of spoiled or fermented foods, etc. [9, 22]. MAO and DAO occur in the gut epithel and thus oxidation products of biogenic amines are getting into the blood circulation. Polyamines are usually in the first place acetylated and consequently oxidized by DAO or polyamino oxidases [14, 24]. People with gastrointestinal problems (gastritis, irritable bowel syndrome, Crohn's disease, stomach and colonic ulcers) are also at risk because the activity of oxidases in their intestines is usually lower than that in healthy individuals. In women, there is premenstrual decrease in the activity of B-type MAO and this can also be a problem [14]. Patients, who are taking medicines with inhibiting effect to MAO and DAO such as antihistamines, antimalaria agents, psychopharmaceutics, might have a changed metabolism of biogenic amines, which can cause healthy problem [4, 9, 14].

6 Toxicity and health risks of biogenic amines

Biogenic amine intoxication is always related with consumption of large contents of biogenic amines in nourishment which stimulates toxicological risks and health troubles and they have psychoactive, vasoactive and hypertensive effects [14, 25, 26]. The origin of foodborne illness could be bacteria, virus, parasite, mold, contaminants, metals, allergens, pesticides, natural toxins, etc., that can contaminate food and cause disease. Nonetheless, there are cases of food poisoning that can be linked to chemical or natural toxins. From among these toxins, the FDA and EFSA pay particular attention to aflatoxins, mycotoxins, histamine. Other biogenic amines, such as spermidine or spermine, have also been associated with food allergies [22]. Toxins produced by microorganisms are responsible for several types of foodborne disease. One of these illnesses, histamine poisoning, can result from the ingestion of food containing unusually high levels of histamine. Fish of the families *Scombridae* and *Scomberesocidae* are commonly implicated in incidents of histamine poisoning, thus the term "scombroid fish poisoning" has been used to describe this type of food poisoning. However, nonscombroid fish, cheese, and other foods have also been implicated in cases of histamine poisoning [22, 24]. These amines have been studied for their potential risk for human health, since they can cause "cheese syndrome" and histamine intoxication related to tyramine and histamine, respectively. Furthermore, diamines (putrescine and cadaverine) can react with nitrites to form carcinogenic nitrosamines [27]. Histamine causes dilatation of peripheral blood vessels, capillaries, and arteries, thus resulting in hypotension, flushing, and headache. Histamine exerts its toxicity by binding or interacting with receptors on cellular membranes in the respiratory, cardiovascular, gastrointestinal and immunological system and skin [4, 14]. Histamine affected constriction of the intestinal smooth muscle, intervened by H_1 receptors, may represent stomach issues, looseness of the bowels, and regurgitating [28]. Gastric acid emission is controlled by histamine through H_2 receptors situated on the parietal cells [24]. Torment and itching associated with the urticarial lesions might be because of sensory and motor neuron incitement through H_1 receptors [28]. The histamine intoxication is conceivable to overcome by utilizing of antihistaminic medications [4]. For a long time, H_1-receptor antagonists have been accessible for the treatment of unfavourably susceptible conditions while H_2-receptor antagonists have been accessible for the treatment of gastric ulcers. By complexity, the H_3-receptor subtype was just found in 1983 and H_3-receptor antagonists were utilized for management of central sensory system issue. The role of H_3 receptors in learning and memory demonstrates that H_3-receptor antagonists could have a role in the management of memory disorders such as Alzheimer's illness [14]. The clearest manifestations of utilization of large dosage of biogenic amines are nausea, vomiting, respiratory crisis (dyspnoea), hot flushes, oral burning, withdrawal of intestinal smooth muscles bringing on stomach spasms and hyper- or hypotension [4, 29]. Psychoactive amines (for example, histamine, putrescine, and cadaverine) can bring about some neurotransmission issue because of their activity as false neurotransmitters. Some aromatic amines (such as tyramine, tryptamine and β-phenylethylamine) demonstrates a vasoconstrictor activity while others (histamine and serotonin) introduce a vasodilator in veins, capillaries, and arteries, causing headaches, hypertension, flushing, gastrointestinal misery and oedema [4, 13, 25].

7 Analysis of biogenic amines in foods

The determination of biogenic amines in different types of food is of great interest not only because of their pseudoallergic effects but also because of the levels of biogenic amines in food products often being considered as a marker of spoilage during storage or ripening. Therefore, such information can be considered as a quality index in the form of different biogenic amines indices [30]. The determination of biogenic amines and free amino acid fractions can provide useful information for the industry regarding freshness or spoilage and sanitary quality used as raw material for foods preparation. High concentrations of certain amines in food may be interpreted as a consequence of poor quality of the raw materials used, contamination, or inappropriate conditions during food processing and storage [31]. A number of swift and accurate analytical methods have been developed to determine biogenic amines levels in different foods. These methods range from the more traditional colorimetric and fluorometric methods focused mainly on determining histamine individually, as is also the case with fast commercial kits based on the Elisa enzyme immunoassay to detect histamine in fish [22]. The analytical techniques used to determine biogenic amines mainly based on chromatographic methods which include, thin layer chromatography (TLC) [8], high performance liquid chromatography (HPLC) [32]. The AOAC procedure is

the official method of analysis for histamine in foods in the U.S. [24].

8 Permissible levels of biogenic amines in foods

The toxicological level of biogenic amines is exceptionally hard to set up on the grounds that it relies on upon the capacity of detoxification arrangement of the intestinal tract of individuals and on the existence of different [4, 29]. Lawful furthest cutoff points of 100 mg histamine/kg nourishment and 2 mg/l alcoholic beverages have been recommended [4]. The European Food Safety Authority [20] reported that although a dose of 50 mg histamine is the no-observed-adverse-effect level (NOAEL), healthy individuals do not experience symptoms unless they ingest a larger amount of histamine than NOAEL The values of 100–800 mg/kg of tyramine and 30 mg/kg of β-phenylethylamine were reported to be toxic doses in food, respectively, and 100 mg histamine per kg of food and 2 mg histamine per liter of alcoholic beverage were suggested as upper limits for human consumption [33].

For phenylethylamine, legitimate breaking points of 30 mg/kg are said for foodstuffs and have been accounted for as the harmful dosage in foods [4]. An admission of 5–10 mg of histamine can be considered as surrendering to some delicate individuals, 10 mg is considered as a fair farthest point, 100 mg affect a medium poisonous quality and 1000 mg is exceptionally lethal and considered hazardous for wellbeing [4, 14]. The European Union has built up directions for histamine levels, as indicated by which histamine level ought to be beneath 100 mg/kg in crude fish and underneath 200 mg/kg in salted fish for species having a place with the *Scombridae* and *Clupeidae* families [14]. The Nutritional codex of the Slovak Republic had decided the maximal bearable farthest point for the histamine (20 mg/kg in lager and 200 mg/kg in fish and fish items), and for tyramine (200 mg/kg in cheeses) [14].

The FDA has set up a risk activity fixation for histamine in fish of 50 mg of histamine/100 g [24]. In Turkish Food Codex, 200 mg/kg of histamine is acknowledged as a deformity pointer for fishes, and 10 mg/kg for wines [34]. In German Fish Order, it is permitted upper-level histamine for Mackerel and Herring angles by 200 mg/kg [24]. From a toxicological point of view, it would be useful to produce foods with low amounts of amines to avoid potential adverse reactions [27].

9 Conclusion

It is critical to screen biogenic amines in nourishment. Daily food diet, for example, fish, meat, cheddar, aged sustenance, dairy items, wiener, eggs, matured vegetables as lager, white and red wine are subject to contain biogenic amines.

The consumption of foods containing high concentrations of biogenic amines has been associated with health hazards [22]. High concentrations of certain amines in food may be interpreted as a consequence of poor quality of the raw materials used, contamination, or inappropriate conditions during food processing and storage [31].

In fact, although several biogenic amines can play important roles in many human physiological functions, their presence in foods is always undesirable because if adsorbed at too high concentration they may induce headaches, respiratory distress, heart palpitations, hypo- or hypertension, and several allergenic disorders [35]. In the human body, there is a detoxification system that broken-down the biogenic amines to a physiologically less active amine. The enzymes diamine oxidase (DAO) and monoamine oxidase (MAO) play an essential role in system detoxification [21].

Nonetheless, these mechanisms can be affected by various factors: genetic, physiological, those arising from eating foods with high levels of amines, or those caused by the consumption of certain specific inhibitors of monoamine oxidases (drugs, tobacco, and/or alcohol). Under these conditions, biogenic amines can have direct effects on human health [1]. Particularly if the person is vulnerable (when the biogenic amines detoxification mechanism is inhibited) biogenic amines in amounts much lower than those mentioned may cause intoxications.

Therefore, biogenic amines content should be limited to a level as law as possible. For this reason, must be developed methods for preventing formation of biogenic amines that aim at eliminating the decarboxylating microbes in foods, the use of high- quality raw materials, amine negative starter cultures and processing conditions which favor growth of the starter strains; furthermore strict legal regulations have to be adapted.

References

1. E. Renes, L. Diezhandino, D. Fernandez, V.R.E Ferrazza, M.E Tornadijo, J.M. Fresno, Food Microbiol., **44**, 271–277 (2014)
2. K. Ekici, H. Okut, O. İşleyici, Y.C. Sancak, R.M. Güneş, Foods, **8**, 1–11 (2019)
3. L. Righetti, A. Tassoni, N. Bagni, Food Chem., **111**, 852–856 (2008)
4. M.H. Silla-Santos, Int. J. Food Microbiol., **29**, 213–231 (1996)
5. J.H. Mah, H.K. Park, Y.H. Jin, J.H. Lee, H.J. Hwang, Foods, **8**, 62 (2019)
6. J.L. Ordonez, A.M. Troncoso, M.C. García-Parrilla, R.M. Callejon, Anal. Chim. Acta, **939**, 10–25 (2016)
7. S.Ş. Ercan, H. Bozkurt, Ç. Soysal, J. Food Sci. Eng., **3**, 395–410 (2013)
8. A.R. Shalaby, Food Res. Int., **29**, 675–690 (1996)
9. A. Halász, A. Baráth, L. Simon-Sarkadi, W. Holzapfel, Trends Food Sci. Technol., **5**, 42–49 (1994)
10. S.F. Chang, J.W. Ayres, W.E. Sandine, J. Dairy Sci., **68**, 2840–2846 (1985)

11. M.H. Silla-Santos, Int. J. Food Microbiol., **39**, 227–230 (1998)
12. A. Önal, Food Chem., **103**, 75–86 (2007)
13. J. Stadnik, Z.J. Dolatowski, Acta Sci. Pol. Technol. Aliment., **9**, 251–263 (2010)
14. J. Karovičová, Z. Kohajdová, Chem. Pap., **59**, 70–79 (2005)
15. G. Suzzi, F. Gardini, Int. J. Food Microbiol., **88**, 41–54 (2003)
16. R. Maijala, E. Nurmi, Meat Sci., **39**, 9–22 (1995)
17. A. Naila, S. Flint, G. Fletcher, P. Bremer, G. Meerdink, J. Food Sci., **75**, 139–150 (2010)
18. J. Lorenzo, S. Martínez, I. Franco, J. Carballo, Meat Sci., **77**, 287–293 (2007)
19. P. Visciano, M. Schirone, R. Tofaloand, G. Suzzi, Front Microbiol., **3**, 1–10 (2012)
20. EFSA J., **9**, 2393–2487 (2011)
21. H.G. Schwelberger, J. Feurle, G. Houen, Inflamm. Res., **66**, 1021–1029 (2017)
22. C. Ruiz-Capillas, A.M. Herrero, Foods, **8**, 62 (2019)
23. C. Ruiz-Capillas, F. Jiménez-Colmenero, Crit. Rev. Food Sci. Nutr., **44**, 489–499 (2004)
24. J.E. Stratton, R.W. Hutkins, S.L. Taylor, J. Food Prot., **54**, 460–470 (1991)
25. H. Bozkurt, O. Erkmen, Meat Sci., **61**, 149–156 (2002)
26. J.D. Coïsson, C. Cerutti, F. Travaglia, M. Arlorio, Meat Sci., **67**, 343–349 (2004)
27. S. Novella-Rodríguez, M.T. Veciana-Nogués, A.X. Roig-Sagués, A.J. Trujillo-Mesa, M.C. Vidal-Carou, J. Dairy Sci., **85**, 2471–2478 (2002)
28. E.A. Jørgensen, U. Knigge, J. Warberg, A. Kjaer, Neuroendocrinology, **86**, 210–214 (2007)
29. T. Komprda, J. Neznalovà, S. Standara, S. Bover-Cid, Meat Sci., **59**, 267–276 (2001)
30. A. Ščavničar, I. Rogelj, D. Kočar, S. Köse, M. Pompe, J. AOAC Int., **101**, 1542–1547 (2018)
31. M. Triki, A.M. Herrero, F. Jiménez-Colmenero, C. Ruiz-Capillas, Foods, **7**, 132 (2018)
32. M. Karmi, Glob. Veterinaria, **12**, 264–269 (2014)
33. B. Ten Brink, C. Damirik, H.M.L. J. Joosten, J.H. Huis In't Veld, Int. J. Food Microbiol., **11**, 73–84 (1990)
34. Turkish Food Codex, Tebliğ No: 2002/63, Resmi Gazete, Sayı: 24885, (2002)
35. D. Restuccia, G. Spizzirri, F. Puoci, N. Picci, Food Add. Contam. Part A, **32**, 1156–1163 (2015)