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Importance and Toxicity of Biogenic Amines in Fresh and Processed Foods

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ABSTRACT

Biogenic amines are decarboxylation products of amino acids and naturally they occur in living organisms and are involved in various biological processes. Nitrogenous compounds such as histamine, tyramine, putrescine, cadaverine, agmatine, spermidine and spermine are called biogenic amines and are found in raw and processed foods. Besides its role in physiological activity in human health, high quantities in food may be hazardous. Consumption of biogenic amines beyond its maximum permissible level could result in nausea, respiratory distress, hot flush, sweating, heart palpitations, headache, bright red rash, burning sensations in the mouth and alterations in blood pressure. In addition to its toxicity, in foods containing abundant amount of protein, the high concentrations of these diamines are indicative for hygienic deficiencies in the postharvest unit operations of agricultural products. Therefore, it is crucial to control the formation of biogenic amines during food processing.

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Introduction

Biogenic amines (BA) are low molecular weight nitrogenous compounds which are essential for natural metabolic and physiological functions in living organisms. BA are produced as a result of amino acids metabolism or by some species of microorganisms [1,2]. Histamine, putrescine, cadaverine, tyramine, tryptamine, 2-phenylethylamine, spermine and spermidine are the major BA in foods which are mainly produced by microbial decarboxylation of amino acids; or by amination and transamination of aldehydes and ketones [3]. For instance, the conversion of histidine resulted in histamine formation via histidine decarboxylase; lysine to cadaverine via lysine decarboxylase; tyrosine and phenylalanine by tyrosine decarboxylase to tyramine and phenylethylamine, respectively. For putrescine formation, there are two different pathways; the first is the conversion of ornithine to putrescine through ornithine decarboxylase and second, via deamination of agmatine [4]. Spermine and spermidine are polyamines derived from putrescine [5].

BA play essential roles in several cellular processes, such as regulation of cell growth, gene expression, intracellular signaling pathways, and tissue repair and regulation of body temperature, stomach pH or brain activity [6-8]. However, exposure to elevated concentrations may result in health risks like headache, anaphylaxis, nausea, hypertension, nervous symptoms, organ failure, renal intoxication, and death [9-11]. Ingestion of high levels of histamine is associated with the onset of histamine poisoning which is characterized by hypertension, flushing, tachycardia, and gastrointestinal symptoms; and tyramine which is associated with hypertensive crisis and cardiovascular symptoms [6]. The occurrence of gastrointestinal cancer cases was reported to link with cadaverine and putrescine after being converted by the bacteria in the digestive tract into stable carcinogenic N-nitroso compounds. Besides, it was reported that the presence of putrescine and cadeverine enhances histamine toxicity, and with nitrites and nitrates in foodstuff, they also form carcinogenic N-nitrosamines via histamine oxidizing enzymes inhibition. The amount and type of BA ingested, and the individual sensitivity and health status determines the degree of BA intoxication. A range of 750–900 mg/Kg total BA level was reported to cause toxicity [12-14].

On the other hand, BA were reported to be used as an indicator of quality and acceptability criteria in some foodstuff [3,15]. A microbial activity in food product could result in higher concentrations of BA, and consequently, these foods are harmful to the health of the consumers [16]. BA formation is certain in fermented food products such as cheese, wine and beer and also commonly produced in many ready-to-eat foods and fermented soybean pastes and soy sauces [17,18]. The availability of free amino acids, the presence of decarboxylase-positive microorganisms and conditions that allow bacterial growth, decarboxylase synthesis and activity food physic-chemical parameters such as NaCl, pH and ripening temperature storage and distribution conditions manufacturing processes and manufacturing practices determines the presence and levels of BA in food products [19-23]. Certainly, the occurrence of BA seems to be quite common and inevitable in processed foods. Therefore, this review emphases on BA that can present in fresh and processed food products, its formation and biochemical properties, health benefits and toxicity, indicator as food quality and safety, production control and quantification techniques.

Biogenic Amines in Raw and Processed Foods

BA might be commonly found in fresh and processed foods and beverages. Researches revealed that BA are certainly present in grapes, raw meats and fresh milk [24-26]. A high amounts of spermidine, putrescine, and cadaverine have appeared in the seeds of grape berries and pericarp of berries during wine making process [27,28]. In fish, histamine is the most common type of BA formed due to the presence of bacteria on their gills, external surfaces, and in the gut of live fish. But, the lowest histamine level was reported in freshly caught fish, which is below 0.1 mg/100 g [29]. Nevertheless, exposure of fish to higher temperatures after fishing and before consumption may cause formation of histamine.

A range of from not detected to 200 mg/kg of putrescine has been found in fruits and nuts, with the highest levels reported in raw orange and orange juice, mandarin, grapefruit and its juice, banana, passion fruit, and pistachio and this variability might be due to the crop type, processing, transport and storage conditions [30-31]. An increase in putrescine content was noticed in different types of green leafy vegetables during storage at 5 °C and observed that there was a positive correlation between putrescine content and the total microorganism counts. Moreover, an increase in histamine content was observed in spinach samples which was stored over 12–15 days at 6 °C [32]. This could be due to a relatively high pH of the vegetable which favored the growth of gram-negative bacteria.

Because several microorganisms are involved in the fermentation process and the raw materials contain considerable amounts of proteins, fermented foods and beverages are more susceptible to formation of biogenic amines [3]. Several BA are often detected in fermented products [33]. For instance, a study revealed that a significant concentrations of putrescine and cadaverine detected in fermented meat and fish [34,35]. In addition, the level of BA in alcoholic beverages such as wine and beer has received much attention since ethanol and acetaldehyde could retard the enzymes responsible for detoxification and increase the risk to human health [36]. A range of 25 mg/Kg to 69 mg/Kg for total biogenic amine contents and 13 mg/Kg to 65 mg/Kg for tyramine content in Boza, a traditional fermented Turkish beverage [37]. Moreover, tyramine was remarked as the most abundant amine found in fermented sausages [38].

Fermented foods, for example cheese, wine, and spiced sausage were found to have histamine and tyramine in high concentrations. Ripening of cheese for 15 days showed a significant increment in BA content. During cheese ripening, the caseins are broken down by the action of the proteases and peptidases present in the cheese, eventually giving an increment of precursors of amines. For putrescine and cadaverine, respectively a values of 579.60 and 1302.86 mg/Kg reported and another study reported a range of 9.9 to 394 mg/Kg and 26.8 to 276.1 mg/Kg in samples of Italian cheese called Pecorino. However, tyramine was found at high concentration, representing more than 40% of the total amines [39-43].

It has been reported that the grape variety, soil composition and fertilization, winemaking process, microbial populations and wine oenological treatments might varied the amount of BA present in wines [19]. A range of few milligrams per liter to about 50 mg/L of total concentration of BA in red wines has been reported [20]. Red wines contain higher amounts of BA than white wines due to higher pH and the occurrence of malolactic fermentation which is much less common in white wines [19]. A values of 394, 263, and 382 mg/Kg were reported for histamine content in samples of fish sauce, fish paste, and shrimp paste, respectively [44]. The histamine content of 15.74–28.70 mg/Kg for Spanish mackerel, 26.95 mg/Kg for canned anchovies, 22.38 mg/kg for canned sardines, and less than 10 mg/Kg for other canned samples tested [45]. A histamine content of 155–579 mg/Kg in fermented fish products made from anchovies whereas Huang et al. reported a range of 63.1–479.0 mg/Kg histamine in dried fish products [46,47].

Table 1: The Maximum Allowable Level of Bas in Some Food Products

Biogenic amines	Type of food products	Max. permissible level (mg/Kg, mg/L)	Reference
Histamine	Fish and fish products Fish sauce Alcoholic beverages Any food	50 50-200 200 400 2 100	FDA, 2011 [42] Shalaby, 1996 [3] WHO, 2013; [51] Codex, 2012 [52] Codex, 2012
Tyramine	Fish	100	FDA, 2011 [42]
	Any food	100-800	Nout, 1994 [49]
Putriscine	Sauerkraut	140	Rauscher-Gabernig et al., 2012 [53]
	Fish	170	
	Cheese	180	
	Fermented sausages	360	
	Seasonings	510	
Cadaverine	Sauerkraut	430	Rauscher-Gabernig et al., 2012 [53]
	Fish	510	
	Cheese	540	
	Fermented sausages	1080	
	Seasonings	1540	
β-phenylethylamine	Any food	30	ten Brink et al, 1990 [48]
Total BAs	Fish	1000	FDA, 2011 [42]
	Any food	750	Ladero et al., 2010 [14]

Biochemical Properties and Formation of Biogenic Amines

As it has been discussed earlier elsewhere in the introduction section of this review, amines are basic nitrogenous compounds in which one, two, or three atoms of hydrogen in ammonia are replaced by alkyl or aryl groups. To highlight, the formation of BA occurs via decarboxylation, transamination, reductive amination, and degradation of certain precursor amino compounds [55] (Figure 1). Researches shows numerous factors could influence BA formation and can be divided into three main groups, namely raw materials composition, microorganisms causing decarboxylase activity, and processing and storage conditions [6,54,56]. The combined effects of these factors determine the final concentration of BA in food. Naturally, foods may contain free amino acids or the free amino acid may be liberated by proteolysis during processing and/or storage. The decarboxylase-producing microorganisms could be part of the associated flora of a food or may be introduced by contamination before, during or after processing. BA formation depends on the availability of the free amino acids and the environmental conditions which favor the decarboxylation activity [57]. The starter cultures applied to the foods and beverages for fermentation could contribute to the production of biogenic amines in the case of fermented foods and beverages [58].

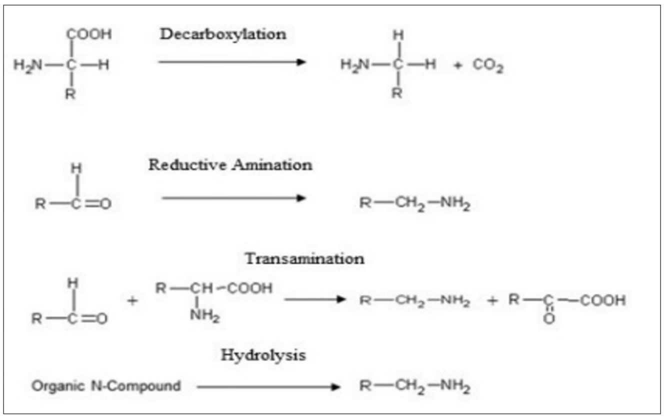

Figure 1: The Main Enzymatic Reactions for the Production of Bas

As it is shown in Figure 2, the names of BA originated from its corresponding amino acid. Histidine, tyramine, tryptamine, and β-phenylethylamine are formed by decarboxylation of histidine, tyrosine, tryptophan, and phenylalanine, respectively. By arginine decarboxylase enzyme, arginine can be converted to agmatine or can be degraded by arginase to ornithine from which by decarboxylation putrescine is formed. By lysine decarboxylase lysine is decarboxylated into cadaverine, and when the content of lysine content is high and ornithine is low, it can also be produced by ornithine decarboxylase [59]. Spermine derives from spermidine, which comes from putrescine by spermine synthase and spermidine synthase, respectively.

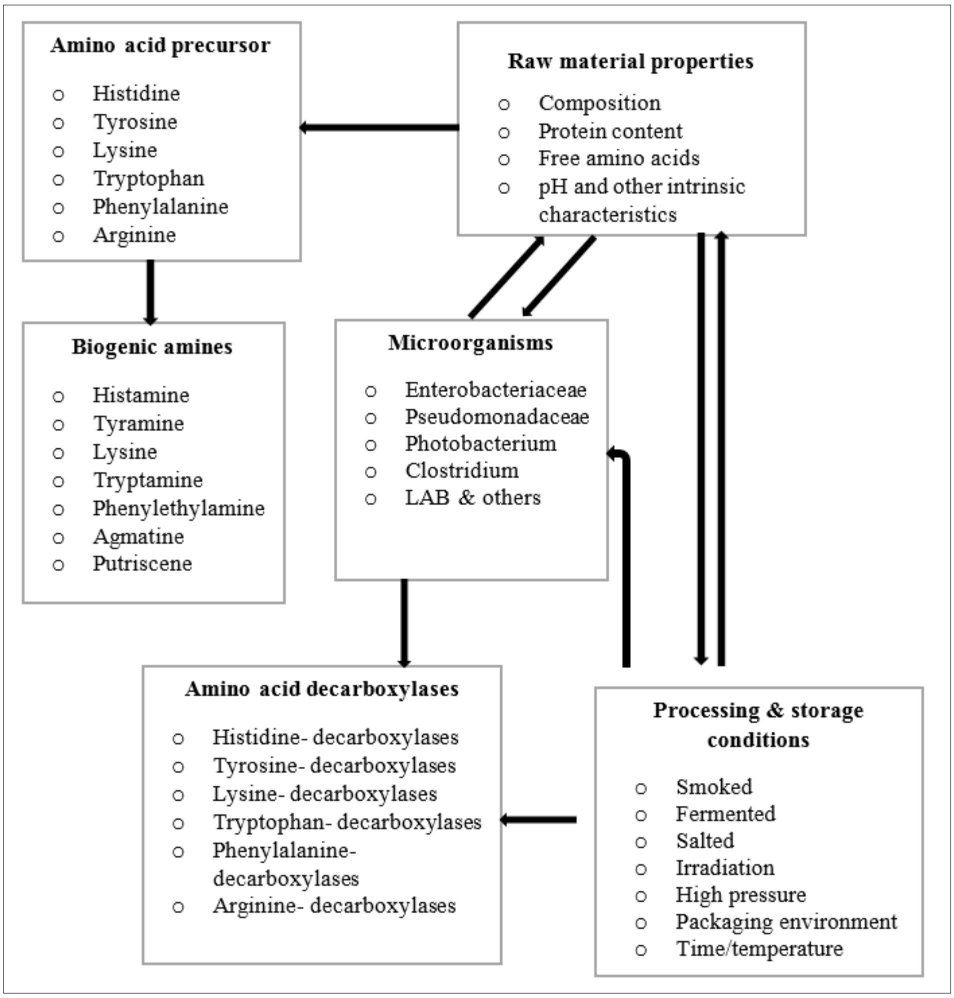

Figure 2: Biogenic Amines Formation and Factors Influencing Its Formation

According to its chemical structure, BA can be classified as aliphatic (putrescine, cadaverine, spermine, and spermidine); aromatic (tyramine and phenylethylamine); and heterocyclic (histamine and tryptamine). Besides, based on the number of amine groups it can also be classified into monoamines (phenylethylamine and tyramine), diamines (cadaverine and putrescine), or polyamines (spermidine and spermine) [18].

Effect of Fermentation on the Ba Content of Foods

In the history of food processing and preservation technologies, fermentation particularly microbial fermentation is one of the oldest and most practical. Fermentation of fish, meat, and soybean which are protein-rich raw materials commonly provides abundant precursor amino acids for BA. Dairy products commonly contain histamine, tyramine, putrescine, and cadaverine. In cheeses, the presence of free amino acids decarboxylating microorganisms and the synergistic effects of microorganisms and free amino acids, pH, salt, and ripening temperature were factors reported to affect the production of biogenic amines. Similarly, wine contains histamine, tyramine and putrescine in higher concentrations in wine, but cadaverine, phenylethylamine and isoamylamine in smaller amounts [60-63].

Biological Importance of Biogenic Amines

BA are endogenous and indispensable components of living cells, and therefore fruits, vegetables, and grains contain different levels depending on their variety, maturity and cultivation condition [64]. Because human intestinal monoamine oxidase (MAO), diamine oxidase (DAO) and polyamine oxidase (PAO) quickly metabolize and detoxify the BA, its usual ingestion generally causes no adverse reactions.

BA have an important biological roles for the synthesis of hormones, alkaloids, nucleic acids, and proteins, and in the human nervous system as neurotransmitter and the cardiovascular system in controlling blood pressure, and play a significant role in the regulation of body temperature and digestion [3,65,66]. For example, in regulating nucleic acid function, protein synthesis, and the stabilization of membranes putrescine, spermidine, spermine, and cadaverine are essential [67]. Spermine and spermidine are involved in the regulating DNA transcription, RNA translation, cell growth and proliferation, protein biosynthesis, the modulation of kinase activity, the activity of ion channels, apoptosis, and in adjusting the immune response. In addition, BA play a role in the growth, maturation, and regeneration of intestinal cells, and possess potent antioxidant activity at physiological concentrations, preventing the damage of cell membranes and DNA [68,69].

Biogenic Amines as an Indicator of Food Quality and Food Safety

The presence and an increase of BA in foods is a concern to food quality and safety, as it serve as a useful indicator of food spoilage [57]. The biogenic amines index (BAI) and quality index (QI) have been used to evaluate the freshness/spoilage of meat products [70]. BAI is the sum of histamine, putrescine, cadaverine and tyramine, and QI is the ratio of (histamine + putrescine + cadaverine) and (1 + spermidine + spermine). Individual BA or a combination of various amines, have likewise been used as a quality index [71-73]. In foods such as meat, fish, and wines BA have been frequently employed as quality indexes to signal foods degree of freshness or deterioration. For instance, in meat and meat products the level of BA has been used as a quality index of undesirable microbial activity as well as for a good manufacturing practice judgment [74,75].

Among the amines, cadaverine was reported to be a reliable spoilage indicator of poultry meat whereas histamine has been observed as an index of the fish quality, primarily dark-muscle fish [76-78]. Total biogenic amines content in food considered as dangerous is 1000 mg/Kg [6]. Shalaby suggested levels of few amines as parameters for the evaluation of good manufacturing practices (GMP): tyramine 100-800 mg/Kg, histamine 50-100 mg/Kg, phenylethylamine <30mg/Kg, while Eerola et al. proposed that the sum of tyramine, histamine, tryptamine, phenylethylamine as a possible indicator of hygienic conditions and good manufacturing practices in the sausage production, which should not exceed 200 mg/Kg [3,79].

The level of amines naturally present in grapes are an important quality and safety parameter in wines. The quantity of BA in the wine is closely related to the microbiota that the amino acid composition of the wine, and the metabolism of yeast and bacteria [80,81]. During secondary fermentation, BA in wines is significantly increased by lactic acid bacteria.

Toxicity of Biogenic Amines

A small concentration of BA in food are not considered as a serious risk. However, they may cause pharmacological, physiological and toxic effects when consumed in large quantity. This might be due to the over-saturation of amine-metabolizing enzymes and/or the impaired metabolic activity by specific inhibitors. Histamine, tyramine and β-phenylethylamine may cause food intoxication and in turn be considered to be toxic substances in humans. Despite the fact that most fermented foods have been found to be beneficial to human health, BA produced through fermentation may cause intoxication [82]. Common forms of allergy-like symptoms such as tingling and burning sensations around the mouth, facial flushing, sweating, nausea, vomiting, headache, palpitations, dizziness, and rash are reported to be an indicator for the toxicity of BA [14].

Due to the effects and functions of histamine in various organs and systems of the body, the symptoms of histamine intolerance are many and highly variable. Its symptom ranges from gastrointestinal (abdominal pain, diarrhea, vomiting), dermatological (urticaria, dermatitis, or pruritus), respiratory (rhinitis, nasal congestion, and asthma) to cardiovascular (hypotonia and arrhythmias), and neurological (headaches), and sometimes more than one disorder could occur simultaneously [83,84]. Research revealed that tyramine could cause food intoxication in ripened cheeses affecting health due to its capacity to potentiate sympathetic cardiovascular activity by releasing noradrenaline, called cheese reaction [85-87]. On the other hand, the administration of spermine and spermidine in animals resulted in an acute decrease in blood pressure, respiratory symptoms, and nephrotoxicity [68]. In addition, they also involved in carcinogenesis, tumour invasion, and metastasis [69].

Normally, BA are metabolised in the intestinal tract by the activities of enzymes. However, the toxicity of BA is subject on the affectivity of detoxification of individuals. Alcohol, acetaldehyde and anti-depressive drugs may interfere with the amino oxidase enzymes activities [48]. Histamine metabolism can be inhibited by tyramine, putrescine and cadaverine by competing for binding sites in the gastrointestinal tract or by saturating the activity of mono- or diamine oxidases [88].

Tyramine levels of 100-800 and 30 mg/Kg of β-phenylethylamine have been reported to be toxic in foods [48]. A total BA level of 1,000 mg/Kg in food is considered to be harmful to human health. Histamine intake higher than 100 mg/Kg may cause intensive poisoning [89]. Til et al. observed the oral toxicity levels for putrescine, spermine, and spermidine were 2000, 600, and 600 ppm, respectively in rats fed a mixture of cereal based diet with BA [90]. But, ingesting greater than 2000 ppm of tyramine and cadaverine could cause acute toxicity. Studies have identified that histamine is the cause of scombroid food poisoning [91].

BA Production Control Mechanisms

BA production can be monitored by several techniques. Hindering microbial growth or inhibiting the decarboxylase activity of microbes is a major method through which BA formation can be controlled. In most cases, formation of BA is temperature dependent and is the most important factor contributing to its formation [92]. Therefore, for stored foods strict adherence to the cold chain is crucial [93]. Research revealed that BA forming bacteria such as Morganella morganii and Proteus vulgaris in skipjack tuna (Katsuwonus pelamis) were inhibited through chilling [94]. For example, yellowfin tuna stored at 0 °C and 22 °C up to 9 days, showed an increase in histamine of 15 ppm at 0 °C and 4500 ppm at 22 °C [95]. Preserving with NaCl and other additives may influence the variation of microbiota composition [96]. Moreover, advanced techniques such as vacuum and modified atmosphere packagings represent popular preservation methods which may prolong the lag phase of microorganisms with amino acid decarboxylase activity [92]. Nieto-Arribas et al. reported that BA accumulation in food can be inhibited by using high quality raw material, controlled temperature, and amine-negative starter cultures [97]. A non- significant change was observed by boiling as BA are heat stable compounds [98,99]. Furthermore, the use of plant extracts in various foods and beverages contributes to a reduction of BAs. A study demonstrated that grape seed extract had a powerful effect on reduction of total BA content of tarhana, a traditional cereal based fermented food produced from cereal flours, yoghurt, vegetables, yeast and spices by lactic acid and yeast fermentation [100].

BA Quantification Techniques

For detection and quantification of BAs in foods various analytical methods which have a difference in sensitivity, selectivity, and ease of sample preparation, speed of separation and cost of analysis are used. Some of them are gas chromatography, reversed phase HPLC or HPLC equipped with fluorescence or ultraviolet (UV) detector, capillary electrophoresis (CE), enzymatic methods and immunoassays [17,101-103] . However, as both HPLC and CE derivatization step is time consuming and may reduce the accuracy of measurements, the use of ultra-high performance liquid chromatography (UHPLC) markedly reduced the elution times of BAs compared to the separation times of HPLC [104]. CE is a good alternative to HPLC and UHPLC as it provides the same high speed separations as UHPLC and has additional high separation efficiency and low running costs. Recently, a combination of laser-induced fluorescence detector (LIF) detector with CE separations have provided remarkable improvements in the sensitivities of CE analysis for BAs [10,107].

Conclusion

BAs naturally exist on raw foods even though the concentration is low enough compared to fermented foods. Processed food is more susceptible to contamination by BA-producing microorganisms at different points of the food chain. High levels of BAs can be prevented through the application of good hygiene practices and proper temperatures during handling, delivery and storage. It is important to control and monitor biogenic amines not only for toxicological and health reasons as mentioned above, but also because they may play an important role as quality and/or acceptability indicators in some foods, and managing this quality is also a way to guarantee and ensure food safety.

Conflict of Interest

The author declares no conflict of interest.

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