

Are consumers aware of the risks related to Biogenic Amines in food?

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Food-fermenting lactic acid bacteria (LAB) are generally considered to be not-toxinogenic and not-pathogenic. Some species of LAB, however, can produce biogenic amines. Biogenic amines (BA) are organic, basic, nitrogenous compounds, mainly formed by the decarboxylation of amino acids. BA are present in a wide range of foods and can occasionally accumulate in high concentrations. The presence of BA in foods has traditionally been used as an indicator of undesired microbial activity. Relatively high levels of certain BA have also been reported to indicate the deterioration of food products and/or their defective manufacture. The consumption of food containing large amounts of these amines can have toxicological consequences. Although there is no specific legislation regarding BA content in many fermented products, it is generally assumed that they should not be allowed to accumulate. The ability of microorganisms to decarboxylate amino acids is highly variable, often being strain-specific. Therefore, the detection of bacteria possessing aminoacid decarboxylase activity is of main importance to assess the risk of foods to contain biogenic amine and to prevent their accumulation in food products.

Key words: Biogenic Amine, Food fermentation, Lactic Acid Bacteria.

Introduction

Biogenic amines (BA) are naturally occurring low molecular weight compounds in humans. They are involved in natural biological processes such as synaptic transmission, blood pressure control, allergic response and cellular growth control. Nonetheless, BA may be hazardous to human health if their levels reaches a critical threshold. The main source of exogenous amines is dietary, through the uptake of food containing high concentrations of these molecules [1-3].

The most important BA found in food are histamine, tyramine, putrescine and cadaverine which are produced by microbial transformation of amino acids during fermentation or spoilage processes [4]. Lactic acid bacteria (LAB) are the main cause of BA production within fermented foods [5]. Between LAB, strains belonging to the genera *Lactobacillus*, *Enterococcus*, *Carnobacterium*, *Pediococcus*, *Lactococcus* and *Leuconostoc* may be able to decarboxylate amino acids in several foods like cheese, fermented meat, vegetables and beverages [6-8]. *Enterobacteriaceae* belonging to the genera *Citrobacter*, *Klebsiella*, *Escherichia*, *Proteus*, *Salmonella* and *Shigella* are associated with production of considerable amounts of putrescine, cadaverine and histamine in fish and meat products or, more generally, in spoilage food [2, 9-11]. Decarboxylase activity was observed in some species belonging to the genera *Micrococcus* and *Staphylococcus* in fermented sausages [12-14]. BA production ability was found to be both species- and strain-dependent [7]. Some authors suggested that the genes encoding for the BA-producing pathway may also be transferred by mobile elements [15, 16].

In general, histamine, tyramine and tryptamine, formed by decarboxylation of corresponding amino acids, are directly responsible for food poisoning [17, 18]. Putrescine, a catabolic product of ornithine or arginine pathways, can be converted in spermidine that can form spermine, being these three molecules interconvertible [19]. Putrescine, spermidine, spermine and cadaverine, also known as polyamines, are mainly indicative of undesired microbial activity [1, 20].

The BA production was suggested as a microbial strategy to survive to acidic environments or to supply alternative metabolic energy when bacterial cells are exposed to suboptimal substrates conditions [21]. In the pathway of amino acid catabolism, generally, the combined action of decarboxylases and a functional substrate/product transmembrane exchanger, results in a proton motive force which generates alkalization of the cytoplasm [22]. The developing of a pH gradient across membrane is associated to metabolic energy production and would be particularly important to microorganisms lacking a respiratory chain for generating high yields of ATP [23].

During food processing, the BA formation is possible only when three conditions are realized: availability of free amino acids; presence of microorganisms with appropriate catabolic pathway; environment which is favourable to the decarboxylation activity [5].

Prompted by the increasing awareness of the risks related to dietary uptake of high BA loads, in this review we report about BA toxicological effects on the human health. An overview of the symptoms and clinical response in the major BA-poisoning events is integrated with a discussion on the main microbiological and technological aspects affecting BA levels during food-processing.

Toxicological effects

Although BA are involved in important physiological processes, high levels in the organism represent a direct threat to human health [2]. The key issue is therefore a correct functioning of the detoxification system, to prevent their accumulation. The catabolic pathway of BA is generally regulated by mono- and di-amine oxidase (MAO and DAO) enzymes. Alternatively, histamine and tryptamine can be removed by specific amine methyltransferases (MT) [24]. The gastro-intestinal tract is the most important source of exogenous BA. Indeed, the higher activity of BA detoxification system were measured in gut lumen and liver. In normal physiological conditions the enzymatic barrier, localized in the intestinal epithelial cells, is considered to play a protective role against the resorption of dietary BA [25, 26]. However, in individuals with a pathological reduction of AO activities, the ingestion of food products containing excess of BA may cause adverse reactions [27, 28]. In addition, substances such as ethanol and some drugs compete or inhibit enzymes of the BA catabolic pathways and may thus interfere with their degradation [29, 30].

Among BA, histamine is extensively reported to play an important role in food poisoning incidents [1, 18]. Histamine acts as neurotransmitter and vasodilator on the central nervous system and on the cardiovascular system, respectively. High histamine levels can induce migraine, headaches [31], vertigo, nausea, vomiting, hypotension, arrhythmia, anaphylaxia [32]. Histamine excites the smooth muscles of the uterus and gastrointestinal tract, often enhancing the release of acid secretion from the gastric mucosa, provoking dysmenorrhea, cramps, stomach ache and diarrhea [32, 33]. Nose congestion, rhinorrhea, and sneezing may occur as a result of histamine-mediated stimulation of mucus secretions and endothelial permeability of the airway. Besides, typical symptoms of histaminosis are the simil-allergic responses of skin, including flush, pruritus and urticaria [32].

Tyramine, tryptamine, and β -phenylethylamine are included in the group of vasoactive amines [1]. Tyramine promotes the efflux of catecholamines from the sympathetic nervous system and the adrenal medulla and may cause an increase of the mean arterial blood pressure and heart rate by peripheral vasoconstriction, resulting in hypertensive crisis [34]. Tyramine also dilates the pupils and the palpebral tissue, causes lacrimation and salivation, accelerates respiration and increases the blood sugar content [1, 35].

Unlike histamine and tyramine, which may cause food poisonings, polyamines are generally not hazardous for human health at the levels of ordinary dietary intake [36]. However, putrescine and cadaverine in particular, may enhance histamine toxicity by inhibiting its catabolism [2]. In addition, since polyamines are involved in cell proliferation, they have been associated with cancer growth and development [37-39]. Evidences of a positive correlation between cancer occurrence and polyamines concentration, are extensively reported [40-42]. As well, polyamines can act as possible mutagenic precursor by formation of carcinogenic N-nitrosamine, such as N-nitrosopyrrolidine or N-nitrosopiperidine, when exposed to nitrite [1, 2, 43].

Scombroid poisoning and fish

Scombroid fish poisoning, also known as histaminosis, is a food-borne illness caused by consumption of fish containing high concentrations of histamine [18, 44, 45]. This disease state occurs generally after consumption of tuna and other fish belonging to the Scombridae and Scomberesocidae families, such as mackerel, bonito and saury that contain high levels of free histidine in their muscles. However, many clinical cases of scombroid poisoning have been also reported with nonscombroid fish, such as bluefish, mahi-mahi, sardine, anchovy, herring, and marlin [46-49].

The European Union regulations stipulate that the critical levels of histamine is 200 mg/kg or 100 mg/kg according to whether the products have undergone enzyme maturation treatment in brine or not [50]. In the United States, a more stringent level of 50 mg/kg is established [51]. However, a histamine concentration of 1270 mg/kg is reported in mackerel [1]. Besides fish, even cheese can be associated to histamine poisoning. Some cases have been reported in the Netherlands, United States, France and Canada that have involved Swiss cheese and aged Cheddar cheese that contained up to more than 100 mg histamine for 100 g of cheese [17].

Histaminosis symptoms occur up to few hours after the poisoning and resemble an allergic reaction [52]. The main clinical manifestations affect the skin (rash, urticaria, oedema and localised inflammation), the gastrointestinal tract (nausea, vomiting, diarrhoea), the haemodynamic (hypotension) and neurological functions (headache, palpitations, tingling, burning, itching) [18]. The most frequent symptoms reported by Lavon et al., [53], included rash, flushing, gastrointestinal complaints and headache. In previous clinical studies, the sign described were similar, with a widespread incidence of diarrhea and skin rush [54-58]. Although scombroid fish poisoning is a mild illness that is resolved with the administration of antihistamine drugs, in severe cases serious complications such as bronchospasm, cardiac and respiratory distress may develop in susceptible individuals [59-60].

Histamine accumulates in fish as a consequence of the microbial decarboxylation of histidine, which is mainly carried out by gram negative bacteria [61-64]. Even if histamine is the most abundant BA in fish, other amines can be generated during the storage [65]. However, only the strongest histamine producers *Hafnia alvei*, *Morganella morganii*, *Klebsiella pneumonia* and, more recently, *Photobacterium phosphoreum* have been isolated from fish incriminated of scombroid poisoning incidents [66, 67].

Several study report the effects of storage time and temperature on the microflora and consequent BA production [68-70]. Although the control of temperature plays an essential role during the storage of fish by inhibition of mesophilic microorganism growth, the occurrence of psychrotrophic bacteria can result in biogenic amines formation also in properly chilled-store samples [67, 71, 72]. Recently, *Morganella psychrotolerans* sp. nov., capable to produce toxic concentrations of histamine at 0-5°C was identified [73]. In another study, Kanki et al. [74], suggested that the enzymatic activity of histidine decarboxylase was responsible for histamine formation and its action could continue even after the bacterial autolysis.

Cheese reaction and dairy products

The cheese reaction is a pathological condition that is commonly associated to adverse interaction between monoamine oxidase inhibitors (MAOIs), a class of antidepressant drugs, and high amounts of dietary tyramine [75, 77]. MAOIs hamper the catabolic pathway of serotonin, relieving the depressive crisis of patients. An adverse side effect is the concurrent failure to inactivate the potent vasopressor tyramine [78]. The resulting hypertensive reactions in more severe cases can lead to stroke and death by brain hemorrhage [79-81].

An ordinary meal contains only 40 mg of tyramine, but in normal physiological conditions up to 400 mg of tyramine can be ingested without causing hypertensive reactions. However, when MAO are irreversibly inhibited, an intake of 8 mg of tyramine is sufficient to increase blood pressure [82, 83]. Though events of similar hypertensive crisis were reported also following consumption of meat products [84, 85], fruit [86] and alcoholic beverages [87], the main dietary intake of tyramine is with cheese [17, 88].

BA are often distributed unevenly within the cheese, depending by several production conditions [89]. Proteolysis is a crucial factor, because it is directly related to availability of free amino acids that provide a rich substrate for BA formation. It was reported that conditions of accelerated or enhanced proteolysis resulted in a dramatic increase of BA during cheese ripening [90-92]. Novella-Rodríguez et al. [93] found that aged, hard cheeses always contained higher levels of BA than unripened cheeses.

Another critical issue is the occurrence of microflora able to transform the free amino acid into the correspondent BA. In cheese, the main microorganisms with decarboxylase activity belong to the genera *Enterococcus* and *Lactobacillus*. In particular, *Enterococcus faecalis*, *Enterococcus faecium* and *Enterococcus durans* strains are considered very strong tyramine-producers [94, 95]. The ability to form histamine, tyramine and putrescine by *Lactobacilli* is not uniformly shared. Strains of *Lactobacillus buchneri*, *Lactobacillus curvatus* were identified as histidine decarboxylase-positive, while *Lactobacillus brevis* and *Lactococcus lactis* were capable to produce tyramine [90, 96]. Tyramine and putrescine were the main BA in mature samples [97], histamine was detected at the end of cheese ripening process [98] and cadaverine has been described as the most abundant BA in Brazilian cheeses [99].

In addition, the combined effect of temperature, salt concentration and pH may further affect the BA production [100]. Therefore, although tyramine is the most frequent BA found in cheese, reaching levels higher than 1000 mg/kg [101], it is difficult to correlate BA concentration with microorganism content.

Biogenic amines and fermented beverages

Fermented beverages represent an important category of foodstuff that can supply significant quantities of BA [102]. Since alcohol is an inhibitor of MAOs, the control of BA in fermented beverages is of considerable importance for consumer's health. BA in wine could also cause commercial import and export difficulties. Certain countries legislation allow the rejections of wines with histamine content higher than legal limits. The upper limits for histamine in wine in some European countries are (mg/L histamine): Germany (2), Holland (3), Finland (5), Belgium (5 to 6), France (8), Switzerland and Austria (10) [103].

Although BA content in wine can vary over a wide range depending on several oenological factors, histamine, tyramine and putrescine are the most abundant BA commonly found [104]. Phenylethylamine and cadaverine were also frequently found, but at lower concentrations [105]. A similar chemical profile was described in cider [106,107]. Putrescine, cadaverine and tyramine are the most representative BA in beer [108, 109].

In wine, the levels of BA, relatively low at the end of alcoholic fermentation, could raise up during malolactic fermentation, suggesting that LAB (but not the yeasts), were responsible for their production. It was proposed that the bacteria exploit the decarboxilation of amino acids as a system for extracting as much metabolic energy as possible from their substrates and allowing to survive the harsh environment of wine [110]. *Oenococcus*, *Leuconostoc*, *Lactobacillus* and *Pediococcus* spp. are the predominant bacterial microflora in wine [8, 111]. For a long time the formation of histamine was attributed to contamination of spoilage *Pediococcus* strains [112]. Instead, in recent years, it has been reported that some *Oenococcus oeni* strains are responsible for histamine accumulation in wine [113, 114]. Molecular methods for the detection of histamine-producing LAB were reported [115], while strains of *Leuconostoc mesenteroides*, *Lactobacillus brevis* and *Lactobacillus hilgardii* were found to be able to produce high levels of

tyramine and putrescine [116, 117]. At present, antimicrobial compounds (e.g. sulphite) represent the only alternative to control the potential problem of BA, by inhibiting the growth of BA-producing microorganisms [103].

Control of biogenic amines in food

Although at present a shared regulation limiting the amounts of BA in foods is still lacking, their presence beyond the limits recommended or suggested by scientific literature may have negative commercial implications. Since the reduction of BA content for the food industry represents a challenge for the future, efforts should be addressed to optimize the technologies that may aid in controlling their formation [118, 119]. The development of analytical standard methods for determination of BA in foodstuff is of great interest not only due to their toxicity, but also because they can be used as food quality markers, allowing BA monitoring from raw materials to processed food [120].

In parallel, methods for the detection of BA-producing bacteria have been developed, to estimate the risk of BA-food content and to prevent their accumulation in food products. In the last years, molecular-based techniques, such as PCR and DNA hybridization, allowed a faster detection and identification of food-borne bacteria and the introduction of early control measures to avoid the development of these bacteria [121, 122]. However, adherence to good hygiene practices, in both raw material and manufacturing environment, is always the best recommendation to reduce the risk of microbial contamination [2, 123]. The selection of microflora involved in the fermentation process is also advised, by adopting microbial starters lacking the pathways to degrade the amino acids [8, 124, 125]. Leuscner et al., [126], proposed to prevent an accumulation of biogenic amines by inoculation of histamine- and tyramine-degrading bacteria. Alternatively, the use of bacteriocin-producing LAB has been advocated, in order to inhibit growth of histamine-producers in cheese [127].

During the manufacturing of food, all the operations leading to an increase of substrates or to favourable conditions for microbial growth, should be limited or avoided. For example, typical oenological practices such as maceration or prolonged contact with yeast lees enhance the amount of free aminoacids, resulting in a worse quality of wine [128]. The control of parameters such as temperature, pH, salt concentration, presence of organic acids, is extensively reported to influence bacterial growth and their metabolic activities [100, 129, 130]. Prolonged storage periods make the food more susceptible to amine formation [131, 132]. For this reason, low temperatures should be applied during storage to inhibit proteolytic and decarboxylase activity of bacteria [72, 133]. In the last years, in order to minimize the risk of toxicological events, the maintenance of cold chain coupled with the use of a modified atmosphere, vacuum packaging or oxygen scavenger, is emerging successfully [65, 134, 135].

Consumer awareness

Attention to the poisoning by BA has been recently increasing, with the aim of ensuring consumer safety. However, the wide variation in clinical response, depending on many factors, both technological and physiological, results in a confused awareness of consumers to the problem. Consequently, the ingestion of food containing high levels of BA is generally underestimated and poorly understood.

Indeed, though the incidence of BA is worldwide-reported and extensively discussed in scientific works, at present, a specific legislation concerning the maximum concentrations of BA in food is still lacking. While for fish products there are clear limits for histamine, upper levels for BA in other foods have only been recommended or suggested [136].

On the other hand, BA-foodborne intoxications are generally under-reported. Several cases are missed because of the usually mild nature of the disturbances, for which patients do not to seek medical attention, or because, due to resemblance to allergic reaction, they may be misdiagnosed [18, 53]. In addition, many countries do not have adequate systems for reporting foodborne diseases and do not keep official records on poisoning incidents. Therefore, although the most frequent events are reported in Japan, United States and Great Britain, it is very likely that many incidents in other countries are underdetected [18].

Another critical question is the wide variation of the clinical response depending on the amount of ingested BA and on the individual susceptibility. Large quantities of BA are not harmful if they are quickly and properly removed from detoxification system. However genetic characteristics, health state, metabolic alterations, age and inhibition by simultaneous consumption of alcoholic beverages, other food components or some drugs, can decrease the activity of intestinal AO and MT.

In addition to the diet, the gut microflora may also contribute to the formation of BA in the intestinal lumen. Moreover, LAB are known for their high resistance to the gastrointestinal stress and frequently can have adhesive properties that allow them to colonize the intestinal tract [137]. Less visible is the threat formed by the BA producing organism that comes with the food and, in principle, introduces the capacity to form BA *in situ* even if the food product itself does not contain high BA levels.

Despite the average levels of BA uptake with a normal diet have been reported [36, 138], the amounts supplied from a single meal have not been evaluated yet. Therefore, while it is known that some foodstuff may be potentially at risk, large differences in BA content are found in the same categories of foods. On the contrary, foodstuffs containing high

levels of BA, such as histamine or tyramine, don't produce “off-flavors”, making the consumer unable to distinguish an altered product. As well, even if the analytical detection of some BA is performed, the existence of suspected enhancer compounds is not verified yet. Thus, when subjected to particular physiological or pathological conditions, the only recommended solution is a dietary restriction, by avoiding the intake of food at higher risk.

Conclusions

Safety is the basic requirement that must be always satisfied in food production. Although high levels of BA are strongly related to consumer health, their concentrations in food have not yet been adequately standardized by regulatory agencies. Currently, there is no common legislation defining the limits of BA tolerance in foodstuff. BA levels are unevenly distributed within food, but a more severe control should be exercised on fermented products of regional origin or obtained with traditional methods. It is considered that the occurrence of BA-foodborne poisoning is generally underestimated because of under-reporting or misdiagnosis. We believe that the scientific dissemination of the mechanisms that determine the formation of BA in food and the risks associated with their ingestion, may contribute to increase the awareness of the operators involved, encouraging a more responsible consumption and a production of higher quality and safety.

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