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Review

The problem of biogenic amines in fermented foods and the use of potential biogenic amine-degrading microorganisms as a solution

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Biogenic amines (BA) are low-molecular-weight nitrogenous organic bases, which can accumulate in high concentration in food due to microbial activity and cause toxic effects in consumers. In some fermented foods it is difficult to prevent the accumulation of BA since the microbiological/chemical/physical conditions of the fermentation can not be easily modified. An alternative in such cases is the use of food microorganisms that are able to degrade BA once they have been synthesized in the food matrix. In this review, we examine the microorganisms that have demonstrated the ability to degrade BA and their technological relevance in fermented foods.

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Introduction

Biogenic amines (BA) are non-volatile low-molecular-weight nitrogenous organic bases, derived through decarboxylation of corresponding amino acids. They can be both formed and degraded as a result of normal metabolic activities in humans, animals, plants and microorganisms. The responsible enzymes, amino acid decarboxylases, are widely present in spoilage and other food microorganisms, i.e. naturally occurring and/or artificially added lactic acid bacteria (LAB) involved in fermentation in foods and beverages.

The primary relevance of BA is that the consumption of foods or beverages containing a high concentration may cause food intoxication with symptoms including flushes, headaches, nausea, cardiac palpitations, and increased or decreased blood pressure, among others (Ladero, Calles-Enriquez, Fernández, & Alvarez, 2010; Silla Santos, 1996). Also, they may have a role in the depreciation of the organoleptic properties of foodstuff and are considered indicators of quality and/or acceptability in some foods (Ruiz-Capillas & Jiménez-Colmenero, 2004; Shalaby, 1996).

Foods likely to contain high levels of biogenic amines include fish, fish products and fermented foodstuffs (meat, dairy, some vegetables, beers and wines) (Bover-Cid, Hugas, Izquierdo-Pulido, & Vidal-Carou, 2000; Shalaby, 1996; Silla Santos, 1996). The most important BAs found in foods are histamine, tyramine, putrescine, cadaverine and phenylethylamine, which are produced by the decarboxylation of histidine, tyrosine, ornithine, lysine and phenylalanine, respectively. Putrescine can also be formed through deimination of agmatine.

The production of BA has been associated with yeast, Gram-negative and Gram-positive bacteria. Thus, several yeast species (*Debaryomyces hansenii*, *Yarrowia lipolytica*, *Pichia jadinii* or *Geotrichum candidum*) have been described as potential BA producers (Gardini *et al.*, 2006; Roig-Sagués, Molina, & Hernandez-Herrero, 2002; Suzzi *et al.*, 2003; Wyder, Bachmann, & Puhan, 1999).

Different species of Gram-negative bacteria that can be found in foods i.e. *Escherichia coli*, *Hafnia alvei*, *Klebsiella pneumoniae*, *Morganella moorganii*, *Pseudomonas* spp. or *Serratia* spp. are able to produce BA. However, the presence of these species in food is a more general food-safety problem that should be solved through good manufacturing practices involving adequate hygienic measures (Linares *et al.*, 2012). In fact, the concentration of BA is used as an indicator of microbial spoilage in non-fermented food (Silla Santos, 1996). In the case of fermented foods, Gram-negative bacteria are often inhibited due to the fermentation process itself (Adams & Nicolaides, 1997; Caplice & Fitzgerald, 1999), Gram-positive bacteria, and especially LAB, being mainly responsible for the production of BA (Linares, Martín, Ladero, Alvarez, & Fernández, 2011). In fact, BA-producing LAB are normal microbiota of fermented foods and may even be part of starter or adjunct cultures. They can even be responsible for organoleptic defects in foods, making the solution to the BA problem more difficult to find.

Tyramine biosynthesis is a species-level characteristic in *Enterococcus faecalis*, *Enterococcus faecium* and *Enterococcus durans*, and putrescine synthesis was found to be a species-level trait of *E. faecalis* (Ladero, Fernández *et al*., 2012). Putrescine production by *Lactococcus lactis* could have been a specific characteristic that was lost in some strains during the adaptation to the milk environment by a process of reductive genome evolution (Ladero *et al*., 2011). However, within microbial groups, in many cases the capacity to produce biogenic amines is a strain-specific characteristic, more widely distributed among certain genera and species, suggesting that horizontal gene transfer may account for their dissemination between strains (Coton & Coton, 2009; Marcobal, de las Rivas, Moreno-Arribas, & Muñoz, 2006).

Knowledge concerning the origin and factors involved in biogenic amine production in fermented foods is well documented, and recently several reviews on this topic have been published (Ancín-Azpilicueta, González-Marco, & Jiménez-Moreno, 2008; García-Muruno & Muñoz, 2012; Linares *et al*., 2011, 2012; Moreno-Arribas & Polo, 2010; Smit, Du Toit, & Du Toit, 2008; Spano *et al*., 2010). At present, a shared regulation limiting the amounts of BA in foods is still lacking, although their presence beyond the limits recommended by scientific literature may have negative commercial implications. For example, to minimize histamine toxicological effects, it is suggested that its concentration should not exceed 2 mg/l in fermented beverages, such as wine (ten Brink, Damink, Joosten, & Huis in't Veld, 1990). The only country with a limit for histamine in wine (10 mg/l) was Switzerland until 2008, but currently there is no legal or regulatory limit for histamine content in wine in any country in the world.

Recently a qualitative risk assessment of biogenic amines in fermented foods was conducted by the EFSA (2011) (European Food Safety Authority) Panel on Biological Hazards (BIOHAZ). Using data from the scientific literature, the BIOHAZ Panel concluded that the accumulation of BA in fermented foods is a complex process affected by multiple factors and their interactions, the combination of which are numerous, variable and product-specific. Hence, risk mitigation options, which are based on controlling those factors/interactions, could not be considered and ranked individually.

Histamine and tyramine are considered as most toxic and particularly relevant for food safety. Putrescine and cadaverine are known to potentiate these effects. Moreover, these amines are thermostable and are not inactivated by thermal treatments used in food processing and preparation. Presently, only prevention and monitoring strategies enable the control of BA formation in foods during the production process and along the food chain. However, specific 'curative' procedures able to eliminate already formed biogenic amines are required, and are therefore presented as a real solution to this problem. Recent evidences displaying the ability of food microorganisms to degrade BA are reported, although few data are available regarding their potential technological interest for specific foods. Considering the current interest by the food industry (and by consumers) in the search for tangible solutions to the problem of BA in foodstuffs, the main objective of this review is, briefly, to raise the particular problem of the BA in fermented foods and to analyze and discuss the current knowledge on the degradation of BA by food microorganisms, as well as to evaluate their practical applications to remove/reduce BA in the context of the modern food chain, with particular focus on fermented foods.

Problems arising from the presence of biogenic amines in foods

BA are produced in nature by microorganisms, plants, and animals, performing important physiological functions, including a number of crucial roles in the physiology of eukaryotic cells (Table 1). Therefore, the intake of BA is normal when we eat. Under normal conditions, BA ingested with food are rapidly detoxified by amine oxidases of the intestinal mucosa. These enzymes are classified as mono (MAO) or diamine oxidases (DAO) depending on the number of amino groups preferentially oxidized. Histamine can also be detoxified by methyl or acetyl-transferases (Linares *et al*., 2011). However, if these enzymes are dysfunctional either genetically or due to the intake of inhibitors such as alcohol or certain antidepressant medications, BA enter the systemic circulation and exert their toxic effect on different organs, causing serious human health problems (Blackwell, 1963; Ladero, Calles-Enriquez *et al*., 2010; McCabe-Sellers, Staggs, & Bogle, 2006). Nevertheless, the most frequent risk from BA is that as the result of uncontrolled microbial activity they can accumulate in high concentrations in certain foods, exceeding the capacity of the detoxification mechanisms and thereby exerting their toxic effect on consumers of such contaminated foods. BA can reach concentrations higher than 1000 mg kg^{-1} (Fernández, Flórez, Linares, Mayo, & Alvarez, 2006; Roig-Sagués *et al*., 2002; Shalaby, 1996), which undoubtedly constitutes a health hazard. There is limited research on the toxicity of BA and most focuses on histamine. Moreover, it is noteworthy that intolerance levels depend on the characteristics of the individual. It is assumed that the intake of foods with concentrations of histamine higher than