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ORIGINAL ARTICLE

Biogenic amines in fermented foods

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Food-fermenting lactic acid bacteria (LAB) are generally considered to be non-toxic and non-pathogenic. Some species of LAB, however, can produce biogenic amines (BAs). BAs are organic, basic, nitrogenous compounds, mainly formed through decarboxylation of amino acids. BAs are present in a wide range of foods, including dairy products, and can occasionally accumulate in high concentrations. 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, and therefore the detection of bacteria possessing amino acid decarboxylase activity is important to estimate the likelihood that foods contain BA and to prevent their accumulation in food products. Moreover, improved knowledge of the factors involved in the synthesis and accumulation of BA should lead to a reduction in their incidence in foods.
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Introduction

Lactic acid bacteria (LAB) can produce metabolic energy and/or increase their acid resistance by using catabolic pathways that convert amino acids into amine-containing compounds referred to as biogenic amines (BA) (Griswold *et al*., 2006). Usually, the consumption of foods containing large amounts of these amines can have toxicological consequences (Shalaby, 1996). These problems are more severe in consumers with less efficient detoxification systems because of their genetic constitution or their medical treatments (Bodmer *et al*., 1999). Foods likely to contain high levels of BA include fish, fish products and fermented foodstuffs (for example, meat, dairy products and vegetables) and beverages (for example, wine, cider and beer). The most important BAs—both qualitatively and quantitatively—in foods and beverages are histamine, tyramine, putrescine, cadaverine and β-phenylethylamine, products of the decarboxylation of histidine, tyrosine, ornithine, lysine and β-phenylalanine, respectively. According to their chemical structure, they can be classified as aliphatic (putrescine, cadaverine, spermine and spermidine), aromatic (tyramine and phenylethylamine) or heterocyclic (histamine and tryptamine). According to their number of amine groups, they can be divided into monoamines (tyramine and phenylethylamine), diamines (putrescine and cadaverine) or polyamines (spermine and spermidine). Recently, the genes of diverse pathways producing BA were identified in LAB (for a review, see Linares *et al*., 2010). Interestingly, the pathways seem to be strain dependent rather than species specific, suggesting that horizontal gene transfer may account for their dissemination in LAB (Lucas *et al*., 2005; Marcobal *et al*., 2006a; Coton and Coton, 2009). In addition, the enzymes of pathways involved in BA production can be encoded by unstable plasmids (Lucas *et al*., 2005; Satomi *et al*., 2008) and

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only strains harbouring BA-related plasmids are able to produce BA (Lucas *et al*., 2005).

The presence of BA in foods has traditionally been used as an indicator of undesired microbial activity. Relatively high levels of certain BAs have also been reported to indicate the deterioration of food products and/or their defective manufacture. Their toxicity has led to the general agreement that they should not be allowed to accumulate in food.

BA accumulation in foods requires the availability of precursors (that is, amino acids), the presence of microorganisms with amino acid decarboxylases and favourable conditions for their growth and decarboxylating activity (Fernández *et al*., 2007; Arena *et al*., 2008). Therefore, BA production by LAB may be controlled at various levels during food fermentation, including food fermentation practices and factors involved in food fermentation processes.

In this article we describe the physiological role and toxic effects of BA, their presence in fermented food products, their production by microorganisms, environmental conditions, some methods available for detecting the presence of BA or BA-producing microorganisms and, finally, methods to reduce BA content in fermented food.

Physiological role and toxicological effects of BAs

In eukaryotic cells, BA biosynthesis is essential, as these compounds function as precursors for the synthesis of hormones, alkaloids, nucleic acids and proteins (Premont *et al*., 2001). Some BAs have an important role as neurotransmitters, whereas others, such as putrescine and spermidine, are needed for critical biological functions (Igarashi *et al*., 2001). In prokaryotic cells, the physiological role of BA synthesis mainly seems to be related to defence mechanisms used by bacteria to withstand acidic environments (Rhee *et al*., 2002; Lee *et al*., 2007). Decarboxylation increases survival under acidic stress conditions (Rhee *et al*., 2002) through the consumption of protons and the excretion of amines and CO_2, helping to restore the internal pH (van de Guchte *et al*., 2002). BA production may also offer a way of obtaining energy: electrogenic amino acid/amine antiport can lead to generation of proton motive force (Molenaar *et al*., 1993). This function would be particularly important for microorganisms lacking a respiratory chain for generating high yields of adenotriphosphate (Vido *et al*., 2004).

Some studies suggest new and interesting hypotheses on the physiological role of amines in microorganisms (Tkachenko *et al*., 2001). In *Escherichia coli*, the expression of *oxyR*, the gene that protects *E. coli* against oxidative stress, was enhanced by physiological concentrations of the BA putrescine. Moreover, putrescine was shown to produce a protective effect if the DNA is damaged by reactive oxygen species (Tkachenko *et al*., 2001). Cells of *E. coli* grown in M9 minimal medium and subjected to a hyperosmotic shock by addition of 0.5 M NaCl immediately started to excrete putrescine, suggesting that putrescine may be involved in osmotic stress tolerance in *E. coli*. Therefore, bacteria that possess amino acid decarboxylase activity could overcome or reduce the effects of factors that induce stress responses in the cell, such as oxygen and NaCl, with the production of BA.

Although BA is required for many critical biological functions, the consumption of foods containing large amounts of BA can have toxicological consequences. After food consumption, small quantities of BA are commonly metabolised in the human gut to physiologically less active forms through the action of amine oxidases (monoamine oxidases (MAOs) and diamine oxidase). Histamine can also be detoxified by methylation (through the action of methyl transferases) or acetylation (Lehane and Olley, 2000). However, the intake of foods with high BA loads, or inadequate detoxification, either for genetic reasons (Caston *et al*., 2002) or because of the inhibitory effects of some medicines or alcohol (Bodmer *et al*., 1999), can lead to BA entering the systemic circulation and causing the release of adrenaline and noradrenaline, provoking gastric acid secretion, increased cardiac output, migraine, tachycardia, increased blood sugar levels and higher blood pressure (Shalaby, 1996). BA levels are also higher in patients with Parkinson's disease, schizophrenia and depression (Premont *et al*., 2001).

The establishment of what constitutes a toxic level of BA is difficult, as this depends on the characteristics of different individuals. Human sensitivity varies according to the individual detoxifying activities of some enzymes involved in BA metabolism, such as histamine methyltransferase or others less specific, such as MAO and diamine oxidase. These enzymes are inhibited by several types of drugs, such as the neuromuscular blocking drugs d-tubocurarine, pancuronium and alcuronium, and ethanol (Sattler *et al*., 1985) or antidepressant drugs (Livingston and Livingston, 1996). As a consequence of this synergistic action, the simultaneous consumption of fermented foods and beverages may cause disorders, including life-threatening serotonin syndrome, even if each separate product might not be considered as hazardous (Lonvaud-Funel, 2001). Because of the wide range of possible monoamine oxidase inhibitor (MAOI) drug and tyramine-rich food interactions, the use of MAOIs has been limited, despite their clinical benefits (Livingston & Livingston, 1996). This risk has also prompted clinicians to propose the so-called 'MAOI diet', in which the tyramine intake is controlled by restricting known tyramine-rich food stuffs corresponding mainly to fermented products (aged cheese; aged or cured meats; sauerkraut; soy sauce and tap beer) (Gardner *et al*., 1996). Secondary amines, such as putrescine and cadaverine, can also react with nitrite to form carcinogenic nitrosamines (ten Brink *et al*., 1990), and the adherence to intestinal mucosa of some enteropathogens, such as *E. coli* O157:H7, is increased in the presence of tyramine (Lyte, 2004). It has been suggested that BAs have been the causative agents behind a number of food poisoning episodes, the most notorious being caused by histamine. Histamine poisoning is also known as 'scombroid poisoning' owing to the association of this illness with the

consumption of scombroid fish (Taylor, 1983). With respect to cheese, BA food poisoning can be caused by high levels of tyramine, especially in combination with the use of MAOIs as antidepressants. This effect is known as the 'cheese reaction' (Silla Santos, 1996).

There is little specific legislation with regard to BA content in foods. Although for fish products there are clear limits for histamine (Commission Regulation (EC) 2073/2005), upper limits for BA in other foods have only been recommended or suggested (for example, 100 mg of histamine per kg of food or 2 mg of histamine per litre of alcoholic beverage). Generally, in alcoholic beverages, the toxic dose is considered to be between 8 and 20 mg/l for histamine, 25 and 40 mg/l for tyramine, whereas as little as 3 mg/l of phenylethylamine can cause negative physiological effects (Soufleros *et al*., 1998).

In addition to toxicological effects, BA in wine can also have consequences for wine retailers trying to export wines, as some countries have established maximum limits for histamine content in wine (Martín-Álvarez *et al*., 2006).

BAs in wine and dairy products

In wine, more than 20 amines have been identified and their total concentration has been reported to range from a few mg/l to about 50 mg/l, depending on the quality of the wine (Lonvaud-Funel, 2001; Landete *et al*., 2005). Similar BA contents have also been described in ciders (Garai *et al*., 2006, 2007). The variability of the amine contents in wine could be explained on the basis of differences in the wine-making process, time and storage conditions, raw material quality and possible microbial contamination during winery operations (Lonvaud-Funel, 2001). BA in wine may have two different sources: raw materials and fermentation processes. Some amines are already found in grapes, namely, histamine and tyramine, as well as several volatile amines and polyamines. Histamine, tyramine and putrescine are the BAs found in higher concentrations in wine, but cadaverine, phenylethylamine and isoamylamine are also present in smaller amounts. Putrescine and cadaverine are normally associated with poor sanitary conditions of grapes (Leitão *et al*., 2005).

Extensive research has been conducted to correlate BA production in wine with species of LAB involved in the wine-making process. It is widely known that *Pediococcus*, *Lactobacillus*, *Leuconostoc* and *Oenococcus* spp. are implicated in BA production in wine (Landete *et al*., 2007). Different strains of *Lactobacillus hilgardii*, *Lactobacillus buchneri*, *Lactobacillus brevis* and *Lactobacillus mali* produce a variety of BA in wine (Moreno-Arribas and Lonvaud-Funel, 1999; Moreno-Arribas *et al*., 2000, 2003; Martín *et al*., 2005; Constantini *et al*., 2006; Landete *et al*., 2007). *Leuconostoc mesenteroides* has a high potential to produce tyramine or histamine in wine (Moreno-Arribas *et al*., 2003; Landete *et al*., 2007). *Oenococcus oeni* is able to significantly contribute to the overall BA content of wines, mainly producing histamine. The ability of *O. oeni* to produce BA varies among strains (Coton *et al*., 1998; Guerrini *et al*., 2002). Moreover, LAB strains have the ability to simultaneously produce different amines (Coton *et al*., 1998; Moreno-Arribas *et al*., 2000; Guerrini *et al*., 2002), suggesting that some strains might possess more than one amino acid decarboxylase activity under specific culture conditions.

Together with wine, dairy products (in particular cheese) can accumulate high levels of BA. In the raw material (milk), polyamines are the most abundant. However, in the final product, tyramine, histamine, putrescine, cadaverine and, at lower concentrations, β-phenylethylamine and tryptamine, are all detected. The BA content of different types of cheese varies; indeed, it can also vary within the same type of cheese and even between different sections of the same cheese (Novella-Rodríguez *et al*., 2003a).

The main BA producers in cheese are Gram-positive bacteria, with LAB being the main histamine and tyramine producers. The genera *Enterococcus*, *Lactobacillus*, *Leuconostoc* and *Streptococcus* include some strains that have been described as BA producers. These can be present in milk microbiota or introduced through contamination before, during or after the processing of dairy products. BA^+-LAB may even form part of the starters or adjunct cultures. Several authors have reported the presence of tyrosine and histamine decarboxylase activity in strains from various starter cultures (Linares *et al*., 2010). It is therefore important to include the inability to produce BA as an indispensable condition of strains intended to be used as starters.

Regarding the safety of starters, the European Food Safety Agency (EFSA) has recently introduced a system for a pre-market safety assessment of selected taxonomic groups of microorganisms leading to a 'Qualified Presumption of Safety' (QPS) European equivalent of the Generally Recognized As Safe (GRAS) status (EFSA, 2007). *Lactobacillus* associated with food, including *L. buchneri*, *L. brevis*, *L. hilgardii*, have obtained a QPS status (EFSA, 2007), although some strains of these species have been described as BA producers (Lucas *et al*., 2005; Martín *et al*., 2005; Coton and Coton, 2009). This could raise the question of the addition of 'absence of BA production and BA production-associated genes' as qualification criteria in the QPS context. In addition, because of a recent increase in BA content in fermented food, as recently reported at the EFSA Network meeting on Microbiological Risk Assessment held in early June 2009, risks associated with BA in foods have been discussed at the 51st plenary meeting of the scientific panel on biological hazards held in Parma (Italy) from 9 to 10 September 2009.

Detection of BAs in fermented food

Early detection of BA-producing bacteria is essential in the food industry to avoid the risk of amine formation. Several methods to detect the production of BA through

microorganisms have been developed, from simple methods such as paper chromatography or spectrofluorimetric determination to more sophisticated techniques such as automated systems for the detection of microbial metabolic activities or automated conductance measurements (Marcobal *et al*., 2006b; Önal, 2007; Linares *et al*., 2010). With respect to the detection of BA-producing microorganisms, screening methods were initially based on the use of differential media containing a pH indicator to identify BA-producing strains (Maijala, 1993; Bover-Cid and Holzapfel, 1999). However, several studies describing the loss of ability to produce BA in LAB after prolonged storage or cultivation of isolated strains in synthetic media have been reported. For instance, the instability of histidine decarboxylase cells of *L. hilgardii* is easily explained by the loss of histidine decarboxylase plasmid, which depends greatly on bacterial culture conditions (Lucas *et al*., 2005).

The improvement of fast, reliable and culture-independent molecular tools, usually based on PCR approaches, has recently allowed a fast and accurate detection of BA-producing bacteria in fermented beverages. In fact, using several target genes, it has become possible to identify and/or quantify all of the LAB involved in BA production in a given sample (Lucas and Lonvaud-Funel, 2002; Coton and Coton, 2005; Marcobal *et al*., 2006b; Ladero *et al*., 2008; Nannelli *et al*., 2008). A relationship between the presence of the gene encoding the decarboxylase and the capacity to synthesise BA has been reported by several authors (Fernández *et al*., 2004; Landete *et al*., 2005; Lucas *et al*., 2005).

PCR has successfully been used with milk curd and cheese samples in this respect (Fernández *et al*., 2004), as well as for the detection of tyramine-producing bacteria during cheese manufacture (Fernández *et al*., 2006) or wine fermentation (Nannelli *et al*., 2008). A multiplex PCR method for the simultaneous detection of histamine-, tyramine- and putrescine-producing LAB has recently been proposed in order to identify BA-producing strains in wine and cider (Marcobal *et al*., 2005). In addition to end-point PCR analysis, a real-time quantitative PCR has been developed for detecting histamine-producing LAB in cheese and wine (Fernández *et al*., 2006; Lucas *et al*., 2008) or successfully used in the different steps of cheese manufacture and wine fermentation (Ladero *et al*., 2008; Nannelli *et al*., 2008).

Methods to reduce BAs content in fermented food

Many LAB strains are used as starter cultures in several fermented foods and beverages. In general, the choice of starter cultures is fundamental to guarantee the quality of the final products. For this reason, the inability to form BA should be an important criterion in the selection of starter cultures for the production of fermented food and beverages. Inoculation with starter cultures that are unable to produce BA is a viable option for the control of these compounds in wine (Martín-Álvarez *et al*., 2006). It seems that co-inoculation of *O. oeni* starter cultures, together with alcoholic fermentation, has the potential to curb BA formation even more than conventional inoculation for malolactic fermentation after the completion of alcoholic fermentation. BAs may also be oxidised by the action of amino oxidase. The potential role of microorganisms involved in food fermentations with amino oxidase activity has been investigated with the aim of preventing or reducing the accumulation of BA in foods (Leuschner *et al*., 1998). Unfortunately, at this stage, amine degradation seems to be restricted to aerobic microorganisms that are of limited use in fermented foods such as wine, which characteristically constitutes an anaerobic environment.

In addition to amino oxidase activity and the use of microbial starters unable to produce BA, several food-processing parameters may affect the final content of BA in food. For example, the relationship between the treatment of milk and BA content has been studied by several authors. The highest degradation rate of histamine is usually observed at 37 °C, although degradation is still considerable at 22 and 15 °C (Dapkevicius *et al*., 2000). The analysis of the BA content of different types of cheese showed that these compounds were more common in those made from raw milk (Fernández *et al*., 2007). Other milk treatments, such as the use of pressure, have also been investigated as a means of reducing BA contents. However, no differences in BA profiles were observed between cheese made with sterilised or pasteurised milk, suggesting that the control of BA-producing microorganisms by adequate treatment of milk is one of the most important factors for reducing BA accumulation in dairy products (Novella-Rodríguez *et al*., 2003b). In the case of wine, the agricultural and oenological practices may control the accumulation of BA. Indeed, viticulture region and grape varieties seem to influence the amounts of BA, as wines of some regions present higher contents of amines than do wines from other regions (Marques *et al*., 2008).

Conclusions

The demand for safer foods has promoted more research into BA over the past few years, but some questions still remain unanswered. Fermented food such as wine and cheese can accumulate large quantities of BA. The synthesis and accumulation of BA in foods require the presence of bacteria with decarboxylase deaminase activity, environmental conditions that allow for their growth and for enzyme activity, and the presence of the appropriate amino acid substrates. The influence of processing parameters such as grape composition, milk quality and the treatment of milk and wine has been analysed, and there is general agreement on the importance of these factors in reducing the presence of BA in dairy products and fermented beverages. Furthermore, there is no doubt regarding the importance of selecting starter strains unable to synthesise BA. Knowledge of the metabolic pathways involved in BA production and the

factors affecting BA accumulation in food may also be useful in suggesting possible means of reducing BA contents. In addition, because many LABs are normal inhabitants of the intestinal microbiota, it may be worthwhile tracing BA-producing LAB, following consumption by human subjects, to analyse their survival in the gastrointestinal tract and their contribution to BA production in the human body.

Finally, although BAs are present in many different foods and beverages and their concentrations vary widely between and within food types, a shared regulation limiting the amounts of BA in foods is still lacking (except for histamine in fish). Information regarding their presence in foods is also important for the food trade sector (in particular import and export) because recommended upper levels of BA content vary between countries. Therefore, even though information on BA is currently not included in food composition databases, information on their existence, distribution and concentration in fermented foods is crucial and may be useful for the food industry, health professionals and consumers.

Conflict of interest

The authors declare no conflict of interest.

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