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

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Abstract

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.

Keywords

Fermented foods, cheese, wine, biogenic amines, histamine, tyramine, putrescine, degrading microorganisms

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 (Silla Santos, 1996; Ladero et al., 2010a). 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 (Shalaby, 1996; Ruiz-Capillas & Jiménez-Colmenero, 2004).

Foods likely to contain high levels of biogenic amines include fish, fish products and fermented foodstuffs (meat, dairy, some vegetables, beers and wines). 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*

51 *Pichia jadinii* or *Geotrichum candidum*) have been described as potential BA producers
52 (Wyder et al., 1999; Roig-Sagués et al., 2002; Suzzi et al., 2003; Gardini et al., 2006).

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

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

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

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

95 Histamine and tyramine are considered as most toxic and particularly relevant for food
96 safety. Putrescine and cadaverine are known to potentiate these effects. Moreover, these
97 amines are thermo-stable and are not inactivated by thermal treatments used in food
98 processing and preparation. Presently, only prevention and monitoring strategies enable

99 the control of BA formation in foods during the production process and along the food
100 chain. However, specific 'curative' procedures able to eliminate already formed
101 biogenic amines are required, and are therefore presented as a real solution to this
102 problem. Recent evidences displaying the ability of food microorganisms to degrade
103 BA are reported, although few data are available regarding their potential technological
104 interest for specific foods. Considering the current interest by the food industry (and by
105 consumers) in the search for tangible solutions to the problem of BA in foodstuffs, the
106 main objective of this review is, briefly, to raise the particular problem of the BA in
107 fermented foods and to analyze and discuss the current knowledge on the degradation of
108 BA by food microorganisms, as well as to evaluate their practical applications to
109 remove/reduce BA in the context of the modern food chain, with particular focus on
110 fermented foods.
111

112 **Problems arising from the presence of biogenic amines in foods**

113 BA are produced in nature by microorganisms, plants, and animals, performing
114 important physiological functions, including a number of crucial roles in the physiology
115 of eukaryotic cells (**Table 1**). Therefore, the intake of BA is normal when we eat. Under
116 normal conditions, BA ingested with food are rapidly detoxified by amine-oxidases of
117 the intestinal mucosa. These enzymes are classified as mono- (MAO) or diamine
118 oxidases (DAO) depending on the number of amino groups preferentially oxidised.
119 Histamine can also be detoxified by methyl or acetyl-transferases (Linares et al., 2011).
120 However, if these enzymes are dysfunctional either genetically or due to the intake of
121 inhibitors such as alcohol or certain antidepressant medications, BA enter the systemic
122 circulation and exert their toxic effect on different organs, causing serious human

123 health problems (Blackwell, 1963; McCabe-Sellers, et al., 2006; Ladero et al., 2010a).
124 Nevertheless, the most frequent risk from BA is that as the result of uncontrolled
125 microbial activity they can accumulate in high concentrations in certain foods,
126 exceeding the capacity of the detoxification mechanisms and thereby exerting their
127 toxic effect on consumers of such contaminated foods. BA can reach concentrations
128 higher than 1,000 mg kg^{-1} (Shalaby, 1996; Roig-Sagués et al., 2002; Fernández et al.,
129 2006), which undoubtedly constitutes a health hazard. There is limited research on the
130 toxicity of BA and most focuses on histamine. Moreover, it is noteworthy that
131 intolerance levels depend on the characteristics of the individual. It is assumed that the
132 intake of foods with concentrations of histamine higher than 400 mg kg^{-1} is dangerous
133 to health (Taylor, 1986). Further research demonstrated that 75 mg of pure oral
134 histamine provoke symptoms in 50% of healthy females with no history of food
135 intolerance (Wöhrl et al., 2004), and the intake of approximately 1,000 mg of histamine
136 is definitely associated with severe intoxications (Rauscher-Gabernig et al., 2009).

137 The effects of tyramine intake are known as "cheese reaction", since it was first
138 associated with cheese consumption (Blackwell, 1963), a food that can reach very high
139 concentrations of this BA. It has been described that tyramine concentrations over 125
140 mg kg^{-1} have effects in healthy individuals, and a concentration of 6 mg kg^{-1} is
141 potentially toxic to patients treated with MAO inhibitors (McCabe-Sellers, 1986).

142 The effects of BA can be classified as reaction, intolerance, or intoxication or poisoning
143 according to the severity of the symptoms (**Table 1**) (Ladero et al., 2010a). Reaction
144 symptoms include nausea, sweating, rashes, slight variations in blood pressure and mild
145 headache. The symptoms of intolerance are more severe, including vomiting, diarrhoea,
146 facial flushing, a bright red rash, bronchospasms, tachycardia, oral burning, hypo- or

147 hypertension and migraine. More exceptional intoxication may occur with hypertension,
148 causing irreversible damage to the heart or the central nervous system (Blackwell,
149 1963).

150 Other pathologies – some really serious – have been associated with BA. The
151 consumption of food with high concentrations of histamine by individuals with low
152 DAO activity has been related to inflammatory diseases such as Crohn's disease,
153 ulcerative colitis and even to colorectal neoplasms (Maintz & Novak, 2007).
154 Abnormally high levels of tyramine in the brain have been associated with depression,
155 schizophrenia, Parkinson's disease, and Reye's syndrome (Ladero et al., 2010a).
156 Secondary amines such as putrescine and cadaverine can also react with nitrite to form
157 carcinogenic nitrosamines (ten Brink et al., 1990). Moreover, there is increasing
158 evidence that putrescine could have a role in promoting the malignant transformation of
159 cells. Dietary putrescine increased the malignancy grade of adenomas in a murine
160 model (Ignatenko et al., 2006). Colorectal cancer cells have a higher polyamine content
161 than the adjacent mucosa or equivalent normal tissue (Wallace & Caslake, 2001),
162 highlighting the possible importance of exogenous putrescine in their development
163 (Gerner & Meyskens, 2004). Elevated concentrations of putrescine have also been
164 detected in gastric carcinomas caused by *Helicobacter pylori* and the putrescine levels
165 are restored if the microbial infection is eliminated (Shah & Swiatlo, 2008).

166 Apart from the toxicological effects, BA could also have an effect on the intestinal
167 microbiota. In fact, tyramine is known to enhance the adherence of the enteropathogen
168 *E. coli* 1057H to epithelial cells (Lyte, 2004). Putrescine has been associated with
169 virulence factors of Gram-positive and Gram-negative pathogens (Shah & Swiatlo,

2008) and it has been proved that it can activate the swarming phenotype needed for pathogenesis in some *Proteus mirabilis* mutants (Sturgill & Rather, 2004)

Since there are foods that are often contaminated with more than one BA, another important problem that requires further research is their synergistic effects. It is known that putrescine and cadaverine play a role as diamine-oxidase inhibitors and therefore act as enhancers of histamine toxicity (Lehane & Olley, 2000).

Additionally, with regards to adverse health implications, at elevated levels (50–100 mg/L) these compounds – mainly cadaverine and putrescine – also exert a considerable impact on the organoleptic properties of fermented foods. In some extreme cases, winemakers have stated that affected wines lose their varietal characteristics, and this can result in the formation of a metallic, meaty, or putrid aroma in the wine.

Procedures/strategies for surveillance and prevention of biogenic amine accumulation in foods

BA production in foods requires the availability of precursors (i.e. amino acids), the presence of bacteria synthesizing amino acids decarboxylases, and favorable conditions for their growth and decarboxylating activity. As a strategy to control BA in foods, different methods (both analytical and based on molecular tools) have been developed. These procedures allow the detection of BA-producing bacteria strains and the quantification and monitorization of amines production through the food chain, respectively.

191 The monitorization of BA concentrations of raw materials and products along the food
192 chain is not only necessary to evaluate the relevance of factors contributing to BA
193 formation and accumulation, but also in order to get advice about the need to implement
194 different corrective strategies. Among the analytical methods, chromatographic
195 techniques, and in particular high-performance liquid chromatography methods (HPLC)
196 involving derivatization of BA (either pre- or post-column), are the most common and
197 suitable methods for the analysis of BA in foods. In fact, the reference method specified
198 in the European Commission Regulation (EC) No. 2073/2005 was for the determination
199 of histamine in fish and treated fishery products using HPLC after dansyl-derivatization.
200 Later, in wines, a reversed phase (RP)-HPLC method that used o-phthaldialdehyde
201 (OPA) for pre-column derivatization and detection by fluorescence was adopted by the
202 International Organization of Vine and Wine (OIV), allowing the simultaneous
203 quantification of 18 biogenic amines (OIV/OENO 346/2009). Derivatization treatment
204 with diethyl ethoxymethylenemalonate followed by ultra-HPLC allows the
205 simultaneous quantification of biogenic amines, amino acids, and ammonium ions in
206 cheese samples in under 10 min (Redruello et al., 2013). Validation of methods for BA
207 analysis is recommended for the different relevant food types, including the
208 standardization and harmonization of procedures, external quality assessment and the
209 availability of certified reference materials (EFSA, 2011).

210 Detection of amino acid decarboxylase-positive microorganisms, both involving *in vitro*
211 differential growth media and sensitive and specific PCR protocols based on the
212 detection of gene-encoding decarboxylases, have been shown by several authors (Coton
213 and Coton, 2005; de las Rivas et al., 2006; Landete et al., 2007). For example, a
214 multiplex PCR method for the simultaneous detection of oenological lactic acid bacteria

215 with the potential to produce histamine, tyramine and putrescine, has been reported
216 (Marcobal et al., 2005). PCR methods for the detection of BA-producing dairy LAB
217 have also been developed (Fernández et al., 2004; Fernández et al 2006). Furthermore,
218 quantitative real-time PCR methods for the detection and quantification of histamine-
219 producing (Ladero et al., 2008; Lucas et al., 2008), tyramine-producing (Ladero et al.,
220 2010b; Torriani et al., 2008) and putrescine-producing bacteria (Ladero et al., 2012b)
221 have been developed and successfully applied to different stages of cheese manufacture,
222 including the final product (Ladero et al., 2010c).
223 The amount and type of biogenic amines formed in foods is strongly influenced by the
224 intrinsic food characteristics, including pH, water activity, composition, and microbiota,
225 and by extrinsic parameters such as storage time and temperature, which allow bacterial
226 growth during food processing and storage. So, different procedures to limit amine
227 formation have been reported depending on the particular foodstuff. Recently, the
228 existing and emerging approaches for the control of BA in foods, with special emphasis
229 on fish and meat products, have been reviewed (Naila et al., 2010). They mainly include
230 the control of temperature below 5ºC, the use of food additives and preservatives, the
231 application of hydrostatic pressures and irradiation, and altering conditions based on
232 microbial modelling of histamine-producing bacteria. These methods only delay the
233 formation of BA in food, primarily through the inhibition of bacteria or the
234 decarboxylase enzyme activity responsible for amine formation.

235 In fermented foods, the selection of lactic acid bacteria microbiota involved in the
236 fermentation process is mainly approached by adopting microbial starters lacking the
237 pathways to degrade precursor amino acids (Moreno-Arribas et al., 2003; Novella-
238 Rodríguez et al., 2002; Fernández et al., 2007; Landete et al., 2007; Del Prete et al.,

239 2009). PCR methods may be used for the characterization and selection of starter
240 cultures. However, in an attempt to control BA, microorganisms intended to be used as
241 starter cultures in any fermented food should be confirmed as not producing BA and be
242 able to outgrow autochthonous microbiota under conditions of production and storage
243 (Gardini et al, 2002; Marcobal et al., 2006b; Moreno-Arribas & Polo, 2008). Also,
244 during the manufacture of food, all the operations leading to an increase of substrates or
245 to favorable conditions for microbial growth should be limited and avoided, for
246 example: by reducing the number of BA producers via the pasteurization of milk to be
247 used in cheese manufacture, reducing the amount of proteolytic activity (thus reducing
248 the availability of the amino acid precursor of BAs), and by reducing ripening times
249 (Fernández et al., 2007). During wine production, surveillance of parameters that
250 influence bacterial growth, such as pH, T^a, presence of organic acids, and/or some
251 typical oenological practices such as maceration or prolonged contact with yeast lees
252 have been proposed to prevent lactic acid bacteria proteolytic activity and
253 decarboxylase activity (Martín-Álvarez et al., 2006). Other strategies, such as adding
254 sulphites, have been recommended for reducing BA accumulation in wine and cider. In
255 spite of limited published information, it seems that biogenic production in ciders may
256 also be controlled by the use of technological regimes and practices limiting precursor
257 amino acid content (Garai et al., 2006; 2013).

258 In brief, all aspects of fermented food processing (including additives, ingredients,
259 fermentation and ripening or storage conditions) and distribution should be adjusted and
260 balanced in each particular product to avoid/minimize potential enhancing effects on
261 BA formation and to enable dominance of starter cultures where used. However, there
262 are some practical limitations on the use of some of these methods depending on the

resources available and the characteristics of the desirable fermented food. The assessment of other novel strategies needs to be further investigated.

Ability of food microorganisms to degrade biogenic amines

Based on the fact that amino oxidases are responsible for the detoxification of dietary BA, and enzymes with the same activity have also been found in bacteria, the first works in this direction focused on the screening of such activities in microorganisms isolated from food. **Table 2** summarizes the studies reporting BA degradation by food microorganisms. Voigt & Eitenmiller (1978) analyzed bacteria isolated from dairy products and came to the conclusion that these bacteria generally lack amino oxidases. Moreover, those few bacteria in which amino oxidase activities were found also have tyrosine or histidine decarboxylase activity and, therefore, are potential producers of BA. It was to be a couple of decades later Leuschner et al. (1998) found food isolates belonging to the species *Lactobacillus plantarum, Lactobacillus sakei, Lactobacillus pentosus, Pediococcus acidilactici, Rhodococcus sp., Arthrobacter sp., Micrococcus sp., Brevibacterium linens,* and *Geotrichum candidum* with the ability to degrade *in vitro* tyramine and histamine. The same group studied the potential of the *B. linens* strains to degrade histamine and tyramine during the surface ripening of Munster cheese, showing for the first time the possibility of using BA-degrading microorganisms to reduce the BA content in food (Leuschner & Hammes, 1998).

A couple of years later, four *Lactobacillus sakei* strains able to degrade histamine in a model system were isolated from naturally fermented fish pastes (Dapkevivius et al., 2000). Histamine degradation by two of these isolates was assayed in ensiled fish slurry

and the authors concluded that their use for fish silage could successfully reduce the risk of this BA. *Bacillus amyloliquefaciens* and *Staphylococcus carnosus* able to degrade histamine, and *Staphylococcus intermedius* and *Bacillus subtilis* able to degrade putrescine and cadaverine, were isolated from another fish product, a Malaysian fish sauce (Zaman et al., 2010). Later, they found that *Bacillus amyloliquefaciens* and *Staphylococcus carnosus* isolates are able to reduce the accumulation of histamine in laboratory fish sauce fermentation (Zaman et al., 2011). Strains of other species of the genus *Staphylococcus* -*Staphylococcus xilosus*- isolated from artisanal fermented sausages produced in Italy were also found to be capable of degrading histamine (Martuscelli et al., 2000). The use of one of these strains as a starter culture in dried sausages slightly reduces the BA content (Gardini et al., 2002). *Lactobacillus casei* and *Lactobacillus plantarum* strains, also isolated from artisanal fermented sausages – but in this case produced in Argentina – can degrade tyramine, although with different efficiency (Fadda et al., 2001). *Kocuria varians* and *Micrococcus varians* strains from the same samples are also able to degrade tyramine, but are at the same time tyramine and/or histamine producers. It is remarkable that resting cells of one of the *L. casei* strains degraded 98% of a 2.5mM tyramine solution in 96 hours. Strains of *L. casei* from very different sources were also able to degrade BA. The inoculation of an *L. casei* strain from a commercial preparation can lower the BA concentration in different vegetable silages performed in the laboratory (Nishino et al., 2007), although the authors suggest this may be a specific antagonism of *L. casei* against BA-producing microorganisms. Samples of different cheeses were screened for the presence of BA-degrading lactic acid bacteria and, surprisingly, the 17 isolates that were able to degrade tyramine and histamine were identified by 16S rRNA sequencing as *L. casei* (Herrero-Fresno et al., 2012). Two of these strains were checked in a mini-cheese model

311 verifying that both avoid tyramine and histamine accumulation over four months of
312 ripening. A collection of wine-associated LAB was screened for their BA-degrading
313 ability, verifying that one *L. casei*, one *Lactobacillus hilgardii,* one *Pediococcus*
314 *parvulus,* one *Oenococcus oeni,* two *L. plantarum,* and three *Pediococcus pentosaceus*
315 strains significantly degrade histamine, tyramine or putrescine in culture media (García-
316 Ruiz et al., 2011). However, in malolactic fermentation experiments, the BA-degrading
317 ability was confirmed only for *L. casei*. In a different work, but also from wine, two
318 strains of *L. plantarum* that can degrade tyramine and putrescine were isolated (Capozzi
319 et al., 2012). Furthermore, it was verified that these strains can survive in a wine-like
320 medium and show a useful aptitude to degrade malic acid. In the vineyard ecosystem
321 were also found fungi with the ability to degrade BA (Cueva et al. 2012). Species of
322 *Pencillium citrinum*, *Alternaria sp*., *Phoma sp*., *Ulocladium chartarum* and *Epicoccum*
323 *nigrum* can degrade at least two different primary amines in a microfermentation
324 system.

325

326 **Enzymatic activities involved on biogenic amines degradation**

327 Monoamine oxidases (MAO, E.C. 1.4.3.4.) are flavoproteins that catalyze the oxidative
328 deamination of a number of biogenic and dietary monoamines forming the
329 corresponding aldehydes, hydrogen peroxide and ammonia. In humans there are two
330 separate MAO isoforms (MAO-A, MAO-B), which exhibit different but overlapping
331 substrate and inhibitor specificities (Wang et al., 2013). As already indicated above, the
332 intestinal mucosa has mono- and diamino oxidases that catabolise BA and are well
333 characterized. However, information concerning the identification and biochemical

334 characterization of enzymatic activities involved on BA reduction in foods is very
335 scarce. Most of the studies attributed these enzymatic activities to amine oxidases.
336 In 2004, Sekiguchi et al. (2004) identified a histamine oxidase in the actinobacteria
337 *Arthrobacter crystallopoietes* KAIT-B-007. Histamine oxidase catalyzes the oxidative
338 deamination of histamine to imidazole aceltadehyde with the simultaneous production
339 of ammonia and hydrogen peroxide. The enzyme was very thermostable (the activity
340 was stable at 65ºC and 70ºC) and fully stable over the pH range of 6 to 9. The enzyme
341 was a copper-containing protein and it was suggested that Cu^{2+} is essential for the
342 expression of histamine oxidase activity. Van Hellemond et al (2008) also characterize
343 a putrescine oxidase from *Rhodocccus erythropolis* NCIMB 11540. The purified
344 enzyme was shown to be a soluble dimeric flavoprotein consisting of subunits of 50
345 kDa and contains non-covalently bound flavin adenine dinucleotide as a cofactor. Most
346 recently, the enzymes responsible for putrescine degradation in wine were isolated and
347 purified from *Lactobacillus plantarum* and *Pediococcus acidilactici* and were also
348 identified as multicopper oxidases (Callejón et al., 2013).
349

350 **Technological relevance of biogenic amine-degrading microorganisms in**
351 **fermented foods production**

352 A novel way to reduce the BA content of foods would be to eliminate them from the
353 food matrix. This might be the strategy of choice with those fermented foods in which it
354 is difficult to avoid the presence of BA-producing LAB because they are part of the
355 usual microbiota, and consequently BA are present at the final stages of the
356 manufacturing process.

357 The use of BA-degrading bacteria has been proposed for the production of fermented
358 meats (Martuscelli et al., 2000; Gardini et al., 2002; Fadda et al., 2001). Amino-oxidase
359 activity has even been suggested as a criterion for the selection of starter cultures for
360 sausage fermentation (Gardini et al., 2002; Fadda et al., 2001). However, although it has
361 been found that the presence of certain starting cultures reduce BA content in a semi-
362 industrial plant (Gardini et al., 2002), it is important to note that there are no
363 biochemical studies that demonstrate that amino-oxidase is the enzymatic activity
364 responsible for BA reduction. Neither has it been verified whether or not the physico-
365 chemical conditions during fermentation are suitable for oxidase activity.
366 Accumulation of BA in fish is usually a problem of freshness and/or deficiencies in the
367 cold chain (Halász et al., 1994). However, in fermented food derived from fish, the
368 problem is similar to other fermented foods and the use of BA-degrading bacteria has
369 been proposed as a potential solution (Dapkevivius et al., 2000; Zaman et al., 2010;
370 Zaman et al., 2011). The presence of amino-oxidase activity has also been proposed as a
371 criterion for the selection of starters (Zaman et al, 2010), but this activity has not yet
372 been characterized in the proposed BA-degrading bacteria. The same authors also
373 emphasize the importance of using fresh fish and hygienic manufacturing practices
374 (Zaman et al., 2011).
375
376 Cheese, especially that made from raw milk, is a particular technological challenge
377 because it is a complex ecosystem involving many different microorganisms with
378 different metabolic machineries, including catabolic amino acid enzymes yielding high
379 amounts of biogenic amines. Concentrations over 1g/kg have been reported in cheese,
380 with tyramine and histamine the most commonly present and most abundant of all BAs
381 (Fernández et al., 2007). In fact, blue cheeses and, in particular traditional Cabrales-type

382 cheeses (made from raw milk) accumulate high BA concentrations, mainly because the
383 tyramine-producing enterococci present in the raw milk used to make it are responsible
384 for the accumulation of tyramine (Ladero et al., 2010c). The pasteurization of milk
385 would lessen the problem, but it could affect the organoleptic characteristics of the
386 cheeses and, in fact, in many cases the rules of the Geographical Indications and
387 Designations of Origin do not allow it. Another factor involved in the accumulation of
388 BA in this type of cheese is the high proteolysis of casein, generating a high release of
389 amino-acid substrates during their characteristic long ripening period. Recently,
390 Herrero-Fresno et al., (2012), identified *L. casei* strains that could be used as highly
391 competitive adjunct cultures capable of reducing the content of tyramine and histamine,
392 the two most toxic BAs, in cheese. Although more work is needed to identify and
393 characterize their BA-degrading enzymatic activity, such a strategy might be
394 particularly useful when making cheeses from raw milk in which a specific non-starter
395 microbiota is essential for the organoleptic characteristics of the final product. In the
396 particular case of blue cheeses, the growth of mold requires the presence of oxygen,
397 which would also allow the activity of amino-oxidases.
398
399 At present, in the market there are no effective procedures or treatments used to limit
400 the content of biogenic amines in wine. Enzymatic removal of amines may be a safe and
401 economic way to eliminate these troublesome compounds from wines and other
402 fermented foods. García-Ruiz et al. (2011) reported for the first time the ability of LAB
403 of food origin (i.e. wine) to degrade putrescine. The biogenic amine-degrading ability of
404 selected wine LAB strains did not appear to be associated with an amine-producing
405 ability. As for cheese, *L. casei* seemed to be an interesting species displaying histamine,
406 tyramine and putrescine breakdown, both in culture media conditions and in model wine

407 malolactic fermentation, suggesting its suitability as a commercial malolactic starter.
408 Meanwhile, the wine composition may interfere with the BA-degrading capacity of the
409 wine strain *L. casei* (García-Ruiz et al., 2011). Further research is needed to provide
410 conclusive evidence of the applicability of wine LAB bacteria in real wine systems.
411
412 The use of amino oxidases to reduce BA in foods has been also considered. The
413 preparation and industrial applications of the amino oxidase of *A. niger* IMI17454 was
414 described in 1985 (Hobson & Anderson, 1985). Although the authors proposed its use
415 in foods, such as cheese, beer, must and yeast extracts, specific data demonstrating the
416 usefulness under real food production conditions were not reported. Dapkevicius et al
417 (2000) attempted to reduce histamine in ensiled fish slurry (pH 4.5) by using
418 commercial diamine oxidase purified from porcine kidney, but it was unsuccessful,
419 limiting its use to food with higher pH values. Lately, a procedure based on the use of
420 an enzymatic extract from *P. citrimun* CIAL-274,760, isolated from vineyards, which
421 added to the wine reduces or even completely eliminate BA in synthetic wines has been
422 reported (Moreno-Arribas et al., 2012). The enzymatic extract is easily obtainable by
423 means of filtration culture of the fungus. Previously, the fungi were grown in defined
424 media using a selection of free amines (i.e. histamine, tyramine and putrescine) as the
425 sole nitrogen source using a microfermentation system. The potential of *P. citrinum*
426 CIAL 274,760 (CECT 20782) extracts for BA detoxification of wines was further
427 demonstrated in commercial red and white wines. Interestingly, in this study,
428 histamine, tyramine and particularly putrescine were significantly degraded in red wine
429 treated with fungi BA-degrading extracts (up to 40, 20 and 70% degradation,
430 respectively) under conditions with a lower presence of oxygen (Cueva et al., 2012).
431 Later, the efficiency and specificity of the enzymatic extract regarding its ability to

degrade BA in winery scale conditions has been tested (unpublished results). In fact, at winery Tª (close to 16ºC) and wine pH conditions (pH 3.5), the fungi's enzymatic extract was able to significantly and simultaneously reduced the concentration of histamine, tyramine and putrescine after 48 h treatment of a red wine following industrial scale malolactic fermentation in stainless steel tanks (unpublished results). The non-production of mycotoxins (i.e ochratoxin A, OTA) by this BA-degrading strain was also demonstrated. Further, no significant changes were observed in the phenolic and volatile composition of the wine, suggesting that the use of the BA-degrading enzymatic extract did not affect the organoleptic properties of the final product. The identification of the enzymatic activities involved, as well as the provision of procedures' formulation of the enzymes to avoid the accumulation of BA in wines and other fermented foods, is underway. The use of such products together with a combination of control measures (i.e. high-quality raw materials and appropriate manufacturing practices) might afford the best way of producing products with reduced BA-associated risks.

Conclusions and future challenges

Fermented foods and beverages have a high probability of accumulating high concentrations of BA, which is undoubtedly a health hazard for consumers. There are many factors that favor the accumulation of BA in these products (Linares et al., 2012; Martín-Álvarez et al., 2006), and unfortunately it is not always possible to modify those factors in order to avoid it. Thus, for example, the presence of BA-producing microorganisms in some raw-milk cheeses can not be avoided. Nor can the accumulation of decarboxilation substrate amino acids be prevented, because

456 proteolysis is essential for the desired organoleptic characteristics of cheeses. Likewise,
457 some enological practices widely used to improve wine quality (by increasing wine
458 complexity), such as storage with lees and skin maceration, strongly influenced BA
459 concentration. Thus, currently, in many areas and world wineries, it is very difficult or
460 not viable to find wines without any BA which maintain all their sensory properties. It
461 is therefore important to seek alternatives for those fermented foods and beverages, in
462 which the accumulation of BA seems inevitable. In this context, and as we have seen
463 throughout this review, the use of LAB capable of degrading BA in the fermented
464 matrix itself is a promising alternative, as has been proven in cheese and wines
465 (Herrero-Fresno et al., 2012; Cueva et al., 2012). However, more studies are needed in
466 order to prove their feasibility and technological relevance during the production of
467 fermented foods.

468 Right now, the main challenge is to identify the catabolic activities responsible for BA
469 degradation. Recent interesting approaches reporting the possibility of reduce BA in
470 wines by using multicopper oxidases from LAB (Callejón et al., 2013). However, it is
471 important to note that many of the published works assume that such activities are
472 oxidases without experimental confirmation. Furthermore, oxidases might not be the
473 ideal BA-degrading activities, because the environmental conditions in fermented food
474 and beverage matrices are not physiologically optimal for them, i.e. with low oxygen
475 concentration, low pH value, presence of NaCl and glucose (Leuschner et al., 1998).
476 The design of immobilization and stabilization enzyme protocols may also contribute to
477 enhancing the performance of these interesting enzymatic activities in such adverse
478 food conditions. It is also important to characterize the products of the reactions since
479 some, such as hydrogen peroxide, are not desirable because they may cause color and

480 aroma failures. Therefore, it is necessary to properly and thoroughly characterize the
481 biochemistry of BA degradation pathways and then evaluate whether they could be
482 really useful in the conditions under which individual food fermentations are performed.

483 The studies published to date indicate that the ability of LAB to degrade BA is a strain
484 characteristic. Furthermore, it was found that some of these strains have the undesirable
485 ability to produce BA. In this regard, next-generation DNA-sequencing techniques offer
486 promising alternatives. The sequence of the genomes of BA-degrading strains would
487 allow the identification of undesirable genes in food bacteria, such as those responsible
488 for the biosynthesis of BA or antibiotic resistance genes. It would also establish whether
489 they are chromosome or plasmid encoded and, therefore, whether they have stable or
490 unstable characteristics, and would check for the absence of undesirable genes, such as
491 those encoding aminoacyl decarboxylases or antibiotic-resistant genes.

492

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744

745 **Table 1.** Biogenic amines in foods and their physiological and toxicological effects (adapted
746 from Ladero et al., 2010)
747
748

Biogenic amines	Precursor	Physiological effects	Toxicological effects
Histamine	Histidine	Neurotransmitter, local hormone, gastric acid secretion, cell growth and differentiation, regulation of circadian rhythm, body temperature, food intake, learning and memory, immune response, allergic reactions	Headaches, sweating, burning nasal sec flushing, right red rashes, dizziness, itc oedema (eyelids), urticaria, diffic swallowing, diarrhoea, respiratory bronchospasm, increased cardiac tachycardia, extrasystoles, blood p disorders
Tyramine	Tyrosine	Neurotransmitter, peripheral vasoconstriction, increase cardiac output, increase respiration, elevate blood glucose, release of norepinephrine	Headaches, migraine, neurological c nausea, vomiting, respiratory disc hypertension
Putrescine and Cadaverine	Ornithine and Lysine	Regulation of gene expression, maturation of intestine, cell growth and differentiation	Increased cardiac output, tachycardia, l carcinogenic effects

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751 **Table 2.** Studies reporting biogenic amines degradation by food microorganisms
752

Biogenic amine	Species	Matrix	Reference
Histamine Tyramine	*Lactobacillus plantarum, Lactobacillus sakei, Lactobacillus pentosus, Pediococcus acidilactici, Rhodococcus sp,. Arthrobacter sp,. Micrococcus sp., Brevibacterium linens, Geotrichum candidum*	*In vitro*	Leushner et al., 1998
Histamine Tyramine	*B. linens*	Munster cheese	Leushner & Hammes, 1998
Histamine	*Lactobacillus sakei*	Ensiled fish slurry	Dapkevivius et al., 2000
Histamine	*Bacillus amyloliquefaciens,* *Staphylococcus carnosus*	*In vitro*	Zaman et al., 2010
Putrescine Cadaverine	*Bacillus subtilis,* *Staphylococcus intermedius*	*In vitro*	Zaman et al., 2010
Histamine	*Bacillus amyloliquefaciens,* *Staphylococcus carnosus*	Fish sauce fermentation	Zaman et al., 2011
Histamine	*Staphylococcus xilosus*	*In vitro*	Martuscelli et al., 2000
Tyramine	*Lactobacillus casei,* *Lactobacillus plantarum*	*In vitro*	Fadda et al., 2001
Histamine Tyramine	*L. casei*	Cabrales cheese model	Herrero-Fresno et al., 2012
Histamine Tyramine Putrescine	*L. casei*, *Lactobacillus hilgardii, Pediococcus parvulus, Oenococcus oeni, L. plantarum, Pediococcus pentosaceus*	Culture media	García-Ruiz et al., 2011
Histamine Tyramine Putrescine	*L. casei*	Wine	García-Ruiz et al., 2011
Tyramine Putrescine	*L. plantarum*	*In vitro*	Capozzi et al., 2012
Histamine Tyramine Putrescine	*Pencillium citrinum*, *Alternaria sp*., *Phoma sp*., *Ulocladium chartarum, Epicoccum nigrum*	*In vitro*/Commercial wines	Cueva et al., 2012

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