Biogenic Amine Production by LAB

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Lactic acid bacteria (LAB) are considered important biogenic amine (BA) producers in fermented foods. These compounds derive from amino acid decarboxylation through microbial activities and can cause toxic effects on humans, with symptoms (headache, heart palpitations, vomiting, diarrhea) depending also on individual sensitivity. Many studies have focused on the aminobiogenic potential of LAB associated with fermented foods, taking into consideration the conditions affecting BA accumulation and enzymes/genes involved in the biosynthetic mechanisms.

Keywords: biogenic amines ; decarboxylase enzymes ; lactic acid bacteria

1. Biogenic Amine Toxicity and Physiological Role in Microorganisms

A large number of metabolites, exerting both beneficial and detrimental properties for human health, can be synthetized by microorganisms. Among these, amino acid derivatives produced during bacterial growth and fermentation can interact with human physiology in several ways, showing health-modulating potential [1]. This group includes bioactive compounds such as biogenic amines (BAs), which are responsible for adverse effects and are involved in several pathogenic syndromes [1]. In fact, ingestion of food containing high BA amounts is a risk for consumer health since these compounds can cause headache, heart palpitations, vomiting, diarrhea and hypertensive crises [2][3][4]. However, their toxic effect depends on the type of BA, on individual sensitivity or allergy and on the consumption of monoaminooxidase inhibitory drugs or ethanol, which interact with aminooxidase enzymatic systems responsible for the detoxification process of exogenous BAs [5][6].

According to their chemical structures, BAs can be classified as aromatic (tyramine and 2-phenylethylamine), aliphatic (putrescine, cadaverine, spermine and spermidine) and heterocyclic (histamine and tryptamine) and they are analogous to those naturally found in fresh food products, which exert a physiological role associated with cell growth and proliferation [7][8].

2. Role of LAB in Fermented Food BA Content and Their Decarboxylase Clusters Genetic Organization

BA content in fermented foods is of great interest not only for its potential health concerns but also from an economic point of view. On the other hand, the presence of small concentrations of these compounds in fermented foods is often unavoidable. Moreover, the presence of decarboxylase positive non-starter microorganisms, deriving from raw material and productive environment, often leads to high BA concentrations in fermented foods, especially in those obtained without the use of starter cultures [9][10][11][12]. Although starter cultures are accurately selected for the absence of decarboxylase activity, non-controlled autochthonous LAB involved in ripening process can contribute to BA accumulation. LAB are known to be the most relevant tyramine production. However, the can contribute to the accumulation of histamine and putrescine.

Enterococci are the LAB characterized by the highest tyraminogenic potential. The first tyrosine decarboxylase locus (*tdc*) described in bacteria was found in *Enterococcus faecalis* JH2-2 [13]. This cluster has been annotated also in the genome sequence of other LAB [14][15][16][17][18][19]. Marcobal et al. [20] evidenced for all tyramine biosynthetic loci a high similarity in both gene sequence and organization, since this locus usually contains the genes encoding tyrosine decarboxylase (*tyrDC*), tyrosyl tRNA synthetase (*tyrS*, located upstream the *tyrDC* gene), putative tyrosine/tyramine permease (*tyrP*, located downstream the *tyrDC* gene) and a Na^+/H^+ antiporter (*nhaC*) [9]. The similar organization of different *tdc* clusters, their distribution, and their high similarity of sequence suggest a horizontal transfer of this cluster from a common source [18]. However, different strains can have different transcriptional organizations of the *tdc* gene cluster, as demonstrated by reverse transcription polymerase chain reaction (PCR) analyses. In fact, the four complete Open Reading Frame (ORF) can be co-transcribed [21] or *tyrS* can be transcribed independently and not included in the catabolic operon [22].

The LAB histidine decarboxylases belong to pyruvoil-dependent decarboxylases group and the encoding histidine decarboxylase gene (*hdcA*) has been identified in several LAB species [23][24][25][26][27][28][29][30][31][32]. The histidine decarboxylase gene clusters (*hdc*) of Gram positive bacteria usually comprise the decarboxylase gene *hdcA* and the histidine/histamine antiporter gene *hdcP*. Frequently, an *hdcB* gene, involved in the conversion of the histidine decarboxylase proenzyme to the active decarboxylase can be found [33]. Moreover, for lactobacilli, a histidyl-tRNA synthetase (*hisS*) gene has also been described [25]. The transcriptional studies demonstrated that these genes are located on an operon transcribed as a polycistronic mRNA. However, some authors demonstrated that the antiporter gene is transcribed as a monocistronic RNA and that transcriptional termination structures are present in the intergenic regions of histamine operon in *Lactobacillus buchneri* [30]. Rossi et al. [26] found that *hdcA* gene of *Streptococcus thermophilus* PRI60 was genetically different from the *hdcA* genes sequenced in other LAB, in agreement with the findings of Calles-Enríquez et al. [25], who reported that *hdc* cluster of *S. thermophilus* was more closely related to genera such as *Clostridium* and *Staphylococcus* than other LAB. Another interesting feature of *hdc* gene is its possibility to be located on a plasmid [24]. Lucas et al. [23][34] found that *Lentilactobacillus hilgardii* 0006, *Tetragenococcus muriaticus*, and *Oenococcus oeni* strains showed 99 to 100% identical *hdcA*- and *hdcB*-encoded proteins, highlighting the presence of a plasmid-encoded histidine decarboxylase system recently transferred horizontally between bacteria. Furthermore, they found that the *hdc* gene cluster, responsible for histamine production in *Lentilactocacillus hilgardii* IOEB 0006, was located on an 80-kb plasmid that proved to be unstable. In fact, the capability to form histamine was lost in relation to the growth conditions.

Depending on the producer bacterium, genes/enzymes involved and the ecological niche from which it originates, two different metabolic routes have been described in LAB for the biosynthesis of putrescine [35][36][37]. The first is a decarboxylation system consisting of an ornithine decarboxylase (ODC) and an ornithine/putrescine exchanger. These enzymes are encoded by a gene cluster containing two adjacent genes: (i) *speC* encoding a biosynthetic/constitutive form of the ODC enzyme and (ii) *potE* encoding the transmembrane substrate/product exchanger protein [38][35][39]. Gram positive bacteria, however, have been infrequently reported to possess an ODC enzyme and putrescine-producing LAB strains via the ODC pathway are essentially, although not exclusively, derived from wine environment, belonging to the species *Ligilactobacillus saerimneri*, *Levilactobacillus brevis* [38][35], *Liquorilactobacillus mali* [40], and *Oenococcus oeni* [41]. In contrast, the agmatine deiminase (AgDI) pathway is relatively frequent in LAB and it is even considered a species trait in some enterococci [42]. This pathway consists of a more complex system, comprising AgDI, a putrescine transcarbamylase, a carbamate kinase, and an agmatine/putrescine exchanger [43][44]. Five genes are grouped in the agmatine deiminase cluster (*AgDI*): the regulator gene *aguR* and the metabolic genes *aguB*, *aguD*, *aguA* and *aguC* (*aguBDAC*). Linares et al. [45] reported that *aguR* is constitutively transcribed from its promoter (P*aguR*) while the catabolic genes are co-transcribed in a single mRNA from the *aguB* promoter (P*aguB*) in a divergent orientation. These pathway genes were occasionally detected in a putative acid resistance locus in LAB species [44]. In this locus, the *AgDI* genes are found adjacent to the genes associated with the tyrosine decarboxylase pathway on the chromosome [21], suggesting the presence of genes for high-alkalinizing routes (such as amino acid decarboxylases) in LAB genome.

3. Main LAB Involved in BA Production in Fermented Foods

All fermented foods are subjected to the risk of BA contamination. Although LAB are considered GRAS (Generally Regarded As Safe) organisms, they can have the capability to produce toxic compounds as BAs. In particular, in fermented foods, NSLAB can accumulate BAs and strains of lactobacilli, enterococci, lactococci, pediococci, streptococci, and leuconostocs have been associated with high levels of these compounds [46]. Genetic studies have revealed that many of these strains harbor genes or operons coding for decarboxylating enzymes or other pathways implicated in BA biosynthesis [20][36].

It is known that this decarboxylase activity provides cell advantages because it allows increasing the environmental pH and leads to the energization of membrane. The genetic clusters responsible for BA production in LAB have been described can show differences that depend mainly on the species and the strain. Nevertheless, it is interesting to note that the decarboxylation mechanisms constitute an important ecological tool which can favor strain competitiveness in stressful conditions (i.e., acid and nutritional stresses) [35][47][22].

The aminobiogenic ability is strain dependent and the selection of specific LAB starters lacking the pathways for BA accumulation and able to outgrow autochthonous microbiota under production conditions is essential to obtain high quality food with reduced contents of these toxic compounds [48].

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