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Review

Formation of biogenic amines in the cheese production chain: Favouring and hindering factors

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ABSTRACT

The presence of biogenic amines in cheeses is due to microbial enzymes showing decarboxylation or amination activity. They are generally low in raw milk, while in fermented or ripened cheeses and dairy products much higher concentrations can be found. This review focuses on the main factors associated with the raw material as well as the different technological processes affecting biogenic amine formation in these foods. Some innovative strategies are also described as important preventive measures to be recommended to operators engaged in the dairy sector.

Contents

1. Introduction

Biogenic amines (BAs) are biologically active substances produced during the regular metabolism of animals, plants, and microorganisms, with some physiological functions, such as the control of blood pressure, cellular growth regulation, neurotransmission, and allergic response (Erdag, Merhan, & Yildiz, 2019). Some BAs have been named according to their amino acid precursor, i.e., histamine from histidine, tyramine from tyrosine, tryptamine from tryptophan, or phenylethylamine from phenylalanine. They are classified by the number of amine groups as follows: monoamines (tyramine, phenylethylamine), diamines (histamine, serotonin, tryptamine, putrescine, cadaverine), or polyamines (spermine, spermidine, agmatine). Exceptions are BAs deriving from other biogenic amines, such as putrescine from agmatine, and spermine and spermidine from putrescine (Lázaro de la Torre & Conte-Junior, 2018). The most important BAs, their biosynthetic pathways and physiological activities are shown in Table 1.

Different BAs can cause adverse effects on consumers, as well as foodborne diseases. Scombroid poisoning is due to the consumption of some fish species (tuna, mackerel, bonito, bluefish, swordfish, sardine, herring, anchovy, etc.) with a high histamine content from decarboxylation of free histidine by microbial decarboxylases

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Table 1
Classification of biogenic amines and their physiological functions.[a]

Amino acid	Biogenic amine	Number of amine groups	Chemical structure	Biosynthetic pathway	Physiological function	Reference
Tyrosine	Tyramine	Monoamine	Aromatic	Tyrosine decarboxylase	Vasoconstriction, hypertension, noradrenalin secretion	Benkerroum (2016)
Phenylalanine	Phenyle thylamine	Monoamine	Aromatic	Tyrosine decarboxylase	Vasoconstriction, hypertension, neurotransmission	Kaur and Kumari (2016)
Histidine	Histamine	Diamine	Heterocyclic	Histidine decarboxylase	Immune system response, gastric acid secretion, vasodilatation, hypotension, neurotransmission	Nakamura, Ishimaru, Shibata, and Nakao (2017)
Tryptophan	Tryptamine	Diamine	Heterocyclic	Aromatic L-amino decarboxylase	Vasoconstriction, hypertension, neurotransmission	Tittarelli, Mannocchi, Pantano, and Romolo (2015)
Tryptophan	Serotonin	Diamine	Heterocyclic	Tryptophan hydroxylase and aromatic L-amino acid decarboxylase	Neurotransmission, appetite, sleep and mood disorder regulation	Zhang, Yan, Luo, Huang, and Rao (2018)
Lysine	Cadaverine	Diamine	Aliphatic	Lysine decarboxylase	Growth regulation, diamine and polyamine formation	Jairath, Singh, Dabur, Rani, and Chaudhari (2015)
Arginine	Agmatine	Polyamine	Aromatic	Arginine decarboxylase	Nitric oxide synthesis, blood glucose regulation, polyamine metabolism	Demady, Jianmongkol, Vuletich, Bender, and Osawa (2001)
Ornithine Agmatine*	Putrescine	Diamine	Aliphatic	Ornithine decarboxylase Agmatine deiminase	Hypotension, cellular growth or division, anti-depression	Valdés-Santiago and Ruiz-Herrera (2013)
Putrescine*	Spermine	Polyamine	Aliphatic	Spermine synthase	Cellular metabolism, intestinal tissue development	Medina, Urdiales, Rodriguez-Caso, Ramirez, and Sanchez-Jimenez (2003)
Putrescine*	Spermidine	Polyamine	Aliphatic	Spermidine synthase	Biological processes regulation, intestinal tissue development	

[a] An asterisk (*) indicates biogenic amine.

produced when they are improperly preserved and/or refrigerated. Within the European Union, maximum limits (200 and 400 mg kg^{-1}) have been established by the Commission Regulation (EC) No 2073/2005 for fish and fish products belonging to *Scombridae*, *Scomberosocidae*, *Engraulidae*, *Clupeidae*, *Coriphaenidae*, and *Pomatomidae* families (EC, 2005), but also, other non-scombroid species, such as mahi–mahi, marlin, amberjack, Australian salmon, sockeye salmon, and swordfish have been involved in histamine poisoning (Visciano, Schirone, Tofalo, & Suzzi, 2012).

In the United States of America, according to the Food and Drug Administration, a defect action level of 50 mg kg^{-1} for histamine should be considered (FDA, 2020). The most common symptoms of histamine intoxication are due to its effects on different systems (gastrointestinal, cardiovascular, respiratory, etc.) causing vomiting and diarrhoea, headache, hypotension, heart palpitations, asthma attacks, urticaria, and other rashes typical of allergies (Feddem, Mazzuco, Fonseca, & de Lima, 2019). As histamine is normally released by mast cell degranulation in response to an allergic reaction, the consumption of foods containing high histamine concentrations can have the same effect (Visciano, Schirone, & Paparella, 2020). In severe cases, if treatment with antihistamines is not ensured, death from bronchospasm, respiratory distress, and vasodilatory shock can occur (Stratta & Badino, 2012).

Other amines, such as putrescine and cadaverine, are also associated with histamine intoxication, as they favour the intestinal absorption and/or hinder its detoxification, by inhibiting the enzymes (mono amine or diamine oxidases and N-methyltransferases) involved in the oxidative biodegradation (Yadav, Nair, Sai, & Satija, 2019). Rauscher-Gabernig et al. (2012) proposed maximum tolerable levels of 180 and 540 mg kg^{-1} for putrescine and cadaverine in cheeses respectively. High concentrations of putrescine, spermidine, and spermine can even cause the development of cancers, as they react with nitrite to form carcinogenic nitrosamines (Nalazek-Rudnicka, Kubica, & Wasik, 2020).

Another important BA related to food poisoning is tyramine. It causes the so-called cheese reaction, which is mainly associated with the consumption of this food, even if it can be found also in meat and derived products. Tyramine concentrations between 100 and 800 mg kg^{-1} have been considered acceptable in fermented foods. However, 600 mg per meal should not be exceeded in healthy individuals, and such amount should be reduced in patients assuming mono-amino oxidase inhibitor drugs (EFSA, 2011). The typical signs of tyramine intoxication are migraine, headache, and increased blood pressure, because it triggers the release of noradrenaline from the sympathetic nervous system (Ruiz-Capillas & Herrero, 2019). Recently, a synergic toxicity of tyramine and histamine towards intestinal cell cultures has been demonstrated. Specifically, they show different cytotoxic effects characterised by cell apoptosis from histamine, and direct cell necrosis caused by tyramine (Linares et al., 2016). It seems that the latter event facilitates the access of histamine into the cells, increasing its toxicity (del Rio et al., 2017).

The presence of BAs in foods is associated with microorganisms showing a decarboxylation or amination activity, but also other factors, such as amino acid content, temperature and time of storage, and technological process (i.e., fermentation, maturation, ripening, cooking, pasteurisation, etc.) can affect their formation. In fermented foods, some lactic acid bacteria (LAB) produce BAs as a survival mechanism against the acidic milieu where they are growing (Romano, Ladero, Alvarez, & Luca, 2014). It is well known that the decarboxylation of amino acids occurs more quickly in acid environments, where pH ranges from 4.0 to 5.5 (Perez et al., 2015). Therefore, the selection of LAB used as starters constitutes a fundamental approach to control BA formation (Fong et al., 2020).

As the daily human diet often includes many protein-rich foods of both plant and animal origin as well as beverages, in which BAs can be present, efforts to prevent and avoid their formation are particularly needed. Cheeses are important dietary components, and their consumption is very appreciated worldwide. However, due to high protein content, they are among the foods associated with greater BA amounts, which are also influenced by feedstock, product type, starter culture strains, proteolytic activity, and production process (Benkerroum, 2016). The description of BA occurrence in cheeses during the main stages of their production is the

main topic of this review. Some important recommendations for the operators engaged in the dairy industry are also detailed.

2. The raw milk collected from different dairy animals

The raw milk composition varies depending on many factors, such as the species, age, nutrition, lactation period, and health status of animals, as well as the environmental conditions. The total protein content of the dairy animal species producing cheeses ranges from 3.4% in cow milk to 3.6 and 5.7% in goat and sheep milk respectively. The cow milk proteins are represented mainly by caseins (approximately 80%), while the remaining 20% corresponds to whey proteins (β-lactoglobulin, α-lactalbumin, and immunoglobulins), which are very resistant to chymosin and proteolysis (Moniente, García-Gonzalo, Ontañón, Pagán, & Botello-Morte, 2021). By contrast, the milk obtained from goat and sheep has a lower casein-whey and higher β-casein-α_S-casein ratio compared with cow milk (Roy, Ye, Mougan, & Singh, 2020).

With regards to the amino acid profile, both essential and non-essential compounds are present in milk. The first group is constituted by the following amino acids, i.e., lysine, valine, methionine, leucine, isoleucine, threonine, phenylalanine, and histidine, at different concentrations in both casein and whey proteins. High levels of valine have been found in cow casein and sheep whey proteins, while isoleucine, phenylalanine and histidine were more represented in goat casein proteins. Among non-essential amino acids there are glutamic acid, proline, arginine, cysteine, asparagine, serine, alanine, and tyrosine. The highest tyrosine levels were detected in goat casein proteins (Rafiq et al., 2016).

The proteolytic activity of microbial strains occurring in milk and derived products, or through proteases used for coagulating milk in cheesemaking, as well as some endogenous enzymes (e.g., trypsin-like endopeptidase plasmin and cathepsin D) can originate the precursor amino acids for BA formation (Moniente et al., 2021; Papageorgiou et al., 2018).

The contamination of milk is strictly associated with the dairy animal species, as well as some environmental-related factors. *Lactococcus* spp. and *Streptococcus* spp. ($10–10^4$ cfu mL^{-1}), lactobacilli ($10^2–10^4$ cfu mL^{-1}), *Leuconostoc* spp. and *Enterococcus* spp. ($10–10^3$ cfu mL^{-1}) are mainly found in cow milk, but also psychrotrophic genera (*Pseudomonas*, *Acinetobacter* and *Aeromonas*) and anaerobic bacteria of the genera *Bacteroides*, *Faecalibacterium*, *Prevotella* and *Catenibacterium* can be present (Ceniti et al., 2017; Quigley et al., 2013). Moreover, the cattle teat surface may contain different coagulase-negative staphylococci, coryneform bacteria, and *Enterobacteriaceae* (Montel et al., 2014) and even the milking equipment (milking machine, bottles, and storage tanks) can be a reservoir of bacteria due to biofilm formation with consequent transfer to milk (Marchand et al., 2012). Goat milk is also typically dominated by LAB ranging from 10^2 to 10^6 cfu mL^{-1}, as well as *Enterobacteriaceae*, *Micrococcaceae*, moulds and yeasts. Mesophilic and psychrotrophic populations corresponding respectively to $10^2–10^6$ and $10^2–10^4$ cfu mL^{-1} have been reported in sheep milk (Quigley et al., 2013; Tilocca et al., 2020).

The main sources of milk contamination derive from soil, faeces, feedstuffs, bedding material attached to teats, udder infections, farm environment and/or staff taking care of animals, as well as milking and processing equipment (Verraes et al., 2015). During the cheese production process, scarce hygiene practices, failure of thermal treatment and/or temperature abuse can also affect both quality and safety of the final product. The microbial contamination of raw matter represents a great concern for cheesemakers, as microorganisms not only alter the sensory characteristics of cheeses (Laslo & György, 2018), but they can produce hazardous substances such as BAs.

2.1. The decarboxylase positive microorganisms in milk and dairy products

In raw milk, the BA concentrations are usually low, even if they can vary due to the different origin and composition, as previously reported. The main BA-producing microorganisms are shown in Table 2. Several LAB belonging to the different genera such as *Enterococcus*, *Streptococcus*, *Leuconostoc* and *Lactococcus* are naturally present in milk and/or introduced during the production process, but only some strains are BA producers (Benkerroum, 2016). Gram-negative bacteria (*Escherichia coli*, *Hafnia alvei*, *Morganella morganii*, *Pseudomonas* spp. or *Serratia* spp.) have been described as usual contaminants of milk deriving from bad manufacturing practices or poor environmental conditions, and some strains have been shown to be able to produce BAs such as histamine, putrescine and cadaverine (Linares et al., 2012). High counts of *Enterobacteriaceae* have been associated with great amounts of cadaverine and putrescine in Montasio cheese samples, while tyramine was mainly produced by some isolates (Maifreni et al., 2013). Similarly, Coton et al. (2012) reported that isolates belonging to the species *Enterobacter hormaechei*, *M. morganii* and *Serratia* spp. showed formation of cadaverine and isoamylamine, while *M. morganii*, *Proteus heimbachae* and *Serratia* spp. were the most represented species producing histamine.

Some yeast strains of *Debaryomyces hansenii* and *Yarrowia lipolytica* isolated from cheese have been described as histamine and tyramine producers, respectively (Gardini et al., 2006). Wyder, Bachmann, and Puhan (1999) and Roig-Sagues, Molina, and Hernandez-Herrero (2002) found the presence of *Yarrowia lipolytica* and *Pichia jadinii* or *Geotrichum candidum* associated with an increase of histamine and putrescine concentrations.

Pasteurisation of raw milk aims to reduce both the total microbial load and spoiling or pathogenic microorganisms, but in the meantime, it decreases those bacteria that typically contribute to the desirable sensory properties. As consequence, starter cultures are added to milk, such as *Lactococcus lactis* ssp. *lactis* and *Lactococcus lactis* ssp. *cremoris*, which are well-known LAB species used in many fermented dairy products. During ripening, also other lactobacilli species can be involved, i.e., *Lacticaseibacillus casei*, *Lacticaseibacillus paracasei*, *Lactiplantibacillus plantarum*/*paraplantarum*, *Lacticaseibacillus rhamnosus*, *Latilactobacillus curvatus*, *Levilactobacillus brevis*, *Lactiplantibacillus pentosus*, *Lactobacillus acidophilus*, etc. In addition, *Streptococcus thermophilus* and *Lactobacillus helveticus* are thermophilic LAB widely used for their ability to grow at relatively high temperature. By contrast, enterococci are not present in starter cultures, but they are often found in artisanal cheeses, where they can predominate over lactobacilli and lactococci. The most common species are *Enterococcus faecium*, *Enterococcus durans*, *Enterococcus faecalis*, and with minor extent, *Enterococcus casseliflavus*. They are considered contaminating microbial populations and can also include amino biogenic strains (Barbieri, Montanari, Gardini, & Tabanelli, 2019; Quigley et al., 2013). Bonetta et al. (2008) demonstrated that *E. faecalis* was the most widespread decarboxylase positive bacterial species in Italian goat cheeses, and all strains were capable of decarboxylating tyrosine to tyramine up to 2067 mg kg^{-1} in ripened samples.

Some autochthonous non-starter lactic acid bacteria (NSLAB) including pediococci, enterococci, and other thermophilic LAB take origin especially from the cheesemaking environment (floors, drains, equipment surfaces) and survive for a long period thanks to their ability to obtain energy from amino acids. They show the opposite kinetic growth in cheeses compared with LAB, because

Table 2
Biogenic amines and their producing microorganisms in cheeses.[a]

Microbial species	Biogenic amine							Reference
	CAD	HIS	ISO	PHE	PUT	TYR	TRP	
Prokaryotic								
*Aerococcus viridans**								Roig-Sagues et al. (2002)
Cedecea spp.		•						
Citrobacter braakii	•	•		•		•		Chaves-López et al. (2006); Martuscelli et al. (2005)
Citrobacter freundii	•	•	•	•	•	•	•	Coton et al. (2012); Durlu-Özkaya, Ayhan, and Vural (2001); Maifreni et al. (2013); Marino, Maifreni, Moret, and Rondinini (2000); Pircher, Bauer, and Paulsen (2007)
Edwarsiella spp.		•						Roig-Sagues et al. (2002)
Enterobacter spp.	•	•			•			Maifreni et al. (2013)
Enterobacter aerogenes	•	•			•	•		Marino et al. (2000)
Enterobacter cloacae	•	•			•	•		Marino et al. (2000); Maifreni et al. (2013); Pircher et al. (2007)
Enterobacter gergoviae	•	•			•	•		Marino et al. (2000)
Enterobacter casseliflavus		•				•		Roig-Sagues et al. (2002); Standarová Borkovcová, Dušková, & Vorlová (2009)
Chronobacter sakazakii	•	•			•	•		Roig-Sagues et al. (2002); Martuscelli et al. (2005)
*Enterococcus durans**				•		•		Perin, Belviso, Dal Bello, Nero, and Cocolin (2017); Roig-Sagues et al. (2002)
*Enterococcus faecalis**				•	•	•		Ladero et al. (2012); Perin et al. (2017); Roig-Sagues et al. (2002)
*Enterococcus faecium**						•		Roig-Sagues et al. (2002)
*Enterococcus hirae**						•		Perin et al. (2017)
Escherichia coli	•	•			•	•		Durlu-Özkaya et al. (2001); Maifreni et al. (2013); Marino et al. (2000); Roig-Sagues et al. (2002)
Escherichia fergusonii	•	•			•			Maifreni et al. (2013)
Hafnia alvei	•	•	•		•	•		Coton et al. (2012); Durlu-Özkaya et al. (2001); Maifreni et al. (2013); Marino et al. (2000); Roig-Sagues et al. (2002)
Halomonas venusta	•	•		•	•	•	•	Coton et al. (2012)
Klebsiella pneumoniae		•						Roig-Sagues et al. (2002)
Klebsiella oxytoca	•	•	•	•	•	•		Coton et al. (2012); Marino et al. (2000)
*Levilactobacillus brevis**					•	•		Ladero et al. (2015); Roig-Sagues et al. (2002)
*Lentilactobacillus buchneri**		•						Kung et al. (2005); Roig-Sagues et al. (2002)
*Lacticaseibacillus casei**		•				•		
*Lactobacillus delbrueckii**		•				•		
*Lactiplantibacillus plantarum**		•				•		
*Lentilactobacillus parabuchneri**		•						Berthoud et al. (2017); Diaz et al., 2016
*Lactococcus lactis**		•		•	•	•		Ladero et al. (2011); Perin et al. (2017); Roig-Sagues et al. (2002)
*Leuconostoc mesenteroides**						•		Roig-Sagues et al. (2002)
Morganella morganii	•	•		•	•	•	•	Coton et al. (2012); Durlu-Özkaya et al. (2001)
Pantoea agglomerans	•				•			Maifreni et al. (2013)
*Pediococcus damnosus**						•		Roig-Sagues et al. (2002)
Pseudomonas putida	•	•		•	•	•	•	Coton et al. (2012)
Pseudomonas lundensis	•	•	•		•	•		
Raoultella ornithinolytica	•	•			•	•		Maifreni et al. (2013)
Serratia liquefaciens	•	•		•	•	•	•	Coton et al. (2012); Marino et al. (2000); Roig-Sagues et al. (2002)
Serratia odorifera		•		•	•		•	Chaves-López et al. (2006); Roig-Sagues et al. (2002)
*Streptococcus thermophilus**		•						Ladero et al. (2015)
Eukaryotic								
Debaryomyces hansenii		•			•			Gardini et al. (2006); Wyder et al. (1999)
Geotrichum candidum		•						Roig-Sagues et al. (2002)
Yarrowia lipolytica	•			•		•		Gardini et al. (2006); Wyder et al. (1999)

[a] Abbreviations are: CAD, cadaverine; HIS, histamine; ISO, isoamylamine; PHE, phenylethylamine; PUT, putrescine; TYR, tyramine; TRP, tryptamine. An asterisk (*) indicates Gram-positive bacteria.

they increase during ripening and as stress response to milk acidification, they encode specific genetic mechanisms that lead to physiological changes such as decarboxylation reactions. Several NSLAB genomes encode for different enzymes, such as glutamate, histidine, or phenylalanine decarboxylases, arginine and serine deiminases, or aspartate and alanine aminotransferases, which are involved in deamination, decarboxylation, and transamination of free amino acids (Gobetti, De Angelis, Di Cagno, Mancini, & Fox, 2015).

3. The influence of the cheesemaking process on biogenic amine production

Cheese manufacturing is one of the most important activities in the dairy industry, developing a wide assortment of cheeses, which are appreciated worldwide for their sensory and nutritional characteristics. The refrigeration of milk after collection at temperatures between 6 and 8 °C and its storage to not more than 6 °C are essential for both quality and safety of the final product, as such conditions favour the development of useful lactic microbiota and hinder, by contrast, the growth of pathogenic or spoilage bacteria.

During the first phases of cheesemaking, an evolution of the raw milk microbiota is often observed due to several factors, such as the intervals of time/temperature of curd cooking, curd sedimentation and whey drainage. Moreover, when the natural bacteria of raw milk are destroyed by pasteurisation, the addition of starter cultures is fundamental to ensure acidification (Giraffa, 2021). The fundamental stages of cheesemaking are acid or rennet coagulation, and other technological operations, such as salting, cutting, and stirring of the curds, or pressing. The basic process includes acid or enzymatic coagulation of casein micelles, removal of whey by cutting and stirring, and lactic acid production (D'Amico, 2014).

The most important critical points to be considered are: (i) the delivery of raw material, as the indigenous microbial populations present in milk can influence the subsequent stages, (ii) the thermal milk treatment intensity or duration, and (iii) the length and conditions of the ripening process (Linares et al., 2012). The curd fusion by pressing and its ripening or curing are the main differences between fresh and ripened cheeses production. The fermentation and maturation of cheeses stimulate proteases and peptidases with subsequent presence of small peptides and free amino acids. Many elements can provide suitable circumstances for BA formation, such as pH ranging from 5.0 to 6.5, high water activity levels from 0.9 to 1.0, and the availability of pyridoxal phosphate, which is an important cofactor for the activity of amino acid decarboxylases. By contrast, the fat content inhibits the proteolytic bacteria. The temperatures of fermentation (25–44 °C) and cheese maturation (10–20 °C) can also favour proteolysis (Benkerroum, 2016). The latter process may result from different sources, such as proteolytic microbial strains, natural heat-stable protease plasmin, and proteases added for coagulating milk or coming from somatic cells (Calzada, Del Olmo, Picon, Gaya, & Nuñez, 2013). Several studies (Ivanova, Ivanova, Ivanov, & Bilgucu, 2021; Ubaldo, Carvalho, Fonseca, & Glória, 2015) reported a greater BA content in cheeses made from milk with high somatic cell counts, probably because mastitis enhances proteolysis. Tyramine and tryptamine have been detected in Mozzarella cheese produced with high somatic cell count milk (Ubaldo et al., 2015). Finally, the storage of the final product at temperature abuse conditions, but also under refrigeration, can trigger the activity of BA-producing microorganisms, even psychrophilic and psychrotrophic bacteria, such as *Pseudomonas* spp. and *Proteus* spp. (Benkerroum, 2016). Some strains belonging to *Pseudomonas* spp. are considered major cheese spoilage microorganisms and are also able to produce BAs (Coton et al., 2012; Martuscelli et al., 2005). By contrast, Calles-Henríquez et al. (2010) reported that *St. thermophilus* strains produced low amounts of histamine when stored at refrigeration temperature (4 °C) after its growth in milk.

3.1. The biogenic amine content in different cheeses and dairy products

The BA levels in dairy products are strictly linked to the production process and can range from milligrams to tens of milligrams per kg. Pekcici, Guler, and Topkafa (2021) reported that tyramine was the major BA found in yoghurt and kefir samples, reaching values of about 6.0 mg kg^{-1}. Putrescine, histamine and spermine were also detected in yoghurt, while cadaverine, phenylethylamine and spermidine were found in kefir. It is probable that poor hygiene conditions or bad manufacturing practices could influence such results.

It is well known that many biochemical reactions take place during cheese ripening, such as fermentation of residual lactose and degradation of lactate to acetaldehyde, CO_2, ethanol, acetic or propionic acid, hydrolysis of lipids and proteins into fatty acids and amino acids, and their subsequent degradation to several mixtures responsible of aroma, i.e., alcohols, aldehydes, ketones, esters or lactones, amines, and phenolic compounds (Moniente et al., 2021). Also, the fermented dairy products show a great variability of BA levels, depending on the different degree of raw material contamination, phases and time of storage/maturation, and use of starter cultures. During fermentation, the conversion of lactose to glucose and galactose and subsequently to lactic acid leads to milk acidification that inhibits the growth of microorganisms (Buňka et al., 2012).

The BA concentrations reported in many studies from literature are shown in Table 3. The highest values are generally found in fermented or ripened cheeses. Kandasamy et al. (2021) observed that the total BA levels in farmstead fresh cheeses ranged from 11.21 to 62.1 mg kg^{-1}, whereas they varied between 257.7 and 384.3 mg kg^{-1} in the ripened cheeses, showing a gradual increase upon the ripening period. The data collected in the European Food Safety Authority (EFSA) Opinion reported maximum histamine and tyramine content in fresh and hard cheeses, corresponding to 119 and 1240 mg kg^{-1} and 457 and 1450 mg kg^{-1}, respectively (EFSA, 2011).

Zdolec et al. (2022) examined several soft (Brie, Camembert, and Gorgonzola type), semi-hard (Trappist and Dutch type) and hard (Parmigiano Reggiano type) cheeses, both in the core and surface of the product, and found the highest mean total BA content in the core of semi-hard cheese (354.0 mg kg^{-1}), followed by soft and hard cheeses (249.0 and 157.4 mg kg^{-1}, respectively). Indeed, in the rind they corresponded to 240.5 and 175.0 mg kg^{-1} in soft and semi-hard cheeses respectively, while the lowest value was detected in hard cheese (107.2 mg kg^{-1}). Among BAs, tyramine was the most represented for 75.4, 41.3 and 35% of the total in soft, hard, and semi-hard cheeses, respectively, with mean concentrations below 200 mg kg^{-1}. Histamine was the second BA found at higher mean levels in the core of semi-hard (87.8 mg kg^{-1}) and hard (28.4 mg kg^{-1}) cheeses than in soft (7.1 mg kg^{-1}) cheeses, reaching levels above 100 mg kg^{-1} in only few samples. Both tyramine and histamine values did not exceed the tolerance or regulatory levels above-mentioned.

Further studies indicated important BA concentrations in mould-ripened blue cheeses, due to the presence of different fungi and biochemical modifications of milk proteins during fermentation and storage (Reinholds et al., 2020). Also, Pleva et al. (2014) found that the total BA content in blue cheeses ranged from 40 to 600 mg kg^{-1}. The occurrence values of tyramine in blue cheeses reported by EFSA (2011) ranged from 453 to 2130 mg kg^{-1}, while histamine ranged from 153 to 1850 mg kg^{-1}. Cadaverine showed the highest levels up to 3120 mg kg^{-1}.

Some stress conditions in ripened cheeses, such as low pH (4.8–5.3), NaCl concentrations ranging between 1 and 3%, low moisture content (45–25%), as well as lack of lactose and competitive microorganisms, can cause adaptation responses in NSLAB strains which are characterised by production of enzymes (i.e., proteases, aminopeptidases, endopeptidases) and increased catabolism of free amino acids for their growth and survival (Gobbetti, De Angelis, Di Cagno, Mancini, & Fox, 2015).

Renes et al. (2014) compared ewe milk cheeses made with commercial starter cultures with batches obtained with autochthonous starter cultures and found the greatest concentrations of cadaverine, spermidine, histamine, and tryptamine in the first group. Such results were probably due to the use of commercial starter cultures selected for their proteolytic capacity, with the purpose of accelerating the ripening period, while the autochthonous strains were characterised by a lower proteolytic and decarboxylase activity. Also, Schirone, Tofalo, Visciano, Corsetti, and Suzzi (2012) investigated samples of Pecorino cheeses produced from ewe milk inoculated with natural cultures of thermophilic LAB (*St. thermophilus*, *Lactobacillus delbrueckii* subsp. *lactis*, and *L. helveticus*) and observed that they decreased during ripening, while enterococci (mainly *E. faecium* and *E. faecalis*) became prevalent. The BA formation in such cheeses was associated with proteases and peptidases of microbial origin, but also coming from the artisanal lamb rennet that was used in the manufacturing process. Moreover, many physicochemical parameters such as pH, salt concentration, water activity, redox potential, fat content, as well as other factors depending on the production process (i.e., pasteurisation, starter culture, temperature and time of ripening, and storage) seemed to favour the BA-producing microbiota.

Table 3
Biogenic amine content in cheeses.[a]

Cheese type	Biogenic amine (mg kg^{-1})					Reference
	PUT	CAD	HIS	TYR	Total	
Herby	nd–847.0	nd – 1844.5	nd–681.5	18–1125.5	99.5–4723.0	Andiç, Gençcelep, and Kose (2010)
Pecorino Carmasciano	100.0	120.0	65.5	136.4		Mercogliano, De Felice, Chirollo, and Cortesi (2010)
Blue						Linares, Martin, Ladero, Alvarez, and Fernandez (2011)
Raw milk	0–875.8	0–756.8	0–1041.8	0–1052.0		
Pasteurised milk	0–237.6	40.0–89.4	0–127.0	0–526.6		
Pecorino di Farindola	9.9–394.1	26.8–276.1	0–21.8	52.3–1171.3		Schirone, Tofalo, Mazzone, Corsetti, and Suzzi (2011)
Blue	–	–	113.4	2269.3	2382.7	Vallejos, Pham, and Barraquio (2012)
Cheddar	–	–	217.9	571.3	789.2	
Edam	–	–	49.9	199.7	249.6	
Blue-veined	17.3–33.5	–	–	7.2–52.2		Calzada et al. (2013)
Koopeh	2.3–2982.6	2.3–4697.8	2.3–1102.2	2.9–2596.9	517.7	Razavi Rohani, Aliakbarlu, Ehsani, and Hassanzadazar (2013)
Lighvan	40.9–758.2	20.9–1280.9	4.5–73.1	137.2–656.5	1009.0	
Red salmas	72.3–843.7	386.5–1075.8	11.6–254.0	10.1–423.6	1426.9	
Egyptian						El-Zahar, El Zaher, and Ramadan (2014)
Mish	100.3–191.0	100.5–201.0	140.6–291.3	120.4–150.4	572.1–1154.3	
RAS	60.2–130.5	nd–130.7	120.5–231.1	30.1–50.3	342.2–782.9	
Blue	10.1–90.3	40.1–110.3	40.1–140.7	nd–80.2	212.1–703.3	
Apulian or Sicilian	nd–594.0	nd–199.0	nd–435.0	4.0–305.0	3.2–12279.0	Guarcello et al. (2015)
Pecorino Sardo	0.1–0.8	0.1–9.7	nd–7.2	nd–19.3		Manca et al. (2015)
Pecorino	nd–92.7	nd–137.0	nd–128.4	1.6–93.0		
Casu Marzu	1.9–165.8	3.1–470.7	nd–126.0	nd–231.4		
Pecorino Toscano	22.0–512.0	2.0–262.0	nd–23.0	147.0–1132.0		Torracca, Nuvoloni, Ducci, Bacci, and Pedonese (2015)
Irish Artisanal A	122.0	5.0	22.9	140.4	290.3	O'Sullivan et al. (2015)
Reblochon	28.2	22.3	8.4	45.1	104.1	
Irish Artisanal B	157.2	74.4	34.4	190.6	456.6	
Manchego	nd	4.0	nd	17.9	21.9	
Morbier	212.7	267.4	85.1	171.3	736.5	
Tête de Moine	nd	35.7	51.6	44.6	131.9	
Pecorino Sardo	66.9	3.5	23.4	40.4	134.2	
Ossau–Iraty	40.1	9.4	20.8	323.4	393.8	
Comté	nd	9.3	nd	4.5	13.8	
Gorgonzola	3.9	1.2	29.2	nd	34.2	
Zamorano	10.0–190.0	5.0–35.0	1.0–55.0	1.0–85.0		Combarros-Fuertes et al. (2016)
Goat	0.8–21.7	0.5–74.8	10.2–60.5	4.2–50.7	26.4–175.1	Poveda, Molina, and Gómez-Alonso (2016)
Cheddar	2.7	1.6	5.8	5.8	21.1	Bonczar, Filipczak-Fiutak, Pluta-Kubica, Walczycka, and Staruch (2018)
Emmentaler	67.0	4.3	2.5	67.6	153.0	
Camembert	6.5	2.4	1.1	6.2	20.8	
Tvorog	6.2	7.4	3.0	7.5	28.4	
Harzer	281.3	377.5	24.1	275.5	1010.4	
Fried	3.11	4.2	1.1	6.9	23.4	
Kashar						Şahin Ercan, Soysal, and Bozkurt (2019)
Fresh	12.5–274.6	9.2–120.6	29.0–106.8	37.7–125.2		
Mature	50.1–440.2	95.5–448.2	52.8–2035.8	71.2–6665.6		
Fiore Sardo	<0.2–730.0	1.0–9.4	<0.7–250.0	0.5–800.0		Zazzu et al. (2019)
Raw milk	0.3–2.5	1.3–3.8	nd–9.5	0.7–5.8	9.3	Pluta-Kubica, Filipczak-Fiutak, Domagała, Duda, and Migdał (2020)
Pasteurised milk	0.2–1.8	1.0–2.8	2.2–2.6	0.8–3.9	8.7	
Mould-ripened blue	1.3–45.5	1.7–131.0	0.2–186.0	1.1.–717.0		Reinholds et al. (2020)
Halloumi						Kandasamy et al. (2021)
Goat	nd	nd	nd	nd	15.2–15.7	
Cow	nd	nd	nd	nd	11.2–19	
String	nd–3.5	nd	nd–13.5	nd	43.0–62.1	
Quark	nd	nd	nd	nd	15.1	
Cottage	nd	nd	nd	nd	26.8	
Hard Cheddar	nd	nd	nd	82.6–16.2	257.7	
Semi-hard Gouda	nd	17.7–92.5	9.7–111.2	59.3–70.8	292.8–384.3	
Mould-ripened	0.6–30.5	0.6–5.4	0.7–14.0	1.0–710.5	2.9–760.4	
Semi-hard	0.8–95.2	<0.6–436.7	4.2–248.6	<0.9–767.0	6.5–1547.5	
Hard	<0.6–11.6	<0.6–119.4	<0.6–116.4	<0.9–263.3	2.7–483.7	Zdolec et al. (2022)

[a] Abbreviations are: CAD, cadaverine; HIS, histamine; PUT, putrescine; TYR, tyramine; nd, not detected.

Traditional cheeses are often preferred by consumers for their qualitative characteristics that result from the cheesemaking process, such as the use of raw instead than pasteurised milk. Schirone et al. (2013) analysed traditional cheeses (Pecorino di Farindola and Pecorino Abruzzese) produced from sheep milk with specific flavours and sensory attributes derived from the manufacturing operations. In cheeses made with raw milk, BAs were always present at total concentrations (tyramine, histamine, putrescine, cadaverine, and phenylethylamine) between 266.7 and 5860.6 mg kg^{-1}, while in cheeses obtained from pasteurised milk, they ranged from 10.3 to 582.4 mg kg^{-1}. The results highlighted that the autochthonous microorganisms in raw milk can influence

the sensory characteristics of cheeses due to higher proteolysis and lipolysis activities, but in the meantime, they can be responsible for a greater BA formation. In fact, many cheesemakers prefer to use raw milk for a good and stronger flavour of the final product compared with pasteurised milk, but they should always consider the risk of formation of undesirable substances such as BAs. The tyramine and histamine producers were also investigated by quantitative real-time PCR aiming at detecting tyrosine decarboxylase (*tdc*) and histidine decarboxylase (*hdc*) genes; the levels of the organisms ranged from 1.6 to 6.4 log cfu g^{-1} and from not detected to 7 log cfu g^{-1}, respectively. However, some samples with high histamine producer concentrations showed low histamine values, suggesting that other factors could influence its accumulation in cheeses (Schirone et al., 2013). The BA content was checked by Manca et al. (2020) in an artisanal cheese produced from ewe raw milk and characterised by intensive fermentation of autochthonous microorganisms, and relatively long ripening (>3.5 months). The authors reported a total BA content of 1270 mg kg^{-1}, and tyramine was the most represented compound (64% of the total) at maximum concentrations of 820 mg kg^{-1}, followed by putrescine (mean value 210 mg kg^{-1}). Cadaverine, histamine, β-phenylethylamine and tryptamine were generally present at concentrations lower than 100 mg kg^{-1}. It could be supposed that the artisanal dairy products were produced under poor or uncontrolled hygiene conditions, which are known to vary among cheesemakers.

4. Biogenic amine formation in cheeses during storage

The BA concentrations can also increase during storage and throughout the shelf-life of the product. Costa et al. (2015) investigated fermented cow and goat milk containing probiotic bacteria (*Lactobacillus acidophilus*, *Bifidobacterium lactis*, and *St. thermophilus*) during a 10-day storage period at 4 °C, when the viability of such microorganisms was highest. Tyramine was the most abundant amine found in both fermented milks due to a great tyrosine decarboxylase production, but its trend differed between the two investigated species. While in fermented goat milk tyramine concentrations (337.1 mg kg^{-1}) remained stable until the seventh day and increased up to 560 mg kg^{-1} at the end of the storage period, in fermented cow milk they increased linearly reaching levels of 249.5 and 560 mg kg^{-1} after three and ten days, respectively. Such behaviour could be associated with differences in the protein composition (especially casein fractions), ratios of free amino acids, and rate of proteolysis.

With regards to the other BAs, higher histamine and putrescine levels were detected in fermented goat milk, reaching on the 10th day values of 53.9 and 22.9 mg kg^{-1} respectively (20.3 and 17.9 mg kg^{-1} in cow), whereas cadaverine and spermidine concentrations predominated in fermented cow milk (respectively 29.1 and 82.0 mg kg^{-1} versus 22.1 and 34.9 mg kg^{-1} in goat fermented milk). Also, the initial histamine concentration (approximately 100 mg kg^{-1}) was higher in fermented goat milk, probably due to the difference in histidine content.

The BA presence was checked in various cheeses at both the purchase day and expiry date, following the time–temperature storage conditions shown on the product label. An additional 10% time was considered to simulate the domestic storage by consumers. In soft cheeses, cadaverine, tyramine and histamine concentrations showed an increase during storage, and in semi-hard cheeses (Gouda type) tyramine reached maximum levels of 1029 mg kg^{-1} at the expiry date. By contrast, the most abundant BAs, i.e., histamine and tyramine, detected in hard cheeses (Parmesan type) remained quite stable with maximum concentrations of 1025 and 561 mg kg^{-1}, respectively. Finally, tyramine was the most represented amine in blue cheeses, up to values of 1306 mg kg^{-1} at the expiry date. The high microbial activity in long time ripened products such as hard cheeses could lead to considerable BA accumulation at the day of purchase compared with semi-hard cheeses with a shorter fermentation time, in which such activity evolved mostly during the shelf-life (Dabadé et al., 2021).

Madejska, Michalski, Pawul-Gruba, and Osek (2018) investigated four mould cheeses (Lazur Blue, Président Brie Natural, Camembert Erival, and Gorgonzola Piccante) and two hard cheeses (Salami and Mlekdamer) after storage at two different temperatures (22 and 4 °C) up to 42 and 112 (mould) or 133 days (hard) respectively. The highest histamine concentrations (730.5 and 405.2 mg kg^{-1}) were detected in Gorgonzola Piccante and Camembert Erival stored at 22 °C for 42 days and 4 °C for 112 days, respectively. Indeed, levels of 35.8 mg kg^{-1} were found in Mlekdamer cheese after 35 days at 22 °C. The higher histamine amounts in mould than hard cheeses could be due to the additional fungi that contributed to the decarboxylation of histidine to histamine.

Smear ripened cheeses from Czech Republic were analysed after storage at three different temperature regimes, i.e., 6 °C for 49 days (group A), 6 °C for 28 days, −18 °C for 7 days and again 6 °C for 14 days (group B), and 6 °C for 35 days, −18 °C for 49 days, and again 6 °C for 7 days (group C, 91 days in total). The total BA content in groups A and C increased up to 259.7 mg kg^{-1} (day 35), then it decreased to 190.4 and 140.7 mg kg^{-1} (day 49), respectively. The cheese samples of group B showed greater values at the end of storage (day 49) than at the time of production, but the highest content (571.4 mg kg^{-1}) among the three groups was found in group A. The last result was probably due to a reduction or cessation of the microbial activity in cheeses of groups B and C, which were stored at freezing temperatures during the experimental trials (Cwiková & Franke, 2019). Further processing of cheese products (i.e., cut, sliced, or grated) causes major handling and potential increase of microbial contamination, with following consequences on BA producers and formation. A high histamine content of 734.1 mg kg^{-1} was found in long ripened (>3 months) grated cheese samples by Ladero, Fernández, and Alvarez (2009).

5. Prevention and control strategies

The production of raw milk with the lowest possible total count is considered a good performance objective in a holistic strategy. The composition of milk varies seasonally and is influenced by the health status of the animals, as well as by the hygiene conditions during milking and storing. Good hygiene management at farm level, regarding both animals and milking process, the time restriction between milk collection and its subsequent manufacture, and maintenance of appropriate temperature during transport and storage can be effective strategies to control microbial development (Verraes et al., 2015).

The correct temperature of storage of raw milk represents another important measure, especially when it is not pasteurised and used to produce traditional and/or artisanal cheeses. The initial raw milk microbial load ranging from 10^2 to 10^5 cfu mL^{-1} can increase under inappropriate milking operations (Montel et al., 2014). According to the Regulation (EC) No 853/2004 (EC, 2004), the plate count at 30 °C in raw cow milk and raw milk collected from other dairy species must be $\leq$ 100,000 and 1,500,000 mL^{-1} respectively, as rolling geometric average over a two-month period, with at least two samples per month. When raw milk from species other than cows is intended for the manufacture of products by a process that does not involve any heat treatment, such a value must be $\leq$ 500,000 mL^{-1}.

Even if these regulatory criteria can stand for a good hygiene level of the raw material, the BA content in cheese depends mainly on the occurrence of microbial species producing decarboxylases.

Therefore, the selection of decarboxylase-negative starter cultures and/or showing BA degrading activity can hinder their accumulation in cheese (Benkerroum, 2016; Gardini, Özogul, Suzzi, Tabanelli, & Özogul, 2016). The addition of starter cultures generally used in the dairy industry for technological purposes is also advised for their probiotic activity and the ability to benefit the human metabolism and immunity system (Cuffia, George, Godoy, Vinderola, & Reinheimer, 2019; Tilocca et al., 2020). Some starter cultures are also applied as bio-preservation agents due to the production of antimicrobials, such as organic acids, hydrogen peroxide, and bacteriocins. Tabanelli et al. (2014) reported that some *L. lactis* strains showed the capability to produce bacteriocins able to inhibit BA production by *St. thermophilus* and *E. faecalis*. Moreover, the starter cultures can hinder BA formation through enzymes such as multicopper oxidases or amine oxidases that directly degrade the amines, or by an inhibitory effect as competitive cultures. Two main classes of amine oxidases (i.e., flavin- and copper-containing amine oxidases) have been described in different microorganisms, plants, and animals (Lee & Kim, 2013).

However, it is not easy to select a universal LAB starter as BA hurdle to be used in fermented foods, as they differ in the type of raw material, the initial microbial population, and the kinds of free amino acids (Zhang et al., 2022). It is also essential to determine if the LAB strains have specific genes, such as histidine decarboxylase (*hdc*) or tyrosine decarboxylase (*tdc*) associated with the production of histamine and tyramine, respectively (O'Sullivan et al., 2015). Wüthrich et al. (2017) reported the location of *hdc* cluster into the genome of strains of *Lentilactobacillus parabuchneri*, while Ladero et al. (2015) found the presence of genes involved in the biosynthetic pathways of BAs in microbial strains belonging to the species *Levilactobacillus brevis*, *Latilactobacillus curvatus*, *L. lactis* and *St. thermophilus*.

By contrast, the selection of amine-negative and amine-oxidising LAB to be used as adjunct/attenuated starter represents an important preventive measure to avoid and/or reduce the accumulation of BAs in cheese. Guarcello et al. (2016) identified a BA degrading enzyme activity in LAB strains isolated from traditional Italian cheeses and found that the gene encoding the multicopper oxidase was mainly present in strains belonging to *Lb. paracasei* subsp. *paracasei*, but also *Limosilactobacillus fermentum*, *Lactiplantibacillus paraplantarum*, and *Pediococcus pentosaceus*. Then, two strains of *Lb. paracasei* subsp. *paracasei* were successfully tested as a single adjunct starter for reducing histamine and tyramine concentrations in industrial Caciocavallo-type cheese.

Several studies investigated the use of polyphenols in plant extracts from pomegranate seed (2%), safflower (4%), bitter melon (2%), mint (1%), artemisia (1%), etc., and/or terpenoids deriving from spices, such as pepper, ginger, star anise, clove, cassia, fennel, bay leaf, cinnamon, etc. A general antimicrobial activity was observed causing a BA formation decrease (10–60%) in many foods, due to the decarboxylase control or direct inhibition of microorganisms (Majcherczyk & Surówka, 2019). However, the addition of such compounds has mainly been explored in sausages and other meat products, probably due to their overall acceptability when added with plant extracts (Jaguey-Hernández et al., 2021). The application of essential oils as food preservatives against BAs has also been studied. Gorji et al. (2014) reported a significant reduction of tyramine and histamine in Gouda cheese after the addition of *Zataria multiflora* essential oil whose major constituent was carvacrol. All the samples with different concentrations of such essential oil were considered acceptable by the panellists that applied the sensory testing.

Different packaging systems have been assessed against BA formation, such as vacuum and modified atmosphere (Todaro et al., 2018) or edible films and coatings (Costa, Maciel, Teixeira, Vicente, & Cerqueira, 2018). The effects of vacuum and non-vacuum packaging on BAs (cadaverine, putrescine, tyramine, tryptamine, phenylethylamine, and histamine) and organic acids (citric, lactic, formic, acetic, propionic, and butyric) in Kashar cheese during storage for 180 days at 4 °C were evaluated by Andiç, Tunçtürp, and Gençcelep (2011). The authors observed that vacuum packaging hindered or limited the formation of phenylethylamine, cadaverine, and histamine, while it caused higher amounts of lactic, formic, acetic, and butyric acid compared with non-vacuum-packaged cheeses.

6. Conclusions

The production of BAs in cheeses generally indicates both their quality and safety. Many factors such as pH, salt concentration, water activity, and redox potential can influence the growth and metabolic activities of milk and cheese microbiota involved in BA production. Besides the initial microbial load of the raw material, the cheesemaking process can be responsible of BA accumulation in the end products, as the proteolysis rate increases with the ripening time, and free amino acids are used by microorganisms as substrate for their decarboxylase activity. The highest probability to detect BAs in cheeses is generally associated with the duration of the aging period. A good storage of the final product is also recommended, considering that high BA concentrations have also been reported in this stage. The most important hindering factors rely on the selection of decarboxylase-negative or BA degrading starter cultures, good hygiene practices during cheesemaking, and appropriate modulation of all parameters influencing the bacterial population responsible for high production of BAs. A global safety assurance program throughout processing, storage, and retailing of cheeses is essential in the perspective of risk reduction for consumers.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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