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Formation, Degradation, and Detoxification of Putrescine by Foodborne Bacteria: A Review

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Abstract: Biogenic amines (BAs) represent a considerable toxicological risk in some food products. Putrescine is one of the most common BAs in food. Its increased occurrence in food may lead to alimentary poisoning, due to enhancement of the toxic effects of other BAs, and also to lower quality of food, this amine is potentially carcinogenic. Increased occurrence of putrescine in food is mainly due to the bacterial metabolism of the Gram-negative as well as Gram-positive bacteria present. The bacterial metabolism of putrescine is very specific due to its complexity (in comparison with the metabolism of other BAs). There are 3 distinct known pathways leading toward the formation of putrescine, in some splices involving up to 6 different enzymes. The existence of more metabolic pathways and the possibility of their simultaneous use by different bacteria complicate the specification of the best conditions for food production and storage, which could lead to a lower content of putrescine. This review provides a summary of the existing knowledge about putrescine production and detection (mainly detection of specific genes for different enzymes using polymerase chain reaction) in both starter and contaminating microorganisms. Thus, this comprehensive review gives a useful overview for further research.

Keywords: bacteria, biogenic amine, food, metabolism, putrescine

Introduction

Putrescine is a low-molecular-weight nitrogenous base with the systematic name 1,4-diaminobutane. It is an aliphatic diamine belonging to the group of biogenic amines (BAs). Two basic amino groups are present, which at the physiological pH of 7.4 carry a positive charge that makes them suitable for a wide range of functions in different cell types. According to some authors, putrescine also belongs, together with cadaverine, spermine, and spermidine, to polyamines (molecules containing 2 or more amino groups in the molecule) (Smith 1981; Bardócz and others 1995). Polyamines are found in all cell types and their presence in various kinds of foodstuffs is partly due to their endogenous origin.

In humans, there are 3 common sources of putrescine: the first one is endogenous biosynthesis within their own cells, the second one includes foodstuffs (alimentary intake), and the last one is the production of putrescine by bacteria of the intestinal microflora. The largest amount of putrescine in humans is taken from food (Bardócz and others 1995). If none of the 3 sources of putrescine becomes excessive, putrescine is used for its physiological functions and the excess is excreted by normal metabolism. However, increased intake of putrescine in food can lead to serious toxicological consequences.

Toxicological effects of other BAs, mainly those of histamine and tyramine, are more frequently mentioned in the literature. Well-known cases of food poisoning include "scombroid fish poisoning" (caused by fish containing histamine) (Lehane and Olley 2000) or "cheese reaction" (caused by an increased tyramine content) (ten Brink and others 1990). Histamine and tyramine can have vasoactive and psychoactive effects and can cause a wide range of health problems such as vomiting, headaches, hyper- or hypotension, and allergic reactions (ten Brink and others 1990; Halász and others 1994; Ladero and others 2010a). There are only sporadic references to the toxicological effects of putrescine in the literature. The explanation could lie in the fact that putrescine on its own has low toxicological activity. However, its effect is significant in that it enhances the toxicological effects of other BAs, especially histamine and tyramine (Taylor 1985b; Straub and others 1995). Putrescine can also be a precursor to the formation of carcinogenic N-nitrosamines (ten Brink and others 1990; Shalaby 1996).

However, the above-mentioned toxicological points of view are not the only reason for studying and monitoring the occurrence of putrescine in food. Another major reason is the negative effect of putrescine on food quality as it is one of the indicators of undesirable changes in proteins (Lehtonen 1996; Rokka and others 2004). Putrescine can give foodstuffs so-called "putrid odor" (Wang and others 1975). Putrescine is one of the most common BAs in food and its increased occurrence in food is caused by the metabolic production of contaminating microorganisms (ten Brink and others 1990). However, putrescine can also be synthetised by starter

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cultures added to food intentionally (Fernández-García and others 2000).

Another reason for the increasing number of studies dealing with the detection possibilities of putrescine producers includes the detection of the metabolic pathways leading to its production in food. However, the metabolic pathways of its origin are, in comparison with those of other BAs, relatively more complicated.

The objective of this review is to provide an overview of putrescine metabolism in bacteria and research possibilities of putrescine metabolism by means of PCR methods. Microbial metabolism and the possibilities of its monitoring are the main areas of interest. This review provides a useful overview of the current state of knowledge in this field.

Putrescine and Its Effects on the Human Body

As mentioned in the introduction, the increased occurrence of putrescine in food can have numerous negative impacts on human health and food quality. This part deals with both physiological functions of putrescine and its negative impact on human health and food quality.

Putrescine fulfills important physiological functions in a wide variety of living cells. This BA shows many physiological functions and it is a precursor in the synthesis of other polyamines (spermine and spermidine). Putrescine is classified as a physiologic amine. Physiological functions of putrescine and other polyamines are related to their polycationic nature, which determines interactions with negatively charged molecules such as DNA, RNA, proteins, phospholipids (Igarashi and Kashiwagi 2010).

Newer studies show that putrescine, along with other polyamines and phosphate ions, forms nuclear aggregates of polyamines in the cell nuclei, which are responsible for the above-mentioned interactions and affect the 3-dimensional structure of DNA (Di Luccia and others 2009). These interactions are related to the regulation of the structure of nucleic acids and protein synthesis (Silla Santos 1996; Hou and others 2001). Analyses have shown that putrescine binds to a minor groove of the DNA molecule and thus affects its stability (Medina and others 2003). The interactions of polyamines with nucleic acids are still much under study (Kabir and Kumar 2013; Wen and Xie 2013).

Putrescine, along with other polyamines, binds to membrane structures such as phospholipids, mainly in erythrocytes. This polyamine may lead to a decrease in membrane fluidity but also to increased resistance to fragmentation due to stabilization of the membrane skeleton (Til and others 1997; Largue and others 2007). It has also been found that apart from the membrane stabilization and the effect on the synthesis of nucleic acids and proteins, polyamines are involved in the removal of free radicals (Kaur-Sawhney and others 2003). Another interesting fact is relatively high concentration of polyamines in the milk of mammals. In many mammals, they play an important role as luminal growth factors for intestinal maturation and growth (Dufour and others 1988; Löser 2000) and can play a significant role in the prevention of food allergies (Dandrifosse and others 2000). In mammals, polyamines have direct effects on several ion channels and receptors, resulting in the regulation of Ca^{2+}, Na^{+}, and K^{+} homeostasis (Johnson 1996; William 1997; Li and others 2007).

It has been found that oral intake of putrescine results in its fast distribution within the body, as shown in experiments with ^{14}C putrescine in adult rats. Within 30 min after the intake of putrescine, radioactivity was detected in the intestines, blood, and various organs, which suggests a very rapid distribution of putrescine in an organism and emphasizes the importance of monitoring and knowing about the putrescine content in foodstuffs (Bardócz and others 1995). From a physiological point of view, putrescine belongs to vasoactive amines and thus it can increase cardiac output, which could lead to heart failure or cerebral haemorrhage (Til and others 1997; Kalač 2009; Mohan and others 2009) as well as tachycardia or hypotension (Ladero and others 2010a).

With respect to important physiological functions, it is clear that disruption of the normal balance due to increased intake of putrescine from food can have serious toxicological consequences. Although the toxic effects of putrescine are significantly lower than that of histamine or tyramine, there are many serious secondary effects. Diamines such as putrescine have a very important role in alimentary poisoning as they can enhance and potentiate the toxic effect of histamine, tyramine, and phenylethylamine by interacting with enzymes that metabolize these BAs (Taylor 1985a). For example, experiments on guinea pigs and rats revealed that putrescine potentiates histamine toxicity up to 10 times (Parrot and Nicot 1966; Lehane and Olley 2000). Putrescine enhances histamine toxicity by inhibiting enzymes oxidizing histamine diaminooxidase (DAO; EC 1.4.3.6) and histamine N-methyltransferase (NMT; EC 2.1.1.8) (Stratton and others 1991; Hernández-Jover and others 1997; Emborg and Dalgaard 2006).

From a toxicological point of view, a serious aspect of putrescine occurrence in foodstuffs is the posibility of forming carcinogenic nitrosamines. Putrescine can form carcinogenic nitrosamines by the reaction with nitrites (ten Brink and others 1990; Shalaby 1996; Bover-Cid and Holzapfel 1999; Kalač and others 2005), which is shown in Figure 1. The initiator of this reaction is nitrogen oxide, produced from nitrites that are regular food additives mainly, in the meat industry, or naturally present in many foodstuffs of plant origin. Heating of putrescine leads to the production of pyrrolidine, from which N-nitrosopyrrolidine is formed, also by means of heat (Gray and Collins 1977; Spinelli-Gugger and others 1981; Karovičová and Kohajdová 2005). N–nitrosopyrrolidine is classified by the Intl. Agency for Research on Cancer (IARC) as a Group 2B carcinogen (possible human carcinogen). It has also been shown that putrescine increases the risk of N-nitrosodimethylamine formation in heat-treated pork (Drabik-Markiewicz and others 2011). This N-nitrosoamine is classified by US Environmental Protection Agency (EPA) as a Group 2B carcinogen and by IARC as a Group 2A carcinogen (limited evidence in humans and sufficient evidence in aminals).

Moreover, putrescine is involved in the development of neoplasms in another way, which is closely related to its physiological function. As mentioned above, putrescine is, along with other polyamines, involved in cell growth and cell proliferation. For this reason, studies in which suppression of tumor cell growth was tested by means of reduction the activity of ornithine decarboxylase (ODC) (Pegg and others 1995), which is one of the enzymes responsible for the formation of putrescine. One of the most common inhibitors of ODC used in cancer therapy is difluomethylornithine (Meyskens and Gerner 1995). However, tumor cells have the ability to absorb extracellular amines from food or amines produced by gastrointestinal bacteria, and therefore, the therapy was not effective (Seiler 2003a,b; Carruthers and others 2007). Nevertheless, preliminary clinical studies have shown that reducing the dietary intake of polyamines and decreasing the production of polyamines by intestinal microflora are beneficial for the quality of patients´ life and pain management (Cipolla and others 2007).

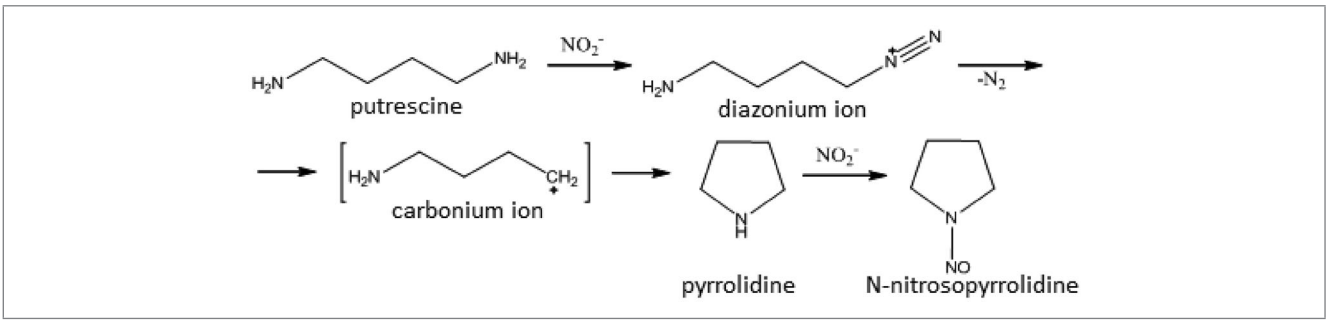

Figure 1–Nitrosation of putrescine giving N-nitrosopyrrolidine.

The Influence of Putrescine on Food Quality

In addition to the toxic effects, the occurrence of putrescine in foodstuffs leads to undesirable organoleptic properties and adversely affects the taste and aroma of food (Lehtonen 1996), for example, in shrimps, it is perceptible at concentrations of 3 mg/kg (Benner and others 2003). Increased occurrence of putrescine indicates food spoilage caused by microbial activity and it is also the main BA that indicates spoiled meat. The amount of putrescine, histamine, and cadaverine shows the freshness of meat and is defined as biogenic amines index (BAI) (Karmas 1981):

$$\mathrm{BAI} = \frac{histamine\left(\frac{mg}{kg}\right) + \text{putrescine}\left(\frac{mg}{kg}\right) + \text{cadaverine}\left(\frac{mg}{kg}\right)}{1 + spermine\left(\frac{mg}{kg}\right)\ apermidine\left(\frac{mg}{kg}\right)} \quad (1)$$

According to this index, the freshness quality of meat is evaluated in the following way: BAI < 5 indicates high-quality fresh meat; BAI between 5 and 20 indicates meat of acceptable quality with initial signs of spoilage; meat with BAI 20-50 is meat of low quality, and meat with BAI > 50 is referred to as spoiled meat (Hernández-Jover and others 1996). Thus, there are 2 main reasons for monitoring of the production and putrescine content in foodstuffs: its potential toxicity and its content being used as the indicator of food quality.

Putrescine is one of the main BAs found in fermented vegetable dishes (264 mg/kg on average), fish sauces (98.1 to 99.3 mg/kg), fermented sausages (84.2 to 84.6 mg/kg), cheeses (25.4 to 65.0 mg/kg), and fermented fish (13.4 to 17.0 mg/kg) (EFSA 2011). Putrescine is abundant in meat and meat products too. According to various studies, putrescine is the prevailing BA in wine (Ancín-Azpilicueta and others 2008) where it occurs in the range of 1 to 200 mg/L (Soufleros and others 1998). Moreover, putrescine has also been found in all of 195 samples of European beers tested (Izquierdo-Pulido and others 1996) and in 111 of 114 Czech beers (Buňka and others 2012). An overview of the occurrence of polyamines (putrescine, spermine, and spermidine) in various foodstuffs can be found in many publications (Kalač and Křížek 2003; Kalač and Krausová 2005; Buňková and others 2010b, 2013; Lorencová and others 2012; Buňka and others 2013), and there are also some databases providing information about the content of polyamines in food (Zoumas-Morse and others 2007; Ali and others 2011). Generally, putrescine is one of the most common BAs found in food (Fernández and others 2007).

So far, there is no legislative limit on putrescine content in food. According to toxicological data, the acute oral toxicity of putrescine in rats was set at 2000 mg/kg body weight (Til and others 1997). Some authors also discussed the proposal on maximum tolerable levels of putrescine in food. For example, Rauscher-Gabernig and others (2012) suggested maximum tolerable concentrations of putrescine in fish (170 mg/kg), fermented cabbage (140 mg/kg), cheeses (180 mg/kg), fermented sausages (360 mg/kg), and seasoning products (510 mg/kg) on the basis of toxicological data, the occurrence of putrescine in foodstuffs, and average human consumption of these foodstuffs.

Putrescine-Producing Microorganisms in Food

High concentrations of putrescine often correspond to activity of the decarboxylation enzymes of the contaminating microflora. The production of putrescine in food is associated mainly with bacteria of the genus *Pseudomonas* and enterobacteria (Smith 1981; ten Brink and others 1990). Technological important bacteria such as lactic acid bacteria (LAB) may significantly contribute to the production of BAs too (Fernandéz-García and others 2000; Buňková and others 2009, 2011, 2012). Table 1 shows a list of putrescine-producing microorganisms in food. Generally, decarboxylase activity of bacteria is dependent on the individual strains and is therefore not species-specific. For example, some strains of *Lactobacillus curvatus* are known for their aminogenesis (BA production), whereas strains of *Lactobacillus sakei* are often referred to as the strains without decarboxylase activity (not producing BA) (Bover-Cid and others 2008). LAB produce mainly tyramine, occasionally they may also produce considerable amounts of putrescine and other BAs (Straub and others 1995; Bover-Cid and others 2000b; Buňková and others 2009, 2010b).

Bacterial Metabolism of Putrescine

With respect to the fact that bacterial metabolism is the main source of putrescine in food, this part deals with a detailed description of the bacterial metabolism of putrescine. The formation of putrescine in food can be controlled through an inhibition of decarboxylase activity of a specific microorganism present (Wendakoon and Sakaguchi 1995), and therefore, an intensive study of its metabolism and its possible influence is very important. This part gives an overview of up-to-date knowledge about microbial metabolism of putrescine in Gram-negative as well as in Gram-positive bacteria.

BA synthesis (including that of putrescine) in bacteria is often related to energy gain or resistance to an acidic pH (Konings and others 1997; Griswold and others 2006). Most BAs are formed in one metabolic pathway catalyzed by a decarboxylase enzyme. In contrast, putrescine can be formed by Gram-negative bacteria via 3 different pathways including up to 8 different enzymes. In the case of Gram-positive bacteria, there are 2 pathways including up to 3 enzymes. Moreover, some of these enzymes can have 2 forms—biosynthetic and biodegradative. The biodegradative forms are induced by many factors (including a low pH, anaerobic

Table 1–List of putrescine-producing microorganisms isolated from food.

Microorganism	Source	*N*[a]	Putrescine production[b]	Reference
Enterobacteriaceae				
Citrobacter braakii	Cheese, sausage	5	+ to +++	Chaves-López and others 2006; Lorenzo and others 2010
Citrobacter freundii	Cheese, meat, ground beef and hamburger, sausage; not specified[c]	18	++ to ++++	Bover-Cid and Holzapfel 1999; Marino and others 2000; Durlu-Özkaya and others 2001; Pircher and others 2007; Coton and others 2012; Wunderlichová and others 2013
Citrobacter youngae	Sausage	1	++	Lorenzo and others 2010
Cronobacter sakazakii	Cheese, spinach	2	+ to ++++	Chaves-López and others 2006; Lavizzari and others 2010
Enterobacter aerogenes	Cheese, meat, sausage; not specified	10	++ to ++++	Marino and others 2000; Pircher and others 2007; Wunderlichová and others 2013
Enterobacter amnigenus	Spinach	8	++++	Lavizzari and others 2010
Enterobacter cloacae	Cheese, meat, sausage, spinach; not specified	26	+++ to ++++	Bover-Cid and Holzapfel 1999; Marino and others 2000; Greif and others 2006; Pircher and others 2007; Latorre-Moratalla and others 2009; Lavizzari and others 2010; Lorenzo and others 2010
Enterobacter georgoviae	Cheese	48	++	Marino and others 2000
Enterobacter hormaechei	Cheese	4	++	Coton and others 2012
Enterobacter spp.	Fish ground beef and hamburger	123	+ to ++++	Kim and others 2009; Durlu-Özkaya and others 2001
Escherichia coli	Cheese, meat, ground beef and hamburger, sausage, poultry skin; not specified	61	+ to ++++	Marino and others 2000; Durlu-Özkaya and others 2001; Chaves-López and others 2006; Pircher and others 2007; Buňková and others 2010a; Lorenzo and others 2010; Wunderlichová and others 2013
Escherichia fergusonii; *E. vulnaris*	Ground beef and hamburger	6	+ to ++	Durlu-Özkaya and others 2001
Hafnia alvei	Cheese, meat, ground beef and hamburger, sausage, cold-smoked salmon, spinach; not specified	117	+ to ++++	Jørgensen and others 2000; Marino and others 2000; Durlu-Özkaya and others 2001; Özogul 2004; Özogul and Özogul 2007; Pircher and others 2007; Lavizzari and others 2010; Lorenzo and others 2010; Coton and others 2012
Klebsiella oxytoca	Cheese, meat, sausage; not specified	6	+ to ++++	Marino and others 2000; Pircher and others 2007; Wunderlichová and others 2013
Klebsiella pneumoniae	Spinach; not specified	17	+ to ++	Özogul 2004; Özogul and Özogul 2007; Lavizzari and others 2010
Klebsiella terrigena	Cheese, meat, sausage, spinach	7	++ to ++++	Pircher and others 2007; Lavizzari and others 2010; Lorenzo and others 2010
Klebsiella spp	Cheese, meat	6	++ to ++++	Pircher and others 2007; Wunderlichová and others 2013
Morganella morganii	Cheese, ground beef and hamburger, spinach; not specified	16	+ to ++++	Durlu-Özkaya and others 2001; Özogul 2004; Özogul and Özogul 2007; Lavizzari and others 2010; Coton and others 2012
Pantoea agglomerans	Cold-smoked salmon	2	++	Jørgensen and others 2000

(*Continued*)

Table 1–Continued.

Microorganism	Source	*N*[a]	Putrescine production[b]	Reference
Pantoea sp.	Cheese, meat, sausage, poultry skin, spinach	20	+ to ++++	Pircher and others 2007; Buňková and others 2010a; Lavizzari and others 2010; Wunderlichová and others 2013
Pectobacterium carotovorum	Not specified	1	++	Wunderlichová and others 2013
Proteus mirabilis	Ground beef and hamburger; not specified	3	++ to +++	Durlu-Özkaya and others 2001; Wunderlichová and others 2013
Proteus penneri	Ground beef and hamburger	4	++	Durlu-Özkaya and others 2001
Proteus vulgaris	Cheese, sausage, poultry skin, gourmed salad	8	+ to ++++	Buňková and others 2010a; Lorenzo and others 2010; Helinck and others 2013; Wunderlichová and others 2013
Proteus spp.	Cheese	10	+ to ++++	Coton and others 2012
Providencia alcalifaciens	Ground beef and hamburger	1	++	Durlu-Özkaya and others 2001
Providencia spp.	Cheese	3	++	Coton and others 2012
Rahnella aquatilis	Sausage	1	++	Lorenzo and others 2010
Salmonella enterica, including *S. enterica* subsp. *arizonae*	Cheese, sausage; not specified	12	+ to ++++	Marino and others 2000; Chaves-López and others 2006; Lorenzo and others 2010; Wunderlichová and others 2013
Salmonella spp.	Poultry	13	not specified	Geornaras and others 1995
Serratia grimesii	Cheese, ground beef and hamburger	3	+ to ++	Durlu-Özkaya and others 2001; Coton and others 2012
Serratia liquefaciens	Cheese, meat, cold-smoked salmon, sausage, poultry skin, spinach	77	++ to ++++	Bover-Cid and Holzapfel 1999; Jørgensen and others 2000; Marino and others 2000; Pircher and others 2007; Buňková and others 2010a; Lavizzari and others 2010; Lorenzo and others 2010; Coton and others 2012
Serratia marcescens	Cheese, sausage, poultry skin, spinach; not specified	8	++ to ++++	Bover-Cid and Holzapfel 1999; Buňková and others 2010a; Lavizzari and others 2010; Wunderlichová and others 2013
Serratia proteamaculans	Meat	1	++	De Filippis and others 2013
Serratia spp.	Cheese, sausage, cold-smoked salmon	5	+ to +++	Bover-Cid and Holzapfel 1999; Jørgensen and others 2000; Chaves-López and others 2006
Yersinia enterocolitica	Cheese, poultry skin; not specified	4	+ to +++	Buňková and others 2010a; Wunderlichová and others 2013
Yersinia ruckeri	Not specified	1	++	Wunderlichová and others 2013
Enterobacteriaceae (unidentified)	Spinach	23	++ to ++++	Lavizzari and others 2010
Pseudomonadales				
Pseudomonas aeruginosa	Not specified	4	++	Wunderlichová and others 2013
Pseudomonas fluorescens	Not specified	1	++	Wunderlichová and others 2013
Pseudomonas lundensis	Milk	1	+	Coton and others 2012
Pseudomonas luteola	Cheese	4	+ to ++	Martuscelli and others 2005
Pseudomonas putida and *Ps.* grp. *putida*	Milk, cheese; not specified	5	+ to ++	Özogul and Özogul 2007; Coton and others 2012
Pseudomonas spp.	Poultry	25	not specified	Geornaras and others 1995
Psychrobacter celer	Cheese	1	++	Coton and others 2012
Acinetobacter sp.	Milk	1	++	Coton and others 2012
Vibrionaceae				
Vibrio harveyi	Not specified	1	++	Özogul and Özogul 2007
Photobacterium phosphoreum	Cold-smoked salmon	3	+ to ++	Jørgensen and others 2000
Other Gram-negative bacteria				
Aeromonas caviae	Poultry skin	7	+	Buňková and others 2010a

(*Continued*)

Table 1–Continued.

Microorganism	Source	*N*[a]	Putrescine production[b]	Reference
Aeromonas hydrophila	Poultry skin, spinach	5	+ to ++	Buňková and others 2010a; Lavizzari and others 2010
Aeromonas sp.	Cold-smoked salmon, poultry skin	12	+	Jørgensen and others 2000; Buňková and others 2010a
Chryseobacterium sp.	Cheese	1	++	Coton and others 2012
Delftia acidovorans	Poultry skin	1	+	Buňková and others 2010a
Halomonas spp.	Cheese	5	+ to ++	Coton and others 2012
Ochrobactrum sp.	Milk	1	+	Coton and others 2012
Sphingobacterium sp.	Milk	1	+	Coton and others 2012
Stenotrophomonas maltophilia	Spinach	2	+++	Lavizzari and others 2010
Stenotrophomonas spp.	Milk	2	+	Coton and others 2012
Lactic acid bacteria				
Lactobacillus brevis	Not specified	4	+++	Bover-Cid and Holzapfel 1999
L. brevis	Cheese, wine, cider, sugarcane, olives, human milk, silage,	90	*agdi*+ or *odc*+	Coton and others 2010; Costantini and others 2013; Romano and others 2014
L. brevis	Dairy	2	not specified	Ladero and others 2012b
Lactobacillus casei	Sugarcane	1	*agdi*+	Romano and others 2014
Lactobacillus collinoides	Cider	31	*agdi*+	Coton and others 2010
Lactobacillus curvatus	Cheese, dairy products, meat, sausage, cold-smoked salmon; not specified	108	+ to ++++	Bover-Cid and Holzapfel 1999; Jørgensen and others 2000; Aymerich and others 2006; Pircher and others 2007; Latorre-Moratalla and others 2009; Buňková and others 2010b; Lorencová and others 2012
L. curvatus	Cheese	2	*agdi*+	Romano and others 2014
L. curvatus	Dairy	1	not specified	Ladero and others 2012b
Lactobacillus fermentum	Cheese, meat, sausage	9	++	Pircher and others 2007
Lactobacillus fructivorans	Wine	5	*agdi*+	Coton and others 2010; Romano and others 2014
Lactobacillus hilgardii	Wine	18	++ to +++	Landete and others 2007b; Arena and others 2008
L. hilgardii	Wine, cider	106	*agdi*+	Coton and others 2010; Costantini and others 2013
Lactobacillus lactis	Cheese, meat, sausage	26	++	Pircher and others 2007
Lactobacillus mali	Wine, cider	21	*agdi*+ or *odc*+	Coton and others 2010; Costantini and others 2013
Lactobacillus paracasei	Cheese, meat, sausage	77	++	Pircher and others 2007
Lactobacillus plantarum	Cheese, meat, sausage; not specified	13	++	Pircher and others 2007; Kuley and others 2013
Lactobacillus plantarum	Wine	50	*agdi*+	Coton and others 2010
Lactobacillus rhamnosus	Cheese, meat, sausage	10	++	Pircher and others 2007
Lactobacillus sakei	Sausage, cold-smoked salmon	188	+ to ++	Jørgensen and others 2000; Aymerich and others 2006
Lactobacillus sanfranciensis	Sourdough	1	*agdi*+	Romano and others 2014
Lactococcus lactis	Not specified	2	++	Kuley and others 2013
L. lactis	Dairy	18	not specified	Ladero and others 2012b
Leuconostoc lactis	Cheese, meat, sausage	13	++	Pircher and others 2007
Leuconostoc mesenteroides	Cheese, meat, sausage, wine	77	++ to +++	Pircher and others 2007; Coton and others 2010;
L. mesenteroides	Cider	1	*agdi*+	Coton and others 2010
Oenococcus oeni	Wine	70	++ to +++	Landete and others 2007b; Coton and others 2010;
O. oeni	Wine, cider	125	*agdi*+ or *odc*+	Coton and others 2010
Pediococcus parvulus	Wine, cider	32	*agdi*+	Costantini and others 2013; Coton and others 2010
Pediococcus pentosaceus	Wine, cider	13	*agdi*+	Costantini and others 2013; Coton and others 2010
Enterococcus faecalis	Cheese, meat, sausage	75	++	Pircher and others 2007
E. faecalis	Dairy, human	5	not specified	Ladero and others 2012b
Enterococcus faecium	Cheese, meat, sausage	84	++ to +++	Pircher and others 2007; Pleva and others 2012
Enterococcus sp.	Dairy	2	not specified	Ladero and others 2012b
Streptococcus thermophilus	Not specified	1	++	Kuley and others 2013
Weisella halotolerans	Sausage	1	not specified	Pereira and others 2009b
Carnobacterium divergens	Cold-smoked salmon	2	+	Jørgensen and others 2000

(*Continued*)

Table 1–Continued.

Microorganism	Source	N[a]	Putrescine production[b]	Reference
Staphylococci				
Staphylococcus carnosus	Food, starter cultures, human	7	+ to ++	Seitter (née Resch) and others 2011
Staphylococcus epidermidis	Fish, sausage	14	+ to ++++	Even and others 2010; Bermúdez and others 2012; Pleva and others 2012; Cachaldora and others 2013
Staphylococcus equorum	Sausage	29	+ to ++++	Bermúdez and others 2012; Cachaldora and others 2013
Staphylococcus haemolyticus	Fish	4	++ to +++	Pleva and others 2012
Staphylococcus hominis	Fish	3	+++ to ++++	Pleva and others 2012
Staphylococcus pasteuri	Fish, sausage	11	+ to +++	Bermúdez and others 2012; Pleva and others 2012; Cachaldora and others 2013
Staphylococcus saprophyticus	Sausage	15	+	Even and others 2010; Bermúdez and others 2012; Cachaldora and others 2013
Staphylococcus warneri	Fish	9	++	Pleva and others 2012
Staphylococcus xylosus	Sausage	1	+++	Latorre-Moratalla and others 2009
Bacilli				
Bacillus amyloliquefaciens	Sausage	6	+	Bermúdez and others 2012
Bacillus licheniformis	Soil; not specified	2	++ to +++	Chang and Chang 2012
Bacillus polyfermenticus	Fermented soybean	1	+	Chang and Chang 2012
Bacillus subtilis	Sausage, fermented soybean, soil; not specified	16	+ to ++	Bermúdez and others 2012; Chang and Chang 2012

[a] Number of tested isolates of given group of bacteria.
[b] Maximum production of putrescine in mg/L; biogenic amines production in the concentration range of: <10 mg/l (+); 10–100 mg/L (++); 100 to 1000 mg/L (+++); >1000 mg/L (++++). In some cases, using PCR- or qPCR-detected genes involved in the production of putrescine (gene shorcuts explained in Figure 3 or text).
[c] Food source of the bacteria not specified or strains from collection of microorganisms.

conditions, presence of saccharides, NaCl concentration, and so on). Presumably, the biosynthetic forms are constitutively transcribed as the 1st part of biosynthesis of polyamines in cells (Tabor and Tabor 1984).

Metabolism of putrescine and its production in Gram-negative bacteria

In Gram-negative bacteria, putrescine can be produced in 3 metabolic pathways (Figure 2). Putrescine can be synthesized either directly from ornithine by ODC (EC 4.1.1.17; ODC pathway) or indirectly from arginine by arginine decarboxylase via agmatine (ADC; EC 4.1.1.19; arginine decarboxylase pathway). In many bacteria, both of these pathways can work simultaneously (Cunin and others 1986; Tabor and Tabor 1972).

In addition, there are 2 variants of the ADC pathway. In both of them, first L-arginine is decarboxylated by ADC to give agmatine. In enterobacteria, agmatine is converted into putrescine and urea by agmatinase (EC 3.5.3.11) (encoded by *speB* gene), whereas in bacteria of the genus *Pseudomonas*, agmatine is first hydrolyzed by agmatine deiminase (EC 3.5.3.12) (encoded by *aguA* gene) to give N-carbamoyl putrescine and ammonia, as in the case of some LAB. The N-carbamoyl putrescine is then converted by N-carbamoyl-putrescine amidohydrolase (EC 3.5.1.53; encoded by *aguB* gene), while splitting off urea to give putrescine. The whole scheme is shown in Figure 2; Table 2 shows a list of enzymes involved in the metabolism of putrescine (both biosynthetic and catabolic pathways), genes encoding these enzymes, and groups of microorganisms in which the given gene usually occurs (the information obtained from the database of metabolic pathways).

In many Gram-negative bacteria, we can find 2 forms of ADC: biosynthetic ADC, encoded by *speA* gene, and biodegradative, encoded by *adiA* gene in enterobacteria (*Escherichia coli*, *Salmonella*). In bacteria of the genus *Pseudomonas*, there is apart from the biosynthetic ADC (*speA* product), another form of decarboxylase capable of arginine decarboxylation, which is usually referred to as "putative" ADC and is encoded by *adi* gene (sometimes also referred to as *ldc* gene). The genes for biosynthetic and biodegradative ADC in Gram-negative bacteria do not show phylogenetic context.

There is a similar situation in ornithine decarboxylase, where *E. coli* has 2 forms of ornithine decarboxylase—constitutive (biosynthetic), encoded by *speC* gene and inducible, encoded by *speF* gene. In *E. coli*, there are isozymes—both genes have a similar structure but differ in the regulation. These 2 genes show a striking similarity and probably share the same evolutionary development (Applebaum and others 1977). The same might hold true for other enterobacteria with both forms of ornithine decarboxylase.

Enterobacteriaceae, as well as *Pseudomonas* spp., were identified as the main producers of putrescine in various types of food. Many publications describe increased putrescine production in relation to the occurrence of enterobacteria in foodstuffs (Table 1). Enterobacteria were responsible for the production of putrescine in fermented sausages (Pircher and others 2007; Lu and others 2010; Curiel and others 2011), minced meat and burgers (Durlu-Özkaya and others 2001), fish products (Özogul and others 2002; Özogul and Özogul 2005; Pons-Sánchez-Cascado and others 2005), in the chilled poultry skin (Buňková and others 2010a), and cheeses (Marino and others 2000). *Enterobacteriaceae* and *Pseudomonas* isolated from spinach were also *in vitro* producers of putrescine

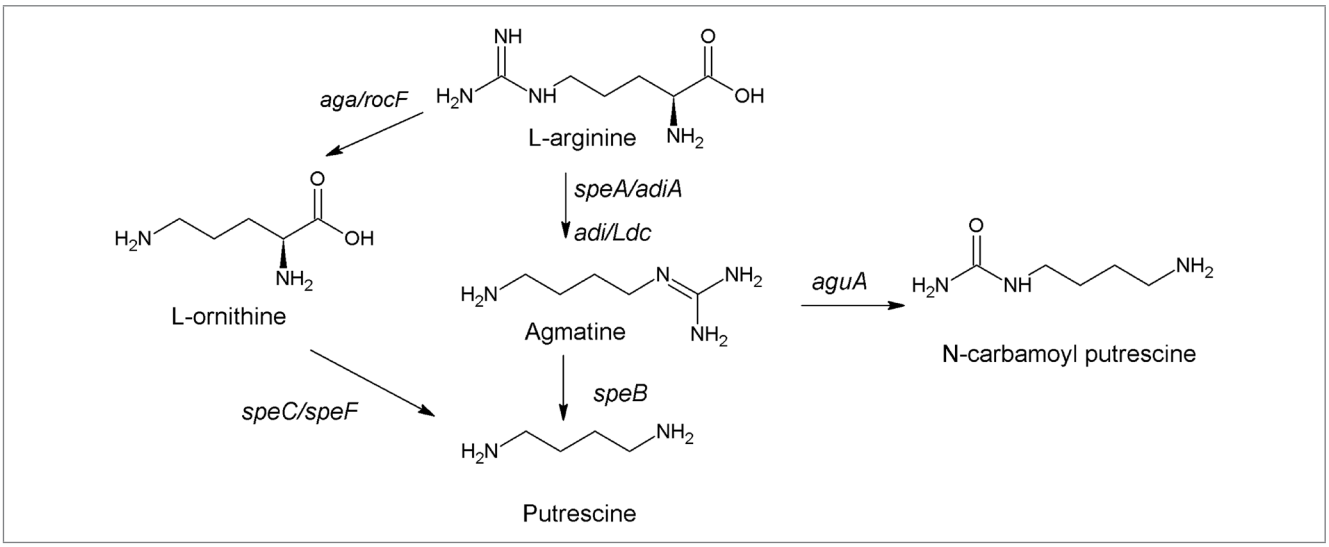

Figure 2–Putrescine metabolism in Gram-negative bacteria, gene shorcuts explained in Table 2.

Table 2–Overview of microorganisms, key enzymes, and genes involved in the production of putrescine in microorganisms.

Enzyme	Gene	Microorganisms that possess the gene
Arginine decarboxylase—biosynthetic	*speA*	*Enterobacteriaceae; Pseudomonas* spp.
Arginine decarboxylase—biodegradative	*adiA*	*E. coli, Salmonella* spp.
Orn/Lys/Arg decarboxylase family protein	*Ldc, adi*	*Pseudomonas* spp.
Agmatinase	*speB*	*Enterobacteriaceae* (except *Yersinia* spp. and *Pectobacterium carotovorum)*
Agmatine deiminase	*aguA*	*Pseudomonas* spp., *Yersinia* spp., Gram-positive bacteria
N-carbamoylputrescine amidohydrolase	*aguB*	*Pseudomonas* spp., *Yersinia* spp.
Ornithine decarboxylase—biosynthetic	*speC*	*Enterobacteriaceae,Pseudomonas* spp.
Ornithine decarboxylase—biodegradative	*speF*	*Enterobacteriaceae,* Gram-positive bacteria
Putrescine carbamoyltransferase	*ptcA*	Lactic acid bacteria
Putrescine carbamoyltransferase	*aguB*	Gram-positive bacteria (in other bacteria as it is *aguA* gene)
Arginase	*aga, rocF*	*Bacillus* spp., *Helicobacter pylori*

(Lavizzari and others 2010). Some strains of *Pseudomonas* were identified as good producers of putrescine in both the model medium (Landete and others 2008, 2010) and fish products (Özogul and Özogul 2005; Pons-Sánchez-Cascado and others 2005).

Some authors also detected the occurrence of agmatine in relation to the occurrence of Gram-negative bacteria in food (Özogul and Özogul 2005; Pons-Sánchez-Cascado and others 2005; Saccani and others 2005; Buňková and others 2010a; Curiel and others 2011; Wunderlichová and others 2013). The presence of agmatine is important evidence of the fact that Gram-negative microorganisms form putrescine, not only by means of the ODC pathway but also by active use of the ADC pathway.

Metabolism of putrescine and its production in Gram-positive bacteria

LAB utilize metabolic pathways of biodegradation (catabolism) of amino acids in order to gain metabolic energy (Fernández and Zúñiga 2006) or as a mechanism of resistance to a low pH (Konings 2002). These LAB carrying catabolic pathways of putrescine formation are then its sources in food (ten Brink and others 1990; Silla Santos 1996). These pathways in LAB are referred to as strain-specific rather than species-specific, suggesting that the presence of these pathways is given by horizontal gene transfer (Lucas and others 2005; Marcobal and others 2006). Recently, there have also been studies confirming species-specific ability to form a particular BA (Ladero and others 2011a). For example, 90% of all *Enterococcus faecium* isolated from cheeses were tyramine producers. Also, Pleva and others (2012) determined almost 85% tyramine production in enterococci isolated from rabbit meat. Among the strains of *Enterococcus faecalis*, putrescine-producing strains are very frequently found (Llácer and others 2007; Ladero and others 2012a), which could indicate species-specific ability to produce putrescine (agmatine deiminase pathway).

Generally, in Gram-positive microorganisms, there can be 2 metabolic pathways in the metabolism of putrescine: ODC (only a biodegradative form) and agmatine deiminase (AgDI). The ODC pathway is more likely to occur in bacteria isolated from wine and the AgDI pathway in bacteria isolated from musts and cheeses (Romano and others 2012). The ADC pathway has been described only in 1 strain of LAB (*Lactobacillus hilgardii* X1B isolated from a wine sample) (Arena and Manca de Nadra 2001). The scheme of putrescine metabolism in Gram-positive bacteria is shown in Figure 3, the list of enzymes involved in putrescine metabolism is covered in Table 2.

The first group of the above-mentioned pathways, the decarboxylation pathways (such as the ODC pathway), always includes 2 proteins—decarboxylase and the transport protein that is responsible for the transport of amino acids into the cytoplasm and antiport of the BA out of the cell. Subsequently, the enzyme decarboxylates the amino acids to produces BAs and carbon dioxide. This pathway produces proton-motive force and alkalizes the cytoplasm (Romano and others 2012).

The AgDI pathway works on a principle different from that of the decarboxylation pathway. It consists of a transport step followed by 2 enzymes. The first enzyme, agmatine deiminase (encoded by

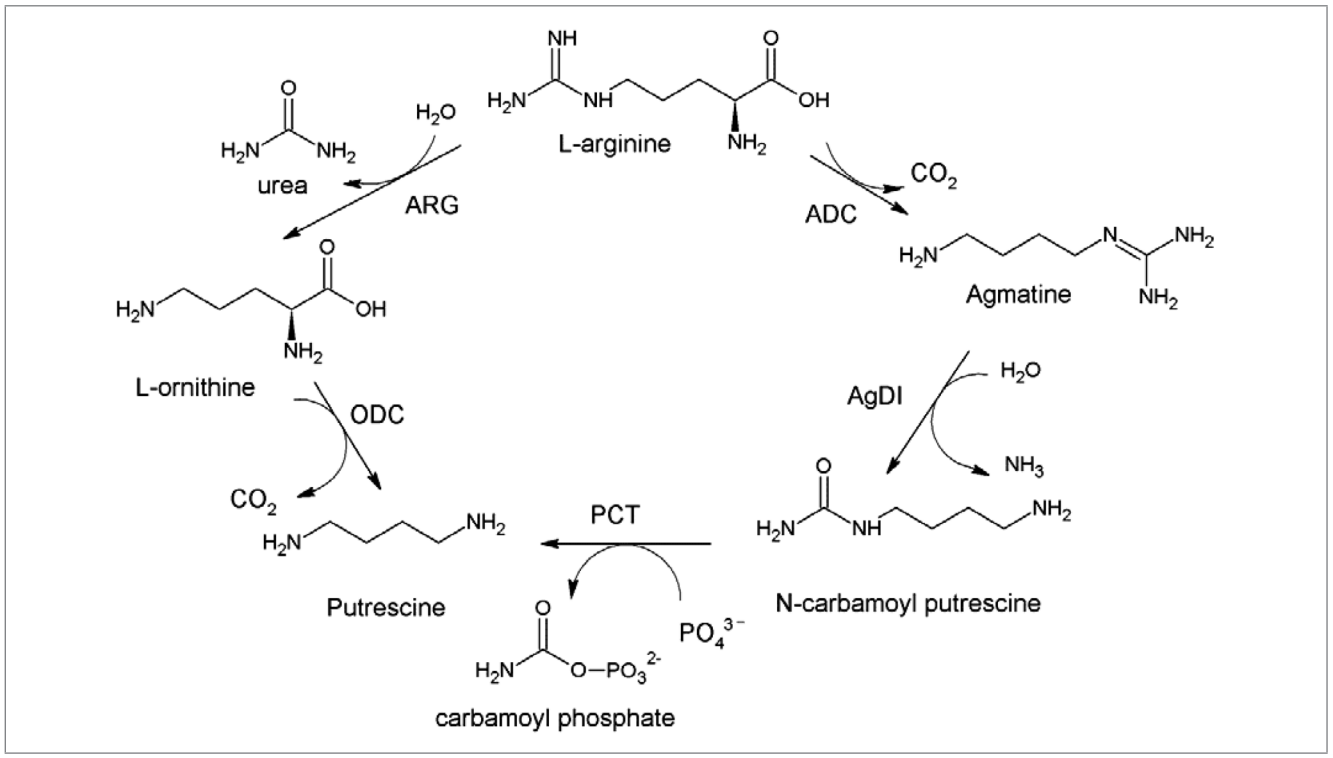

Figure 3–Ornithine and agmatine catabolism in lactic acid bacteria. ADC, arginine decarboxylase; AgDI, agmatine deiminase; ARG, arginase; ODC, ornitine decarboxylase; PCT, putrescine carbamoyltransferase.

aguA gene), converts agmatine into N-carbamoyl putrescine and ammonia. The other enzyme, putrescine carbamoylase (encoded by *ptcA* gene, also referred to as *aguB* by some authors), produces carbamoylphosphate and putrescine. The carbamoylphosphate is then broken down by kinase (encoded by *aguC* gene) to give ATP, carbon dioxide, and ammonia. In this way, LAB can produce energy. The substrate and product are again exchanged by antiport (Driessen and others 1988). The presence of *ptc* gene has been determined only in a small number of bacteria (Llácer and others 2007; Lucas and others 2007; Chen and others 2011).

All AgDI pathway genes are located on the agmatine deiminase gene cluster (AGDIc). In most LAB, the AgDI pathway occurs together with the tyrosine decarboxylase pathway because the AgDI pathway genes are linked to the tyrosine decarboxylation operon in a putative acid resistance locus (Lucas and others 2007). However, this rule does not always apply, recently it has been found that in the strains of *E. faecalis*, the clusters for the TDC and AgDI pathways occur separately (Ladero and others 2012a).

The AgDI pathway has recently been demonstrated in *Lactobacillus brevis* (Lucas and others 2007; Coton and others 2010), *Lactobacillus collinoides*, *Lactobacillus mali*, *Leuconostoc mesenteroides*, and *Oenococcus oeni* in must and in *Lactobacillus fructivorans* in wine (Coton and others 2010), *Pediococcus parvulus*, *Lactobacillus paracollinoides* (Ladero and others 2011b), *L. hilgardii* (Alberto and others 2007; Coton and others 2010), *Streptococcus mutans* (Griswold and others 2004), *E. faecalis* (Simon and Stalon 1982; Driessen and others 1988; Llácer and others 2007; Ladero and others 2012a), and clusters of similar genes were also found in *Lactococcus lactis*, *Listeria monocytogene*s, *L. sakei*, and *Pedicoccus pentosaceus* (Naumoff and others 2004).

Some *O. oeni* have the ODC pathway (Marcobal and others 2004), which was also confirmed by Coton and others (2010), Izquierdo Cañas and others (2009), Ladero and others (2011b), and Romano and others (2012) who identified other ODC positive strains of *O. oeni*. In the strains of *O. oeni*, the ODC pathway probably occurs due to the horizontal transfer (Marcobal and others 2006). ODC was also proved in the strain of *Lactobacillus* sp. 30a (Hackert and others 1994), *L. mali* (Coton and others 2010), and *L. brevis* IOEB 9906 (Romano and others 2012). Genes highly similar to those for ODC were also found in *Lactobacillus acidophilus* (Azcarate-Peril and others 2004) and in some strains of *Lactobacillus johnsonii* (Pridmore and others 2004; Wegmann and others 2009).

Only a few rules have been observed in the metabolic pathways of LAB. For example, according to Coton and others (2010) and Ladero and others (2011b, 2012b), the strains of LAB with AgDI pathway were dominant in must, cider, and dairy products. In contrast, according to Nannelli and others (2008), the main producers of putrescine in wine are LAB carrying the ODC pathway. Romano and others (2012) published a study in which they assume the existence of 2 different ODC pathways in LAB. The second, newly published pathway consists of ODC and L-2,4-diaminobutyric acid and a transporter that provides 1-way transport of ornithine into the cytoplasm. Diamines formed by this system are retained within the cytosol. This 2nd pathway was shown, for example, in *Lactobacillus gasseri* and *Lactobacillus casei* and may be similar to the biosynthetic pathway commonly occurring in Gram-negative bacteria.

LAB are the main bacteria responsible for the presence of putrescine in wine (Ancín-Azpilicueta and others 2008). So far, no LAB carrying the ODC pathway has been isolated from cheeses. LAB isolated from cheeses produce putrescine by agmatine deamination via the AgDI pathway. This pathway was proved, for example, in the strains of *E. faecalis*, *Lactobacillus brevis*, *L. curvatus*, and *Lactococcus lactis* (Joosten and Northolt 1987; Komprda

and others 2008; Ladero and others 2011a,c). The AgDI pathway in the strains of *L. lactis* was species-specific and was probably not acquired by recent horizontal transfer. However, many strains of *L. lactis* carry an insertion (IS983 element) in the AgDI cluster, which inactivates the transcription of this cluster, and thus these *L. lactis* do not produce putrescine (Ladero and others 2011a).

Many Gram-positive bacteria are used as starter cultures and many of them are responsible for putrescine increase in fermented products. On the other hand, suitable starter culture (not producing BA or producing only a limited amount) may help reduce the accumulation of BA (Fernández-García and others 1999; Bover-Cid and others 2001).

Degradation of Putrescine—Detoxification

The detoxification system of BAs in mammals involves specific enzymes—aminooxidases, which catalyze the oxidative deamination of amines to give the corresponding aldehyde, ammonia, and hydrogen peroxide (Figure 4). These aldehydes are quickly converted by intracellular aldehyde dehydrogenases into amino acids and lactams (Seiler and Douaud 1998). This pathway is called "termination pathway" because the products formed can no longer be recycled into polyamines. All derivates of polyamines formed during the terminal degradation then become components of urine (van den Berg and others 1985).

The main pathway of polyamine catabolism in mammals is oxidative deamination by Cu^{2+} diaminooxidase enzyme (DAO, EC 1.4.3.22) (Brazeau and others 2004). Substantial quantities of DAO are found in the intestinal mucosa, liver, and kidneys. Apart from putrescine, these diaminooxidases also deaminate histamine and cadaverine. In different tissues, these DAOs have various biochemical properties (Seiler and Douaud 1998). Putrescine is converted by this enzyme into 4-aminobutanal to give ammonia and hydrogen peroxide. The aminoaldehyde formed is subsequently metabolized into γ-aminobutyric acid (Bagni and Tassoni 2001).

Another way how to degrade putrescine is by means of monoaminooxidase enzyme. For this reaction, putrescine is first acetylated by diamine acetyltransferase (EC 2.3.1.57) to give N-acetylputrescine, which is subsequently converted by means of monoaminooxidase (N-acetylputrescine oxidase, MAO, EC 1.4.3.4) into 4-acetamidobutanal. It is further dehydrogenated and hydrolyzed to γ-aminobutyric acid. This pathway occurs, for example, inside mitochondria of mammalian brain cells (Seiler and Al-Therib 1974).

Under certain conditions, polyamine catabolism in humans is not sufficient and may lead to toxicological symptoms caused by increasing levels of the individual polyamines. Risk groups include mainly children, allergy sufferers, people taking monoamine and diamine oxidase inhibitors (antidepressants, anti-Parkinsonian drugs), and people with gastrointestinal problems (gastritis, Crohn´s disease, and gastric ulcers), because oxidase activity in these individuals is lower than in healthy people. The toxicological effects of putrescine can be amplified by the presence of ethanol and acetaldehyde because they support their transport through the intestinal wall. The simultaneous effect of putrescine and alcohol is particularly serious when consuming alcoholic beverages with a higher content of putrescine (Silla Santos 1996). Another factor reducing aminooxidase activity is smoking. The aminooxidase activity in smokers was observed to be lower by 30% due to the inhibitory effect of some compounds contained in tobacco or tobacco smoke (Berlin and Anthenelli 2001).

Factors Affecting the Occurrence of Putrescine in Food

The main sources of BA in food are microorganisms with decarboxylase activity. Microbial formation of BA is affected by many factors—the microorganisms present, pH, temperature, NaCl content, and so on.

Decarboxylase and deimination activities have been described in different genera, species, and strains of both Gram-positive and Gram-negative bacteria. For these bacteria, the production of BAs can be a source of energy, a form of resistance to acidic environments (Konings and others 1997), a form of DNA regulation, or they may act as antioxidants (Kaur-Sawhney and others 2003).

In some cases, the ability to produce BAs is species-characteristic, such as putrescine production in the agmatine deiminase pathway in some species of *Lactococcus* (Ladero and others 2011a). In other cases, the ability to produce BAs is strain-specific (Bover-Cid and Holzapfel 1999; Buňková and others 2011), as in Gram-negative bacteria, mainly enterobacteria and *Pseudomonas* spp. However, the latest research has shown that many Gram-positive bacteria have this ability and it has been shown that in certain types of food (such as wine), LAB are the main source of putrescine (Ancin-Azpilicueta 2008).

However, the presence of an increased amount of putrescine is usually associated with high occurrence of Gram-negative bacteria (ten Brink and others 1990; Pircher and others 2007; Buňková and others 2010a; Delbès-Paus and others 2012), usually resulting from a bad manufacturing process, poor quality, or insufficient hygiene. There is no such direct correlation in the case of Gram-positive bacteria, which may be caused by the fact that decarboxylase and deimination activities are often strain-specific (Halász and others 1994). Generally, high occurrence of microorganisms does not necessarily lead to increased production of BAs. Microorganisms use the above-mentioned metabolic pathways often under specific conditions. Thus, the occurrence of BAs can be influenced by a combination of other important factors.

One of the most important factors is pH, which is related to the pH optimum of decarboxylases. It is known that bacterial inducible decarboxylases generally have an acidic pH optimum (Gale 1946). Many studies have confirmed that a slight decrease in pH actually leads to increased production of putrescine (Greif and others 2006). On the other hand, many studies have shown that a rapid decrease in pH has the opposite effect due to the reduced growth of decarboxylation microorganisms (Maijala and others 1993; Bover-Cid and others 2001; Gardini and others 2001). An increasing pH leads to a decrease in putrescine production (Greif and others 2006).

One of the enzymes that have been well studied in this respect is biodegradative ADC. It is very strongly induced in an acidic environment in a rich medium and in an excess of substrate. Expression of the *adiA* gene, which encodes this decarboxylase is induced by a low pH (Stim and Bennett 1993). Also, biodegradable ODC in *E. coli* is induced by a low pH and plays a role in regulating the intracellular pH (Applebaum and others 1977). The decarboxylation of ornithine to putrescine and subsequent exchange of putrescine for new ornithine is a cycle that produces proton-motive force and is induced at a low pH in order to protect the bacterium at a low pH (Romano and others 2012).

Among LAB, only the existence of the biodegradative form of ODC has been proved so far in *Lactobacillus* 30a. It is also induced by a low pH, by means of which it compensates for the decrease in pH resulting from the production of lactic acid (Gale 1946).

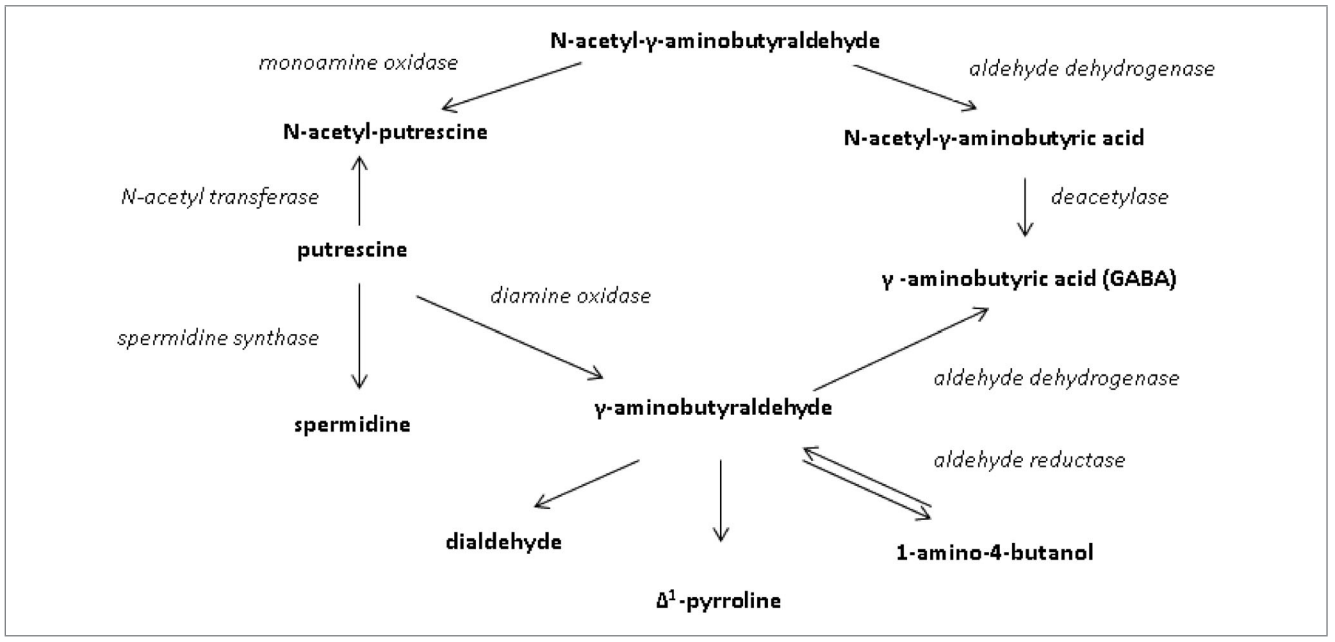

Figure 4–Oxidative deamination of amines.

Not only decarboxylases are induced by a slightly acidic pH. Similar behavior has also been observed in agmatine deiminase, an enzyme in the agmatine deiminase pathway. It has been discovered that *aguA1* gene of *L. brevis* is transcriptionally induced by a low pH (Arena and others 2010).

Another important factor affecting the bacterial production of BAs is NaCl content. Many studies have confirmed that a higher concentration of NaCl leads to a decrease in BA production. It is due to a reduced number of bacterial cells (Gardini and others 2001) and reduced activity of membrane-bound decarboxylases (Chander and others 1989; Sumner and others 1990). This trend was described, for example, in the *Lactobacillus bulgaricus* strain (now *Lactobacillus delbrueckii* subsp. *bulgaricus*) (Chander and others 1989) or in *E. faecalis* EF37 (Gardini and others 2001), where a decrease in tyramine production was observed. A decrease in BA production with an increased NaCl content was also described in some types of foodstuffs, including fermented sausages (Roseiro and others 2006), feta cheese (Valsamaki and others 2000), and white brined cheese (Aliakbarlu and others 2009).

In contrast, higher production of tyramine in *E. durans* CCDM 53 was observed in an environment with a higher concentration of NaCl (Buňková and others 2012). Similarly, Buňková and others (2011) found that 5 strains of *L. lactis* used in cheese-making technology produced more tyramine in an environment with 2% (w/v) NaCl than in an environment with 1% (w/v) NaCl or without the addition of salt. Also, in Gram-negative bacteria *Enterobacter* or *Morganella*, higher production of BAs was found in an environment with a higher concentration of NaCl in comparison with an environment with a lower concentration or without the addition of salt (Greif and others 2006; Emborg and Dalgaard 2008). According to Wolken and others (2008) and Pereira and others (2009a), higher production of tyramine in an environment with a higher concentration of NaCl can be explained by the fact that Na^+ ions are involved in the regulation of the intracellular pH. These ions are important in the sodium/proton antiport system, as they are exchanged with H^+ ions that are removed out of the cells. Thus, Na^+ ions play an essential role in the tyrosine decarboxylation pathway.

Reduced production of putrescine in *Enterobacter cloacae,* as a result of an increased concentration of NaCl, was published by Greif and others (2006). Bover-Cid and others (2009) also observed a decrease in putrescine production by enterobacteria in relation to an increased NaCl content.

Sugar content also significantly influences BA production in food. As mentioned above, suitable starter culture may help reduce the accumulation of BAs. It has been found that the addition of sugar significantly promotes the growth of starter cultures, which leads to suppression of the growth of *Enterobacteriaceae* and thus reduces the accumulation of putrescine (Bover-Cid and others 2000a, 2009).

Similarly, temperature affects the production of BAs. Many publications confirm an increased BA content in many types of foodstuffs with increasing temperature and storage period (Stratton and others 1991; Halász and others 1994; Martuscelli and others 2000; Gardini and others 2001; Pinho and others 2001; Gennaro and others 2003; Santos and others 2003; Buňková and others 2010b). However, long-term storage of meat at a low temperature (4 °C) can lead to the accumulation of putrescine due to the activity of psychrotrophic pseudomonads (Paulsen and Bauer 1997). It has also been discovered that some BA-producing genera such as *Photobacterium*, *Aeromonas*, and *Micrococcus* can survive during the storage of fish and shrimp on ice (Lakshmanan and others 2002). In contrast, increased temperature in fermented products can lead to enhancement of the starter LAB and thus suppress the growth of nonstarter BA-positive microorganisms (Maijala and others 1995).

Other factors affecting the production of BAs in food include free amino acid content, the presence of oxygen, water activity, the presence of other substances, or interactions between microbial cultures (Naila and others 2010). Several studies describe factors that affect the production of BAs at the same time, for example, observation of the influence of storage duration and temperature on ripened cheese (Buňková and others 2010b; Komprda and

others 2012; Pachlová and others 2012). Hernández-Orte and others (2008) studied wine and the influence of various bacterial cultures on BA production during malolactic fermentation (MLF) (comparison of natural and inoculated MLF cultures) and the influence of ripening period in oak barrels. After MLF, the content of all the observed BAs, including putrescine, increased. However, the increase was significantly lower in the wines with starter culture. With increasing duration of the ripening period, the content of all BA was rising. Direct influence of factors on the production of BAs was studied in 2 strains of *O. oeni*. The effects of pH, ethanol content, and malic acid content were observed. Only a decrease in pH had a more significant influence on putrescine production in the ODC pathway (Marques and others 2008). The influence of some factors (time, temperature, pH, amounts of ethanol, sugar, and organic acids) on putrescine production in the agmatine deiminase pathway was analyzed in *L. hilgardii* X1B. It was found that the highest putrescine production occurs at pH 4 to 6; sugar and arginine contents significantly inhibited putrescine production and, in contrast, higher concentrations of tartaric acid and lactic acid increased putrescine production; the addition of putrescine did not have any influence on the production of putrescine in this strain (Arena and others 2008).

For more information about the influence of factors on BA production in food, see the reviews by Chong and others (2011), Kalač (2014), and also Kalač and Krausová (2005). Further reviewers describe factors affecting the occurrence of BAs in dairy products (Linares and others 2011, 2012; Loizzo and others 2013), meat and meat products (Kalač 2006; Ruiz-Capillas and Jimenez-Colmenero 2004; Suzzi and Gardini 2003), fish and fish products (Bulushi and others 2009; Prester 2011), alcoholic beverages (Anli and Bayram 2009; Beneduce and others 2010; Kalač and Křížek 2003).

Methods for the Determination of Putrescine and Agmatine

In the last few years, a large number of methods have been developed to determine the contents of putrescine and agmatine (as one of the putrescine precursors) or their producers in food. The most commonly used methods are: (i) microbiological methods using a decarboxylation medium containing a pH indicator; (ii) analytical methods—mainly separation methods in different modifications (usually HPLC, capillary electrophoresis [CE]); and (iii) molecular–biological methods (including mainly the methods of polymerase chain reaction (PCR)). The reasons for determining BAs are the possibilities to use them as spoilage indicators of foods, to examine toxicity, and to initiate some pharmacological reactions.

Analytical methods

Many authors have dealt with the detection of BA content in different types of foodstuffs (under different conditions of treatment and storage) by means of HPLC methods, thin layer chromatography, gas chromatography, and CE. For a more detailed overview of the analytical methods, see the review by Önal (2007) or Erim (2013). The BAs may be detected as well by biosensors, enzymatic methods (Erim 2013), or ion mobility spectrometry (Karpas 2013).

Most authors determined only the concentration of putrescine. Only a few of them included agmatine among the BAs observed. In order to confirm the fact that putrescine in food is produced in more metabolic pathways, it is important to prove the presence of the intermediate product of ADC pathways—agmatine. Many authors have detected agmatine in different samples of food. By means of ion exchange chromatography, agmatine was detected by Saccani and others (2005), Buňková and others (2010a), and Curiel and others (2011). By means of the HPLC method, agmatine was also detected in different samples of food by Arena and Manca de Nadra (2001), Pons-Sánchez-Cascado and others (2005), and Özogul and Özogul (2007). The HPLC method can also be used for the simultaneous detection of BAs and precursors amino acids (Mazzucco and others 2010). In order to decrease, the time of analysis ultra-performance liquid chromatography (UPLC) can be used. Dadáková and others (2009) used the UPLC method for BAs detection, including putrescine, in chicken meat and fish. This method was succesfully used for the *in vitro* putrescine production in some foodborne bacteria, for example, decarboxylase activity of staphylococci and enterococci isolated from rabbit meat and fish intestines (Pleva and others 2012), or LAB and bifidobacteria isolated from dairy products and beer (Lorencová and others 2012, 2014).

Bacterial production of putrescine can also be detected by electromigration methods, for example, by CE, or micellar electrokinetic chromatography. CE is after HPLC the second most described analytical technique for BAs detection. The main advantages of this versatile and robust method are speed, high efficient and automated separation, small sample volumes, and low consumption of solvents and reagents (Oguri 2000; Önal 2007; Erim 2013). CE can be used for BAs detection including putrescine in solid food samples and in beverages. For a more detailed overview of the electromigration methods, see the reviews by Castro-Puyana and others (2012) or Erim (2013).

Biosensors for analysis of various analytes including BAs are a good alternative to chromatographic or electromigration methods. Novel electrochemical sensors for BAs detection are rapidly developed due to their short time of analysis, low cost, miniaturized devices, simplicity, and easily adaptation for particular analysis without pretreatment of analyzed samples. The basic principle in electrochemical detection of BAs is enzymatic reaction catalyzed by selective oxidases such as monoamine oxidase (EC 1.4.3.4), diamine oxidase (EC 1.4.3.6), and putrescine oxidase (EC 1.4.3.10). The detection limits of different biosensors for BAs varying between 0.05 μg/kg and 10 mg/kg (Kivirand and Rinken 2011; Erim 2013). Recently, putrescine alone or simultaneously with another BA was detected by biosensors, for example, during meat-spoilage process (Bóka and others 2012a), in alcoholoic beverages (Di Fusco and others 2011; Bóka and others 2012b); fish samples (Alonso-Lomillo and others 2010; Henao-Escobar and others 2013a), seafoods (Inaba and others 2004; Henao-Escobar and others 2013b), or fermented soybean paste (Lee and others 2013).

Precursors of putrescine, amino acids ornithine, and arginine can be quantifying in food by chromatographic methods, particularly by ion exchange chromatography, HPLC (mostly with postcolumn derivatization with ninhydrine or *o*-phthalaldehyde), gas chromatography, or CE (Peace and Gilani 2005; Buňka and others 2009; Domínguez-Vega and others 2009; Ali and others 2010; Martínez-Gil and others 2012).

Molecular–biological methods

However, the classical analytical methods only give us information about the amount of BA that has already been produced. The methods of molecular biology, mainly PCR and its modifications, can provide information of a different kind. These methods enable us to detect the mere presence of microorganisms that

Table 3–List of primer sets used to control targeting genes involved in the microbial production of putrescine.

Set of primers	Targeting gene	Microorganisms	Source
3′ + 16′	*odc* (*speF* and *speC*)	lactic acid bacteria, some Gram-negative bacteria	Marcobal and others 2005
4′+ 15′	*odc* (*speF* and *speC*)	lactic acid bacteria	Marcobal and others 2005
PUT1-F + PUT1-R	*odc*	lactic acid bacteria, Gram-negative bacteria (except *Pseudomonas* spp.)	Muñoz and others 2004
PUT2-F + PUT2-R	*odc*	*Pseudomonas* spp.	Muñoz and others 2004
AODC1 + AODC2	*odc*	lactic acid bacteria	Costantini and others 2006
agdif + agdir	*aguA*	lactic acid bacteria	Nannelli and others 2008
AguA-F + AguA-R	*aguA*	lactic acid bacteria	Landete and others 2010
ptcA-F + ptcA-R	*ptc*	lactic acid bacteria	Landete and others 2010
AgD1 + AgD2	*aguA*	lactic acid bacteria	Coton and others 2010
ODC1 + ODC2	*odc*	lactic acid bacteria	Coton and others 2010
PTC2 + PTC1C	*aguB*	lactic acid bacteria	
AgdI1 + AgdI1C	*aguA*	*Lactococcus lactis*	Ladero and others 2011a
IS1 + ISCO	IS983	*L. lactis*	Ladero and others 2011a
AgmSq1 + AgmSq2	AGDIc	lactic acid bacteria	
PTC2 + AgDdr	AGDIc	lactic acid bacteria	Ladero and others 2012a
QAgmE3F + QAgmE3R	AGDIc	enterococci	Ladero and others 2012b
QAgmLBF + QAgmLBR	AGDIc	lactobacilli	Ladero and others 2012b
QAgmLCF4 + QAgmLCR4	AGDIc	lactococci	Ladero and others 2012b
adc5F + adc5R	*speA*	Gram-positive bacteria	Wunderlichová and others 2013
agm4F + agm4R	*speB*	*Enterobacteriaceae*	Wunderlichová and others 2013
adi5F + adi5R	*adi/ldc*	*Pseudomonas* spp.	Wunderlichová and others 2013
AgDI4F + AgDI6F	*aguA*	*Pseudomonas* spp., *Yersinia* spp.	Wunderlichová and others 2013
adiA3F + adiA3R	*adiA*	*E. coli, Salmonella* spp.	Wunderlichová and others 2013
odc1F + odc1R	*odc*	Gram-positive bacteria	Wunderlichová and others 2013
speF1F + speF1R	*speF*	Gram-positive bacteria	Wunderlichová and others 2013

have the potential to produce these amines (Landete and others 2007a). Thus, we can detect potential formation of BAs. By means of these methods, we can also detect the presence of key genes involved in the metabolism of the individual BAs and determine which microorganisms are responsible for the production of BAs in a particular food (de las Rivas and others 2005; Landete and others 2007a; Torriani and others 2008). Moreover, the methods of molecular biology allow us to study the metabolism of amines and the possibilities of influencing it; the real-time PCR method enables direct quantitative evaluation of the extent of genes/microorganisms present or monitoring the gene expression of key genes (Fernández and others 2006; Nannelli and others 2008; Ladero and others 2010b). By means of methods monitoring the gene expression, we can experimentally observe the expression of key genes under different conditions (Arena and others 2010), or we can observe the influence of factors on the expression of these genes (Calles-Enríquez and others 2010).

The metabolism of putrescine includes several enzymes that are encoded by the corresponding genes (see Table 2). PCR enables to amplify several molecules of the target gene (DNA template) and generate millions of copies of the gene observed. In this way, we can detect sequences of genes corresponding to the enzymes examined and thus predict whether a given microorganism has the potential to produce BA.

Only a few PCR methods have been developed to detect the producers of putrescine. Most of the primers developed are designed to detect a mixture of genes encoding ODC in both Gram-negative and Gram-positive bacteria (de las Rivas and others 2005, 2006, 2007; Marcobal and others 2005; Costantini and others 2006) and to detect *aguA* gene encoding agmatine deiminase that produces putrescine from agmatine in some LAB and *Pseudomonas* spp. (Nannelli and others 2008; Coton and others 2010; Landete and others 2010). Some of these primers were also used in multiplex PCR for simultaneous detection of more decarboxylase genes (Nannelli and others 2008; Costantini and others 2009; Coton and others 2010). Table 3 shows an overview of the published primers, target genes, and information sources.

PCR primers were mainly developed to detect *odc* gene, especially in Gram-positive bacteria. For the detection of *odc* gene in LAB, the following primers were developed: odcf/odcr (Nannelli and others 2008), ODC1/ODC2 (Coton and others 2010), AODC1/AODC2 (Costantini and others 2006), and 4/15 (Marcobal and others 2005). For the detection of *odc* genes in both LAB and enterobacteria, 2 sets of primers were developed. The first one was designed by Marcobal and others (2005); 3/16 primers were developed for the detection of *odc* genes in LAB as well as for *odc* genes in some Gram-negative bacteria. For example, they enable to detect ODC in *E. coli* and *Morganella morganii*. Unfortunately, this set of primers did not detect *odc* gene in *Proteus vulgaris,* which is known to be ODC positive. The primer set 3/16 is not designed to detect *odc* gene in bacteria of the genus *Pseudomonas*. The other set of primers designed for the detection of *odc* in LAB and enterobacteria is PUT1-F/PUT1-R (Muñoz and others 2004). This set of primers reliably detects the presence of *odc* genes in enterobacteria. However, it is not designed for *Pseudomonas*. Fadhlaoui-Zid and others (2012) showed that this set of primers amplifies the mixture of *speC* and *speF* genes. A special set of primers PUT2F/PUT2-R was designed for the detection of genes in *Pseudomonas* (Muñoz and others 2004).

For the detection of *aguA* genes in LAB, a few sets of primers were designed: AGDIfor/AGDIrev (Lucas and others 2007), agdif/agdir (Nannelli and others 2008), and AgD1/AgD2 (Coton and others 2010). Landete and others (2010) made a set of primers AguA-F/AguA-R for the detection of *aguA* gene in LAB and *Pseudomonas* spp. The same report also presents a set of primers designed for the detection of putrescine transcarbamoylase (encoded by *ptc* gene) in the AgDI pathway in LAB. Moreover, other sets of primers were developed for the detection of the gene cluster involved in the AgDI pathway for LAB. One set was mainly used for enterococci (a major putrescine producer in dairy products) in which PTC2 and AgdDr primers are used for detection of this pathway (Ladero and others 2012a). The second set (primers Agmsq1 and Amgsq2) was constructed for lactococci, these primers are also used for detection of functional putrescine-producing pathway in this species (Ladero and others 2011a). The

region amplified by this last pair of primers was successfully used for the design of qPCR (Ladero and others 2012b). Special sets of primers were developed to distinguish between putrescine-producing (via AgDI pathway) and nonputrescine-producing *L. lactis* by means of detecting the presence of an inactivating insertion (IS983) (Ladero and others 2011a).

Also, there were developed multiplex PCR methods that make the use of these primers more effective in practice. For example, Coton and others (2010) developed multiplex PCR with 4 sets of primers for simultaneous detection of tyrosinedecarboxylase, histidinedecarboxylase, ODC (using ODC1/ODC2 primers), and agmatine deiminase (detection of *aguA* gene using AgD1/AgD2 primers) in LAB. Costantini and others (2009) used 3 sets of primers for the detection of TDC, HDC, and ODC (with 16/AODC1 primers in LAB). Wunderlichová and others (2013) described a method for the detection of *speC, speF,* and *speA* genes in Gram-negative bacteria. An overview of the published primers is shown in Table 3.

Also, some qPCR methods for the quantification of putrescine producers were published. Nannelli and others (2008) and Ladero and others (2011c) used agdif/agdir and odcf/odcr primers for the quantification of LAB-producing putrescine. qPCR method is a very useful tool to quantify and screen undesirable BA producers in various foods and beverages. This culture-independent method is also suitable for estimation of the risks and factors influencing BA accumulation in food, selection of starter cultures, and studying the population dynamics of BAs-producing microbiota during the manufacture of fermented products (Ladero and others 2010b,c, 2011b, 2012b; Schirone and others 2013).

In addition to PCR, qPCR, and their modifications, the presence of decarboxylases in bacteria can be studied also using proteomic approaches. Pessione and others (2005, 2009, 2010) used proteomic approach to studying bacterial producers of BAs (mainly lactobacilli and enterococci) and energy metabolism in LAB including amino acid decarboxylation and arginine deiminase pathway.

Conclusion

Although putrescine is not classified within the group of BA with the highest potential toxicity, elevated levels of this amine in food and drinks are connected with certain risks. Therefore, there are several compelling reasons to study and monitor its concentration and to focus on the methods reducing its content in foodstuffs.

The aim of this review was in detail to describe production of putrescine in both Gram-negative and Gram-positive bacteria including all specific genes and enzymes related to putrescine metabolism. Factors influencing their expression and activity were also described. Possibilities of putrescine-producing strain detection by PCR are included, along with a complete list and characteristics of available specific primers designed for putrescine-related gene detection and eventual quantification.

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