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Comparative survey of putrescine production from agmatine deamination in different bacteria

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ABSTRACT

This article aims to study putrescine production in *Lactobacillus hilgardii* strain X_1B, an agmatine degrader isolated from wine, and to compare it with three other different species, previously reported as putrescine producers from agmatine: *Pseudomonas aeruginosa* PAO1, *Enterococcus faecalis* ATCC11700 and *Bacillus cereus* CECT 148^T. The effect of different biogenic amines, organic acids, cofactors, amino acids and sugars on putrescine production was evaluated.

In some cases, a similar effect was found in all the strains studied but the magnitude differed. Arginine, glucose and fructose showed an inhibitory effect, whereas the presence of agmatine induced the production of putrescine in all microorganisms. In other cases, the effect differed between *P. aeruginosa* PAO1 and the other microorganisms. Histamine and tyramine poorly influenced the utilization of agmatine, although a small increase in putrescine production was observed in *P. aeruginosa* PAO1. Succinate, spermidine and spermine also led to an increase in putrescine production in *P. aeruginosa* PAO1, whereas the succinate had no effect in the other microorganisms. Spermine and spermidine always produced a diminution in agmatine deamination.

In this work, we have also demonstrated that pyridoxal 5-phosphate, Mg^{2+} and Mn^{2+} had no effect on putrescine production from agmatine. Results presented in this paper indicate differences in regulation mechanisms of agmatine deiminase pathway among *P. aeruginosa* PAO1 and *L. hilgardii* X_1B, *E. faecalis* ATCC11700 and *B. cereus* CECT 148^T.

These results are significant from two points of view, first food quality, and second the toxicological and microbiological aspects. It should be taken into account that putrescine, whose origin is still controversial, is quantitatively the main biogenic amine found in food.

1. Introduction

Biogenic amines are organic bases, endowed with biological activity, that are commonly present in living organisms (Dudkowska et al., 2003). They can be naturally present in many foods, such as fruits, vegetables, meats and juices (Ruiz-Capillas et al., 2004; Landete et al., 2005a), or can also be produced by microorganisms via activity of amino acid decarboxylases (Farías et al., 1993; Suzzi and Gardini, 2003; Kalăc and Krausová, 2005; Landete et al., 2005b).

Excessive consumption of foods containing these amines can be of health concern (Joosten and Northold, 1989; ten Brink et al., 1990). Putrescine, the main biogenic amine associated with microbial food alteration, can be formed from arginine via ornithine, by ornithine decarboxylase (ODC) (Marcobal et al., 2004). Besides, putrescine and the polyamines spermine and spermidine can also be formed by another biochemical pathway that involves the deamination of agmatine (Lu et al., 2002).

Few microorganisms are able to use agmatine, and they are found among various groups of bacteria. The agmatine deiminase pathway was reported to be present in *Pseudomonas aeruginosa* PAO1 (Nakada et al., 2001; Nakada and Itoh, 2003), *Enterococcus faecalis* ATCC11700 previously referred to as *Streptococcus faecalis* (Simon and Stalon, 1982; Simon et al., 1982), *Bacillus cereus* ATCC14579 (Ivanova et al., 2003) and *Lactobacillus hilgardii* X_1B (Arena et al., 2008). Transformation of agmatine into putrescine occurs by these two reactions in *L. hilgardii*:

$$\text{Agmatine} \xrightarrow{\text{Agmatine deiminase}} \text{ammonia} + \textit{N}\text{-carbamoylputrescine}$$

$$\textit{N}\text{-carbamoylputrescine} \xrightarrow{\textit{N}\text{-carbamoylputrescine hydrolase}} \text{ammonia} + \text{putrescine}$$

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Agmatine can be formed from arginine decarboxylation in *L. hilgardii* X_1B as an intermediate in the formation of putrescine (Arena and Manca de Nadra, 2001).

One of the objectives of this work was to compare the production of putrescine from agmatine in four bacterial species in which there are either activities related to agmatine degradation or genes codifying for the enzymes responsible for it. The studied species were: *P. aeruginosa* PAO1, *E. faecalis* ATCC11700, *B. cereus* CECT 148^T and *L. hilgardii* X_1B. Moreover, *E. faecalis*, *B. cereus* and *L. hilgardii* strains are responsible for some food-borne illnesses. For example, Landete et al. (2005b) observed that the main species responsible for high histamine production in wines seem to be *L. hilgardii* and *Pediococcus parvulus*. Besides, *L. hilgardii* strains are also able to produce tyramine, phenylethylamine and putrescine in wine (Landete et al., 2007). Dahlberg and Kosikowsky (1948) demonstrated that *E. faecalis* strains produce the highest amounts of tyramine in cheese. All *E. faecalis* strains analysed by Bover-Cid and Holzapfel (1999) were able to produce tyramine. *B. cereus* is responsible for some food-borne illnesses. It is known to create strong nausea, vomiting and abdominal cramps (Kotiranta et al., 2000). *Bacillus* food-borne illnesses occur due to survival of the bacterial spores when food is improperly cooked. This problem worsens when food is then improperly refrigerated, allowing the spores to germinate (McKillip, 2000).

P. aeruginosa is an aerobic, rod-shaped bacterium and opportunistic human pathogen. It is able to produce putrescine from agmatine deamination. *P. aeruginosa* was also studied in this work as a representative of Gram-negative bacteria.

Another issue of interest was to know how different products, such as sugars (glucose and fructose), cofactors (pyridoxal phosphate, Mg^{2+}, Mn^{2+}), amines (histamine, tyramine, spermine and spermidine) and succinic acid and arginine, influence the transformation of agmatine into putrescine. There are a number of reasons that led us to test these factors: arginine is a precursor of agmatine (Arena and Manca de Nadra, 2001); spermine and spermidine are produced from putrescine (Bardocz, 1993; Lima and Glória, 1999); pyridoxal phosphate, Mg^{2+}, Mn^{2+} are cofactors for many enzymes (Christen and Mehta, 2001); glucose and fructose exert an effect on histamine production (Landete et al., 2008); histamine and tyramine are biogenic amines present in food together to putrescine (Landete et al., 2005a). Succinate was studied because putrescine could be converted into succinate by the action of the enzymes putrescine transaminase (EC 2.6.1.82) and 4-aminobutyraldehyde dehydrogenase (EC 1.2.1.19). All these factors are commonly present in foods and could influence their putrescine content negatively or positively.

The results of this study are important in order to know the risk of encountering high putrescine concentration in food. This is important from the sanitary and economic point of view, as foods exceeding recommend putrescine limits cannot be sold.

2. Material and methods

2.1. Microorganisms

L. hilgardii X_1B was isolated and identified from an Argentinean wine (Strasser de Saad and Manca de Nadra, 1987). The rest of microorganisms were provided by the Spanish Type Culture Collection (CECT): *P. aeruginosa* PAO1 (CECT 4122) and *B. cereus* CECT 148^T (ATCC14579^T), and by the American Type Culture Collection: *E. faecalis* ATCC11700 (previously referred to as *S. faecalis*).

2.2. Culture conditions

L. hilgardii X_1B was grown in MRS broth (Scharlab, Sentmenat, Spain). *E. faecalis* ATCC11700 was grown in Tryptone Soya broth containing in g/l: tryptone 15, soya peptone 5 and NaCl 5. *B. cereus* CECT 148^T in Nutrient I broth, containing in g/l: beef extract 5, peptone 10 and NaCl 5. Finally, *P. aeruginosa* in Nutrient II broth, containing in g/l: beef extract 1, yeast extract 2, peptone 10 and NaCl 5. The media were adjusted to pH 6.5 with 1 mM KOH before sterilisation at 121 °C for 20 min. In the experiments aiming to test whether precultivation on agmatine induces agmatine deamination, 0.5 g/l of agmatine were added. Agmatine was added to sterile medium after filtration through a 0.22-μm filter (Sarstedt, Nümbrecht, Germany). Agmatine and the rest of compounds contained in media were purchased from Sigma Chemical Co. (St. Louis, MO).

The number of viable cells (cfu/ml) was estimated by plating samples on the above-mentioned media supplemented with 20 g/l of agar. Plates were incubated at 28 °C in aerobiosis.

2.3. Putrescine formation from agmatine by resting cells

Cells grown on the culture media described above were harvested after 24 h of static incubation at 28 °C (exponential growth phase). Cells were washed with 0.2 M sodium phosphate buffer pH 6.5. Centrifuged cells were resuspended in the same buffer to obtain an $O.D._{600\,nm} = 0.7$. This $O.D._{600\,nm}$ corresponds to 3.4×10^8 cfu/ml of *L. hilgardii* X_1B, 5.65×10^8 cfu/ml of *E. faecalis* ATCC11700, 1.7×10^8 cfu/ml of *B. cereus* CECT 148^T and 1.87×10^8 cfu/ml of *P. aeruginosa* PAO1.

The reaction mixture to determine putrescine formation contained (in a final volume of 2 ml): 0.5 ml of 1 g/l-agmatine solution, 1 ml 0.2 M sodium phosphate buffer pH 6.5 and 0.5 ml cell suspension D.O. 0.7. To study the effect of different compounds on putrescine production from agmatine 0.1, 0.5 and 1 g/l of arginine, glucose, fructose, pyridoxal phosphate, Mg^{2+}, Mn^{2+}, histamine, putrescine, tyramine spermine, spermidine and succinic acid were added to the reaction mixture separately. In addition, 10 g/l of arginine and 1 g/l of sugar mixture (glucose and fructose 0.5 g/l each) were also tested.

The mixtures were incubated at 28 °C for 8 h. The reaction was stopped, eliminating the cells by centrifugation at 12000 rpm at 4 °C for 3 min, and amines were determined in the supernatant.

2.4. Agmatine and putrescine quantification

These amines were quantified by a reversed phase column HPLC. For analysis, samples were diluted 1:10 with sodium phosphate buffer (0.2 M, pH 6.5) Agmatine and putrescine were precolumn derivatized with *o*-phthaldialdehyde (OPA) (Sigma chemical Co., St. Louis, MO). The reaction solution consisted of 200 mg OPA in 9 ml methanol, 1 ml 0.4 M sodium borate pH 10, and 160 μl 2-mercaptoethanol (MCE).

The samples were injected into the HPLC system (Merck, Darmstadt, Germany) equipped with an L-Intelligent pump (Merck-Hitachi), AS-2000A Autosampler (Merck-Hitachi), a T-6300 thermostated column and an L-7485 LaChrom fluorescence spectrophometer (Merck-Hitachi). The excitation wavelength was 335 nm and emission wavelength was 450 nm. A Merck-Hitachi 100 RP-18 column (25 cm × 5 μm) was used for the stationary phase with a flow of 1.0 ml/min. The column apparatus was at 40 °C. Gradient of solvent A (2.268 g KH_2PO_4 and 14.968 g $Na_2HPO_4 \cdot 12H_2O$ adjusted to pH = 5.8 with H_3PO_4 and filled up with deionized water to 1 l) and solvent B (100% methanol) were applied as follows: 0–20 min, 40–55% B linear

gradient, ml/min; 20–45 min, 55–85% linear gradient, ml/min. Standard concentrations of agmatine and putrescine were used to quantify these amines.

2.5. Statistical analysis

To validate the method the MINITAB Student test was used, and all the experiments were carried out three times. Relative standard deviations for amine concentrations were $\leqslant 5\%$.

3. Results

The presence of *N*-carbamoylputrescine, a product of agmatine degradation by agmatine deiminase, was detected in the reaction mixture of *L. hilgardii* X_1B, but urea was not.

A comparative survey was made to establish the amount of putrescine formed by four different microorganisms.

Results obtained from quantification of putrescine produced from agmatine with induced or uninduced cells (related to the number of viable cells) showed that *P. aeruginosa* PAO1 was the highest putrescine producer (Fig. 1), followed by *L. hilgardii* X_1B strain. *B. cereus* produced the lowest amount of putrescine under the conditions studied. *P. aeruginosa* PAO1 produced between 2.5- and 5-fold more putrescine than the other microorganisms. The amounts of putrescine produced by the Gram-positive bacteria *E. faecalis* ATCC11700 and *L. hilgardii* X_1B were similar, both of them produced twice as much putrescine as *B. cereus* CECT 148^T. When the microorganisms were precultured with agmatine, putrescine production increased in all microorganisms, the highest increase was observed in *P. aeruginosa* PAO1, and in decreasing order *L. hilgardii* X_1B, *B. cereus* CECT 148^T and *E. faecalis* (Fig. 1).

3.1. Effect of arginine on putrescine production

The presence of arginine in the reaction mixture reduced putrescine production from agmatine in all the strains studied (Fig. 2).

Comparatively the highest inhibitory effect was observed with 10 g/l of arginine: reduction percentages of putrescine production were 83%, 80%, 75% and 68%, respectively, in *E. faecalis* ATCC11700, *B. cereus* CECT 148^T, *L. hilgardii* X_1B and *P. aeruginosa* PAO1.

3.2. Effect of pyridoxal phosphate, Mg^{2+}, Mn^{2+} and succinate on putrescine production

None of the factors: pyridoxal phosphate, Mg^{2+} and Mn^{2+} modified the putrescine formation in any of the strains studied.

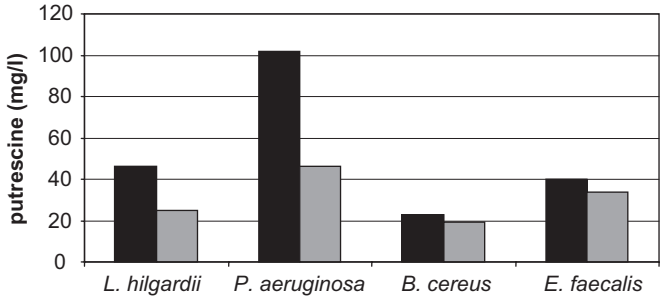

Fig. 1. Production of putrescine via agmatine deiminase by *Lactobacillus hilgardii* X_1B, *Bacillus cereus* CECT 148^T, *Enterococcus faecalis* ATCC11700 and *Pseudomonas aeruginosa* PAO1 by viable cells (10^8 cfu/ml) resuspended in sodium phosphate buffer with (■), and without agmatine induction (■).

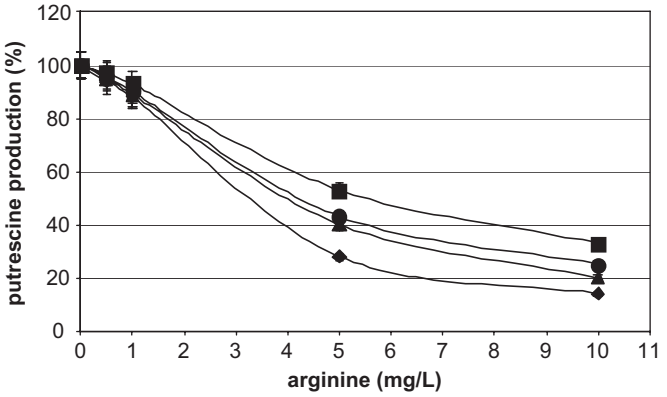

Fig. 2. Effect of arginine concentrations on putrescine production by *Lactobacillus hilgardii* X_1B (♦), *Bacillus cereus* CECT 148^T (▲), *Enterococcus faecalis* ATCC11700 (●) and *Pseudomonas aeruginosa* PAO1 (■).

When succinic acid was added to the reaction mixture no significant effect was observed on agmatine utilization or putrescine production by *L. hilgardii* X_1B, *E. faecalis* ATCC11700 and *B. cereus* CECT 148^T. However, putrescine production in *P. aeruginosa* PAO1 was higher in the presence of this acid, thus 1 g/l of succinate increased putrescine production by 35%, although agmatine degradation remained constant.

3.3. Effects of biogenic amines on putrescine production

The influence of other biogenic amines usually found in wine (histamine and tyramine) on putrescine formation from agmatine was determined (Fig. 3). Histamine and tyramine did not modify the production of putrescine in *B. cereus* CECT 148^T, *E. faecalis* ATCC11700 and *L. hilgardii* X_1B. However, in *P. aeruginosa* PAO1 the presence of these amines increased putrescine production, with 1 g/l of tyramine proving to be the condition leading to the highest increase: 20% (Fig. 3).

Spermine and spermidine can be formed by putrescine degradation. The effects of these compounds on putrescine production from agmatine were analysed. The addition of spermine and spermidine produce a minor consumption of agmatine (data not shown) and an accumulation of putrescine in *P. aeruginosa* PAO1 (Fig. 3), 1 g/l of spermidine and spermine produced an increase of the putrescine production (32% and 23%, respectively). The addition of spermidine and spermine diminished putrescine production in *B. cereus* CECT 148^T, *E. faecalis* ATCC11700, *L. hilgardii* X_1B, between 27% and 22% for spermine (1 g/l), and 24% and 20% for spermidine (1 g/l) (Fig. 3).

3.4. Effects of sugar on putrescine production

Glucose and fructose partially inhibited putrescine formation from agmatine in the four strains studied (Fig. 3). Glucose showed the highest inhibitory effect on putrescine production in *B. cereus* CECT 148^T, *E. faecalis* ATCC11700 and *L. hilgardii* X_1B. Putrescine production diminished by 73%, 79% and 66% in *L. hilgardii* X_1B, *E. faecalis* ATCC11700 and *B. cereus* CECT 148^T, respectively, when 1 g/l of glucose was added to the reaction mixture, whereas in *P. aeruginosa* PAO1 this was only by 19%.

Fructose exerted the principal inhibiting effect on putrescine production in *P. aeruginosa* PAO1 (70%). When the concentration of sugar increased in the reaction mixture, the inhibitory effect increased.

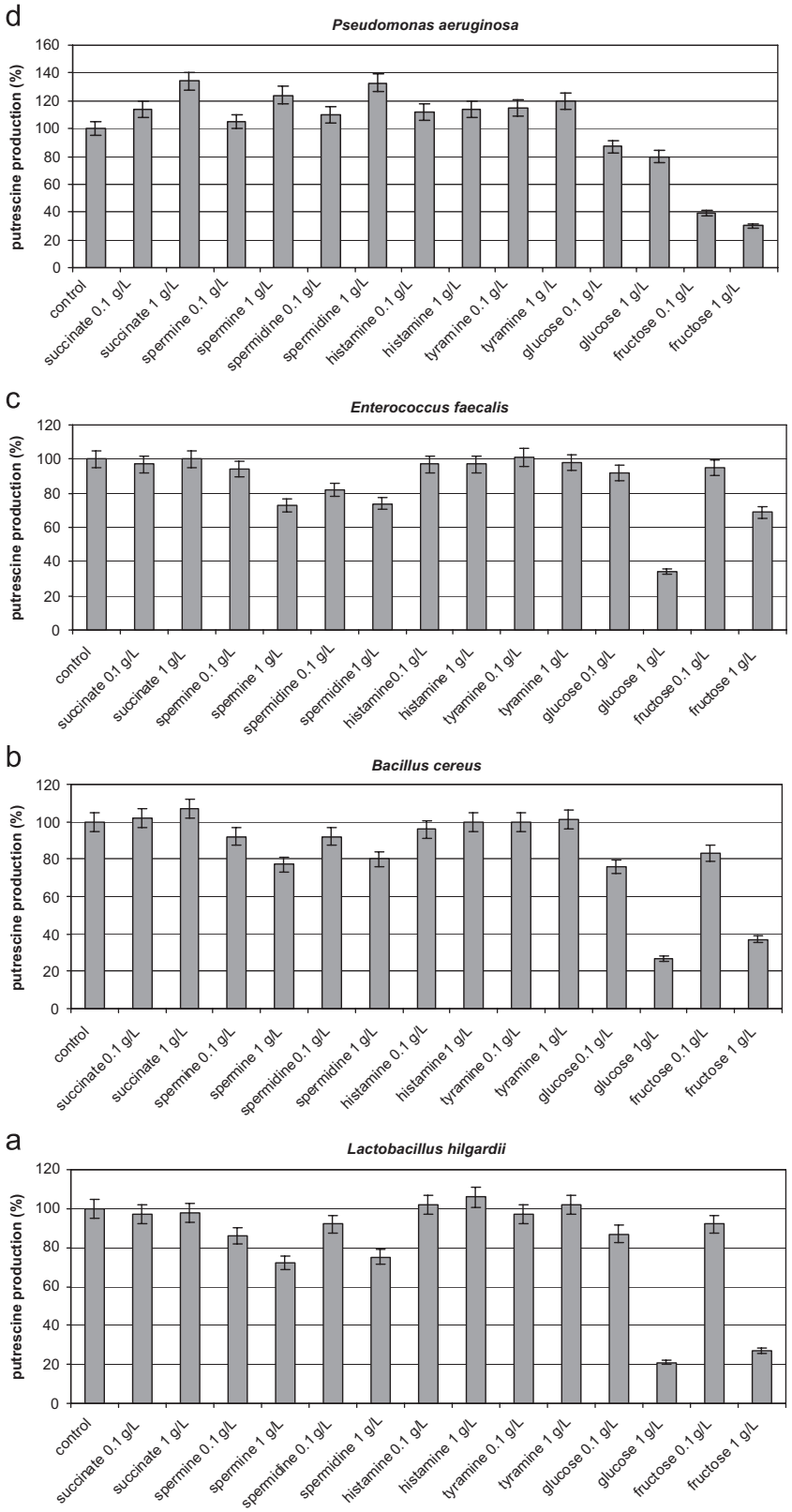

Fig. 3. Effect of succinate, spermidine, spermine, histamine, tyramine, glucose and fructose on putrescine production by *Lactobacillus hilgardii* X_1B (a), *Bacillus cereus* CECT 148^T (b), *Enterococcus faecalis* ATCC11700 (c) and *Pseudomonas aeruginosa* PAO1 (d).

One g/l of sugar mixture (0.5 each of one glucose and fructose), had an inhibitory effect on putrescine formation in *B. cereus* CECT 148^T, *P. aeruginosa* PAO1, *E. faecalis* ATCC11700 and *L. hilgardii* X_1B: 67%, 22%, 45% and 32%, respectively (data not shown).

4. Discussion

Although putrescine has a beneficial effect on cell-survival of *Escherichia coli* exposed to oxidative stress, as reported Tkachenko

et al. (2001), the presence of this amine in food is undesirable from a sanitary point of view (Tkachenko et al., 2001). Putrescine has toxicological effects on man (Kalăc and Krausová, 2005) and can negatively modify wine flavour (Woller, 2005), thus it can have both health and economic consequences. Agmatine, which could be one of the precursors of putrescine, is present in important amounts in raw material, such as barley, milk, etc. (Santos et al., 2003).

Contamination with common spoilage microorganisms, such as *B. cereus*, *P. aeruginosa*, or lactic acid is an important risk factor that must be studied not only in order to eliminate the spoilage but, also, in order to avoid sensorial modifications to the food.

P. aeruginosa PAO1 was demonstrated to have a greater ability to produce putrescine than the other microorganisms tested. The presence of agmatine in preculture broth and arginine in the reaction mixture affected this ability to a greater extent in *P. aeruginosa* PAO1 than in other species.

Lu et al. (2002) reported that agmatine can act as a precursor for polyamines synthesis in *P. aeruginosa*. Results from this paper showed that putrescine production was induced by the presence of agmatine in the preculture in all microorganisms studied. Griswold et al. (2006) observed that an agmatine deiminase-system-deficient strain was unable to grow in the presence of 20 mM agmatine, suggesting that the agmatine deiminase system converts a growth-inhibitory substance into products that can enhance acid tolerance and contribute to the competitive fitness of the organism at low pH (Griswold et al., 2006). The genes for agmatine catabolism from *E. faecalis* SD10 have been cloned and overexpressed in *E. coli* DH5α, and the gene cluster has been definitively identified (Llácer et al., 2007). These authors also reported that ornithine could be a genuine but poor substrate for the putrescine transcarbamylase (EC 2.1.3.6). Lu et al. (2006) also demonstrated that a catalytic core associated with the common chemical function was conserved in the superfamily of the arginine deiminase from *P. aeruginosa*, whereas the substrate-binding residues show some divergence that explain the expansion of the substrate range.

In this paper, we have studied how different factors influence putrescine production from agmatine in different species of microorganisms. The results have demonstrated different behaviours depending on species. *P. aeruginosa* PAO1 showed a different response to Gram-positive bacteria when succinate, spermine, spermidine, histamine, tyramine and the sugars on agmatine deamination were tested. Moreover, this microorganism proved more able to produce putrescine than the other bacteria, whereas arginine and agmatine have less influence on inhibition and stimulation of pathway agmatine deamination in *P. aeruginosa* PAO1 than in other species.

Although the effects of spermine, spermidine and succinic acid were different for *L. hilgardii* X_1B, *E. faecalis* ATCC11700 and *B. cereus* CECT 148^T, a similar proportional response was obtained for each product in each microorganism. This could mean that a general mechanism rules putrescine synthesis in these three microorganisms.

Therefore, control of putrescine production in the agmatine deiminase pathways appears to be similar between microorganisms that are phylogenetically more closely related and different in microorganisms with a more distant relationship, like *P. aeruginosa*.

Arginine in the reaction mixture was observed to diminish the production of putrescine from arginine in all the strains studied. Similar behaviour was reported in *E. faecalis* (Simon et al., 1982), where arginine was demonstrated to inhibit agmatine and putrescine carbamoyltransferase synthesis and also arginine was shown to inhibit the agmatine deiminase pathway.

It seems clear that agmatine deiminase behaves differently to arginine decarboxylase (and other amino decarboxylases) in pyridoxal, Mg^{2+} or Mn^{2+} requirements. Agmatine deiminase did not modify its activity when these cofactors were present in the reaction mixture, whereas in 2001 Arena and Manca de Nadra demonstrated that they stimulated arginine decarboxylase. Supporting our results, Simon and Stalon (1982) also observed that pyridoxal phosphate, Mg^{2+} or Mn^{2+} were not required for the activity of enzymes involved in the agmatine deiminase pathway in *Pseudomonas*.

Putrescine synthesis was negatively correlated to glucose and fructose content. This is in agreement with the findings by Griswold et al. (2004) about the regulation of the agmatine deiminase system by agmatine induction and carbohydrate catabolite repression in *Streptococcus mutans* UA159. A possible reason to explain this fact would be that the microorganisms use glucose and fructose to generate metabolic energy. When the cells have these metabolites in the medium, the genes of agmatine deamination pathway are repressed, because production in this way is not necessary. When the levels of these substrates decrease, the microorganisms can obtain energy to survive through agmatine deamination in a medium poor in nutrients. Similar results were reported by Liu et al. (1996), who observed that lactic acid bacteria obtain metabolic energy through of the deamination of arginine. The analysis of an agmatine deiminase gene cluster in *S. mutans* UA159 by Griswold et al. (2004) demonstrated that the agmatine deiminase system is regulated by carbohydrate catabolite repression. Molenaar et al. (1993) showed that amino acid decarboxylation can provide energy to lactic acid by the same mechanism as malic acid decarboxylation that was demonstrated by Poolman et al. (1991).

It would seem that the putrescine production mechanism from agmatine in *P. aeruginosa* responds very differently as compared to other species tested. Although the presence of *N*-carbamoylputrescine or the agmatine deiminase gene has been demonstrated in all the species assayed in this work, it has yet to be clarified whether the conversion of this intermediate into putrescine is due to the same enzyme in all four strains.

The results of this work have implications not only in terms of wine quality but also in terms of toxicological and microbiological issues, given that putrescine is quantitatively the main biogenic amine found in wine.

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