

Chromatographic methods for biogenic amines determination in foods of animal origin

Métodos cromatográficos para determinar aminas biogênicas em alimentos de origem animal

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Abstract

Biogenic amines (BAs) are formed as a result of specific free amino acid decarboxylation. Analysis of these metabolites may be of great importance to determine food quality and for monitoring the levels of biogenic amines such as histamine and tyramine related to intoxication episodes in humans. Chromatography is a chemistry separation technique used to characterize biogenic amines in foods. Variations of this technique (liquid, thin layer and gas chromatography) have been widely applied; however, the food matrix complex requires that changes in the methodology of extraction, derivatization and detection must be performed according to each group of foods. High-performance liquid chromatography is the most widely used chromatographic method applied for biogenic amines in foods. However, due to the current importance of biogenic amines in quality control and consumer safety, researchers try to develop new methods for a fast, reliable analysis of foods in the market. This review presents some chromatographic techniques applied to monitoring BAs in different foods of animal origin.

Keywords: Biogenic amines. Chromatography. Foods of animal origin.

Resumo

Aminas biogênicas são formadas como resultado da descarboxilação de aminoácidos livres específicos. A análise desses metabólitos é de grande importância na determinação da qualidade e monitoramento de biogênicas como histamina e tiramina relacionadas com episódios de intoxicação em humanos. A cromatografia é uma técnica de separação química usada para caracterizar aminas biogênicas. Variações da técnica (cromatografia líquida, em camada delgada e gasosa) têm sido amplamente usadas, porém a complexidade da matriz alimentar faz com que sejam realizadas mudanças nos processos de extração, derivatização e detecção em concordância com cada grupo de alimento. A cromatografia líquida de alta eficiência (CLAE) é o método mais utilizado na determinação de aminas biogênicas em alimentos. Contudo, devido à importância das aminas biogênicas no controle da qualidade e a segurança do consumidor, os pesquisadores tentam desenvolver novos métodos com o intuito de uma análise mais rápida e precisa para o controle de alimentos no mercado. O objetivo da revisão é apresentar algumas técnicas cromatográficas aplicadas no monitoramento de aminas biogênicas em produtos de origem animal.

Palavras-chave: Alimentos de origem animal. Aminas biogênicas. Cromatografia.

Introduction

Due to increases in the global demand for foods of animal origin, suppliers are obliged to implement specific controls to guarantee food safety and high quality. These products are especially susceptible to protein degradation and the determination of substances that originate by this process can be used as quality indicators. Biogenic amines (BAs) are low molecular weight substances, primarily produced by amino acid decarboxylase enzymes produced by some microorganisms.

There are two reasons for the determination of BAs in foods: their potential toxicity and a possibility of using them as food quality indicators. Some of the major applications of BA analysis are: quality control

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of raw materials, intermediates and end products, monitoring fermentation processes, process control and research & development (ÖNAL, 2007). The presence of these molecules in foods is directly related to amino acid composition, spoilage or starter bacteria, storage temperature, maturation time, packing, and other factors (HALÁSZ et al., 1994). Bedia Erim (2013) reviewed analytical approaches to the analysis of BAs in foods and noted different purposes: (1) developing new analysis methods or improving the current methods; (2) reporting the BA contents of products from different countries and regions, using known methods; (3) using BA analyses to control the effectiveness of methods developed in food preparation, storage, and packaging in order to reduce BA production; and, (4) dealing with the connection between the contents of BAs and BA-producing microorganisms.

Analytical determination of BAs is not simple due to the complexity of the real matrices to be analyzed. The extraction of amines from real matrices is the most critical in terms of obtaining adequate recoveries for

all amines. Most analysis include derivatization step, which is time consuming in the analytical process. It is necessary to develop sensitive, less time-consuming and easier analytical methods for the determination and detection of BAs in foods (ÖNAL, 2007).

Origin and classification of biogenic amines

BAs are organic, basic nitrogenous compounds of low molecular weight, usually formed by decarboxylation of free amino acids: Removal of the alpha-carboxyl group from a proteinogenous amino acid leads to corresponding BAs, e.g., histamine originates from histidine, tyramine from tyrosine, tryptamine from tryptophan, and so on (Figure 1) (BODMER; IMARK; KNEUBÜHL, 1999; GLORIA, 2005). Prerequisites for the formation of amines in foods are the availability of free amino acids, high processing temperatures, or the presence of decarboxylase-positive microorganisms and favorable conditions for microbial growth and decarboxylase activity, storage temperature, maturation time,

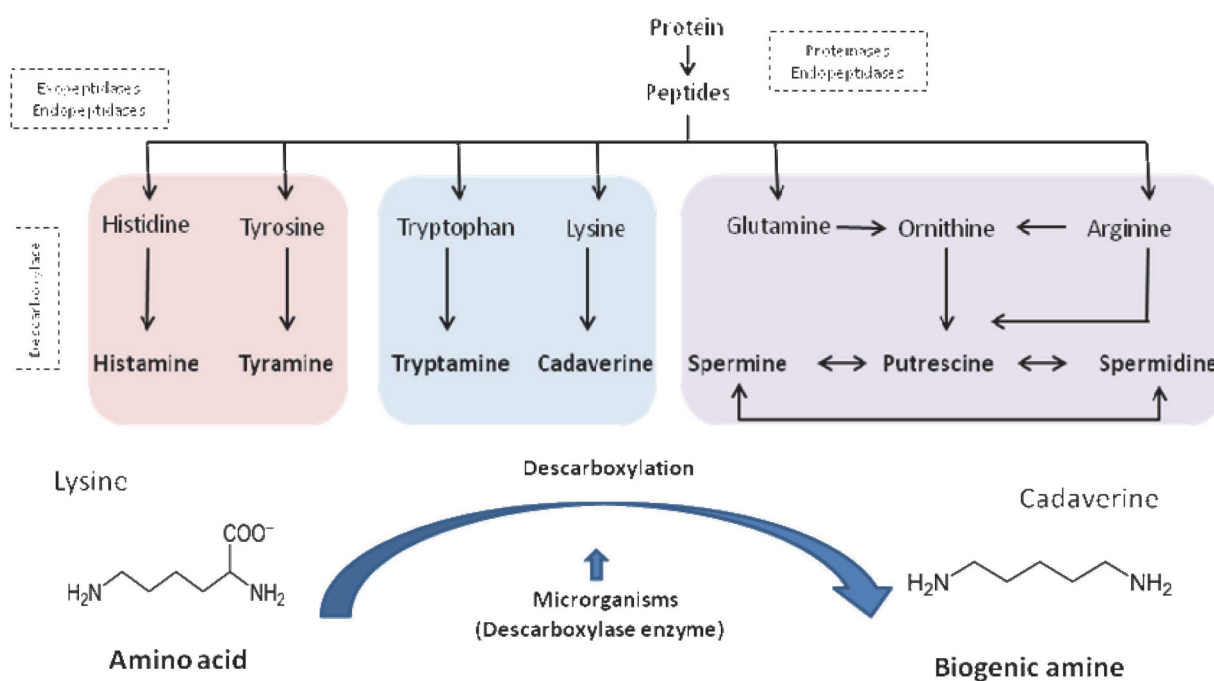


Figure 1 - Biogenic amine formation and decarboxylation process in biogenic amine formation
Source: Adapted from Ruiz-Capillas and Jiménez-Colmenero (2004).

packing, and other factors (HALÁSZ et al., 1994). Free amino acids occur as such in foods, but may also be released from proteins as a result of proteolytic activity or thermal degradation (GLORIA, 2005).

Bioactive amines can be classified on the basis of the number of amine groups, chemical structure, biosynthesis, or physiological functions. Shalaby (1996); Silla Santos (1996) and Ruiz-Capillas and Jiménez-Colmenero (2004), made an interesting amine classification. According to the number of amine groups, there can be monoamines (tyramine, phenylethylamine), diamines (histamine, serotonin, tryptamine, putrescine, cadaverine), or polyamines (spermine, spermidine, agmatine). Based on chemical structure, amines can be aliphatic (putrescine, cadaverine, spermine, spermidine, agmatine), aromatic (tyramine, phenylethylamine), or heterocyclic (histamine, tryptamine, serotonin). Amines can also be classified as indolamines (serotonin) and imidazolamines (histamine). According to the biosynthetic pathway, amines can be natural or biogenic. Natural amines – spermine, spermidine, putrescine and histamine – are formed during *de novo* biosynthesis, e.g., *in situ* as required from their precursors. Histamine can be either natural (stored in mast cells or basophils) or biogenic. Based on physiological functions, amines are classified as polyamines and biogenic amines.

Toxicological aspect

Levels of BAs have been widely studied in several foods because of their potential toxicity. Among all BAs, high concentrations of histamine represent a risk factor for food intoxication, whereas moderate levels may lead to food intolerance. Sensitive persons, with insufficient diamine oxidase activity, suffer from numerous undesirable reactions after consuming foods with significant levels of histamine. Besides spoiled foodstuffs, especially fermented foods contain important levels of BAs, although their concentrations vary extensively not only between different food varieties but also within the varieties

themselves (BODMER; IMARK; KNEUBÜHL, 1999; HUNGERFORD, 2010).

Consumption of foods with high concentrations of BAs can cause migraines, headaches, gastric and intestinal problems and pseudo-allergic responses, chiefly brought about by the toxic action of histamine and tyramine, known respectively as “histamine poisoning” and “cheese reaction”. The most frequent food-borne intoxication caused by amines involves histamine. Histamine intoxication is also referred to as “scombroid poisoning” due to its association with the consumption of scombroid fish; however, non-scombroid fish, cheese, and other foods have also been implicated in some cases. Signs and symptoms appear several minutes or a few hours after ingestion of foods. At first, a flushing of the face and neck is usually observed, accompanied by a feeling of heat and general discomfort. This is often followed by an intense throbbing headache (SHALABY, 1996; SILLA SANTOS, 1996; BODMER; IMARK; KNEUBÜHL, 1999; EFSA, 2011).

Leuschner et al. (2013) reported that, according the Rapid Alert System for Food and Feed (RASFF), the current histamine situation continues to be of public health importance considering the number of human cases and concentrations reported and that the animal origin products concerned with high histamine concentrations are mainly fish products and cheese.

Biogenic amines as quality indicator

BAs have been used as a quality index and indicator of unwanted microbial activity in meat and cooked meat products. A combination of putrescine and cadaverine has been suggested as an index of acceptability in fresh meat because their concentrations increase prior to spoilage and correlate well with the microbial load (RUIZ-CAPILLAS; JIMÉNEZ-COLMENERO, 2004). The concentrations of tyramine, putrescine, and cadaverine normally increase during the processing and storage of meat and meat products, while spermidine and spermine decrease or remain

constant (HALÁSZ et al., 1994; BARDÓCZ, 1995).

The usefulness of BAs as a quality indicator depends on the nature of the product; the results tend to be more satisfactory in fresh meat and heat-treated meat products than in fermented products (VECIANA-NOGUÉS; MARINÉ-FONT; VIDAL-CAROU, 1997). Several factors affect the levels of Bas, including types and degrees of contamination of raw materials, manufacturing practices, certain processing stages (maturation, cooked, etc.), and the use of culture starters. All these factors vary according to the nature of the product and, in some cases, can mask changes in the type and concentration of BAs through the different phases of treatment and storage, delaying visible signs of spoilage and/or off-odor development (RUIZ-CAPILLAS; JIMÉNEZ-COLMENERO, 2004).

Use of chromatography methods in biogenic amine determination

Several methods to analyze BA in food based on thin layer chromatography (TLC), gas chromatography (GC) and liquid chromatography (LC) have so far been described and used by researchers. TLC is simple and does not require special equipment, but most published methods suffer from the excessive time needed for analysis and/or inaccuracy of obtained results (semi-quantitative). GC is not so often applied for the determination of BAs. LC with pre- or post-column derivatization is by far the mostly frequently reported technique for BA separation and quantification (BOMKE et al., 2009).

Sample preparation

Extraction is the most critical step in the detection procedure of BAs. According to the method, this step negatively affects the analytical recoveries. The extraction of BAs from a solid matrix is usually carried out with acids such as hydrochloric acid (HCl), perchloric acid (HClO₄), trichloroacetic acid (C₂HCl₃O₂) or with methanesulfonic acid (CH₄O₃S). Nevertheless, organic solvents such as methanol,

acetone, acetonitrile-HClO₄ or dichloromethane-HClO₄ can be used. The extraction is a process influenced by many factors such as type of acid, type of organic solvent, salt used for saturation, pH at which amine extraction (liquid-liquid partition with the organic solvent) is carried out, and the time and type of stirring. Improper techniques may cause erroneous results, so strict validation of separation methods, especially recovery studies, is necessary to ensure the accuracy and precision of the sample-preparation processes (MORET; BORTOLOMEAZZI; LERCKER, 1992; MORET; CONTE, 1996).

Some authors have compared the extraction capability of several acids for different amines, but did not obtain the same results. The choice of acid is related to the characteristics of the matrix analyzed. Moret and Conte (1996) determined that 0.1 M HCl appears to be a good choice for the analysis of cheese; however, it is not a suitable acid for fish or meat products where 5% TCA represented a better choice. As amines are strong organic bases, it is very useful to take advantage of this feature for their separation from sample matrix. For this purpose perchloric acid is widely used as an extraction agent (DADÁKOVÁ; KŘÍŽEK; PELIKÁNOVÁ, 2009). The effect of three extracting solvents, 75% methanol in water (MeOH), 75% methanol in 0.4 N HCl (MeOH-HCl) and 75% methanol in 25% 0.4 N HCl plus 0.5% KCl (MeOH-HCl-KCl), on fish meat was evaluated by Richard et al. (2008). They determined that MeOH-HCl resulted in a more complete recovery of cadaverine, putrescine, and histamine. Kőrös, Varga and Molnár-Perl (2008) evaluated the extraction step in cheese with four acids, one by one: perchloric, chloridic, sulfosalicylic and trichloroacetic and confirmed that perchloric acid provided a 30% higher yield, compared to the other acids.

Custódio, Tavares and Glória (2007) compared the efficiency of different extraction procedures to recover ten BAs from cheese using hydrochloric acid (0.1-1M), sulfosalicylic acid (12%), methanol and ethanol. In general, extraction efficiency varied significantly

for the BAs analyzed and was affected by levels of amines in the cheese matrix, the type, concentration and temperature of the solvent used. Extraction with HCl (1.0M) is a relatively simple, inexpensive and rapid method to allow an adequate extraction from several cheeses. It is important to note that after acid extraction, the solution must be alkalinized with sodium hydroxide (NaOH) in order to obtain a good derivatization reaction. A strict control of pH in the extraction phase is absolutely essential to obtain reproducible data. A pH of 11.5 allows satisfactory recoveries for some BAs, but above of 11.5, tyramine recovery is drastically reduced. On the other hand, pH 10.0 is the optimum for tyramine, but quite unsuitable for putrescine, cadaverine, spermidine, spermine and histamine (MORET; CONTE, 1996).

Other methods such as solid phase extraction (SPE) and matrix solid-phase dispersion (MSPD) have been performed to extract BAs in different kind of cheeses (CALBIANI et al., 2005; RESTUCCIA et al., 2011; SPIZZIRRI et al., 2013). Both methodologies reduce the time of BA extraction from homogeneously dispersed food samples with a sorbent phase (e.g. C18 silica). The homogenized sample is placed in a glass-syringe-barrel column and the BAs are selectively eluted with suitable organic solvent (e.g. methanol), followed by immediate instrumental analysis (e.g. ESI-MS/MS). Compared to conventional extraction procedures, this technique requires a smaller sample size, shorter analysis time, and uses less organic solvent (HELLE; BADEN; KAJ, 2011).

MSPD and SPE differ in several ways: 1) MSPD involves a complete disruption, dispersal and extraction of the sample. In SPE sample disruption is performed in separate steps in preparing samples for SPE and many of the sample components must be discarded in the process of making the sample suitable for addition to an SPE column. 2) In SPE the sample is usually absorbed onto the top of the column packing material, not throughout the column as in MSPD. 3) The physical and chemical interactions of the components of the system are greater in MSPD

and different in many respects from those seen in classical SPE or other forms of liquid chromatography (BARKER, 2007).

Separation techniques

In general, BA separation is performed in C8 or C18 columns, in gradient elution with mobile phase consisted in water and acetonitrile or methanol (LANFRANCO; MORET; PURCARO, 2011). An alternative to reverse phase columns can be a capillary electrophoresis in conjunction with pulsed amperometric detection. This method is advantageous because no derivatization procedure is needed, small sample volumes can be used and a superior response is achieved in terms of limit detection compared with HPLC (SUN; YANG; WANG, 2003).

Lapa-Guimarães and Pickova (2004) suggested a one dimensional, double development technique, using the solvent system chloroform–diethyl ether–triethylamine (6:4:1), followed by chloroform–triethylamine (6:1), for their ability and accuracy to separate dansyl derivatives of agmatine, putrescine, tryptamine, cadaverine, spermidine, histamine, spermine, tyramine and β -phenylethylamine in fish meat by TLC.

Detection system

In a chromatography system the detector is the component responsible for turning a physical or chemical attribute into a measureable signal corresponding to concentration or identity (SWARTZ, 2010). Due to low volatility and lack of chromophores, most of BAs involve a derivatization procedure (pre- or post-column). For this purpose different chemical reagents have been used and their choice depends on the kind of detector. *o*-phthalaldehyde (OPA), Dansyl-, benzoyl- and dansyl- chloride, fluoresceine, 9-fluorenylmethyl chloroformate (FMOC), naphthalene-2,3-dicarboxaldehyde, 4-chloro-3,5-dinitro-benzotrifluoride (CNBF), 1,2-naphthoquinone-4-sulfonate (NQS), 6-aminoquinolyl-N-hydroxysuccinimide

(AQC), N-hydroxysuccinimide ester (DMQC-Osu) (ÖNAL; TEKKELI; ÖNAL, 2013). Some of derivative reagents are shown in the Figure 2.

OPA can easily react with primary amines within about 30 s in the presence of a reducing reagent, such as N- acetylcysteine or 2-mercaptoethanol to

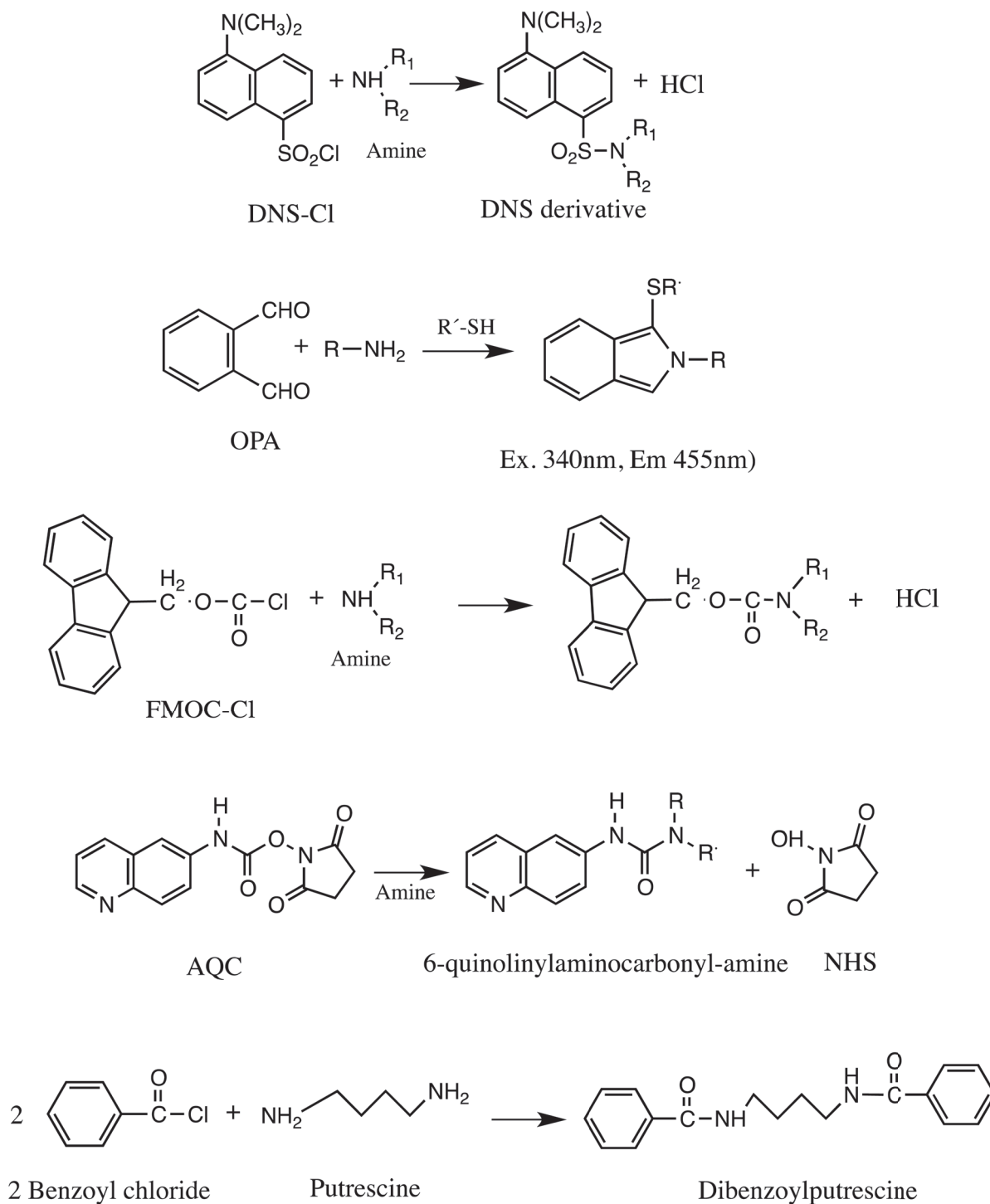


Figure 2 - Reaction of different derivative reagents with biogenic amines. Aminoquinolyl-N-hydroxysuccinimidy (AQC), N-hydroxysuccinimide (NHS), 5-dimethylaminonaphthalene-1-sulfonyl chloride or Dansyl chloride (DNS-Cl), OPA (o-phthalaldehyde), 9-Fluorenylmethyl Chloroformate (FMOC-Cl)

Source: Adapted from Ho (2005); Molnár-Perl (2005); Silva (2005) and Weiss (2005).

give highly fluorescent isoindole derivatives for a specific and sensitive determination of polyamines (putrescine, cadaverine, spermidine and spermine). The derivatization is complete within about 2 min in a mixture of borate buffer (pH 6-8) and methanol at room temperature. This procedure can be performed in pre- or post-column stage, but the derivatives are not very stable (YAMAGUCHI; ISHIDA, 1999).

As previously described, derivatization with OPA has a short life. The use of dansyl or benzoyl chloride is preferred for derivatization because of affinity for

most of the naturally occurring di and polyamines and the reaction products are more stable (ZAITSU; KAI; HAMASE, 1999; ÖNAL, 2007). The use of benzoyl chloride is advantageous due to the long elution time in with dansyl derivatives (ZAITSU; KAI; HAMASE, 1999). A procedure using benzoyl chloride was described for several foods like cheese, chicken meat and fish by Cunha et al. (2012); Lázaro et al. (2013, 2012a,b) and Rodrigues et al. (2013) respectively, with excellent results (Figure 3). Contradictory results were reported by Tahmouzi, Khaksar and Ghasemlou

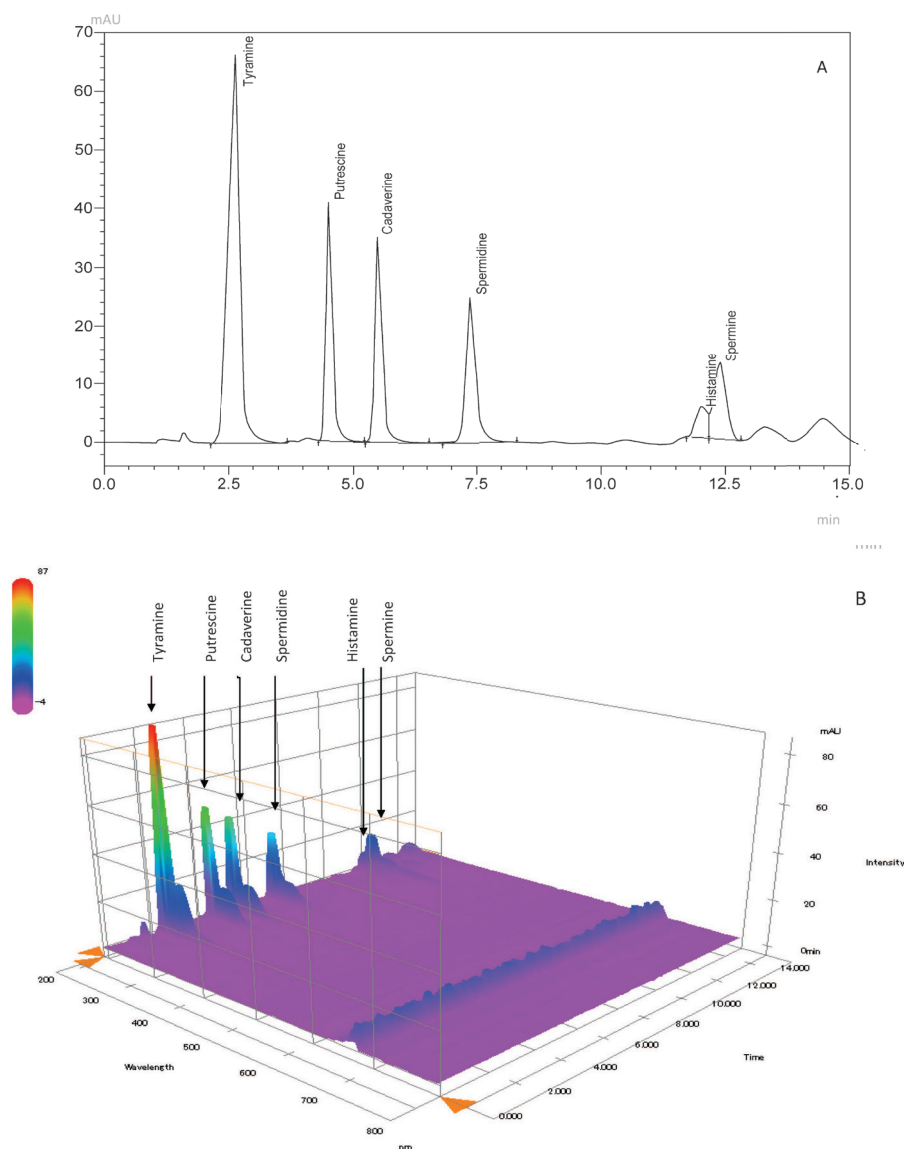


Figure 3 - Chromatogram of biogenic amines standard obtained from an HPLC-PDA system. (A) Chromatogram detected at 198nm and (B) Three-dimensional (3D) plot of absorption spectra (200-800nm) as a function of retention time. Standard solution contained 0.01 mg/mL of each biogenic amine. HPLC conditions are according to Lázaro et al. (2013)

(2011), who compared OPA and benzoyl chloride for rapid determination of histamine in tuna fish and found that the derivatization process with benzoyl chloride was longer and more complex.

De Mey et al. (2012) compared both HPLC methods to determine BAs in dry fermented meat using dansyl chloride and dabsyl chloride. The use of dabsyl chloride at 70°C resulted in a 25-min reduction of the derivatization time, in comparison with the dansylation at 40°C. Furthermore, the use of irritating ammonia to remove excess dansyl chloride can be avoided. These authors also showed that the SPE cleaning procedure on the C18 cartridge resulted in a reliable and sensitive method of BAs determination in a complex protein-fat matrix, which is typical of dry fermented sausages.

The use of powerful mass spectrometric detectors in combination with liquid chromatography (LC/MS) has played a vital role in solving many problems related to other detection methods (MALIK; BLASCO; PICÓ, 2010). LC-MS has been applied to the detection of BAs in cheese (CALBIANI et al., 2005), fresh and processed meat (SACCANI et al., 2005), and fish (SELF; WU; MARKS, 2011; SAGRATINI et al., 2012). However, LC-MS of BAs in fish and other foods are not used in research, presumably because UV and fluorescence detectors are less expensive instrumentation and are good enough for detection of BAs (HUNGERFORD, 2010).

Bomke et al. (2009) developed a LC/MS method for the determination of selected BAs in fish and other food samples. A precolumn derivatization with succinimidylferrocenyl propionate with subsequent EPI allows an unambiguous identification of BAs by their mass spectra compared with the established OPA/fluorescence method. Jia et al. (2011) developed a novel liquid chromatography coupled with quadruple time-of-flight mass spectrometry (LC-QTOF/MS) method for the simultaneous determination of 23 amino acids and 7 BAs in cheese and sausage samples. The linearity for both molecules had a relatively wide range with $r^2 > 0.99$. The intra- and inter-day precision, expressed

as relative standard deviation (RSD), ranged from 1.1 to 4.6% and from 2.0 to 11.2%, respectively. The limit of detection was between 0.005 and 0.4 µg/mL. With a simple dilution, recoveries of around 80–120% were obtained for most of the compounds.

Chromatography applied in animal origin matrices

Foods likely to contain elevated levels of BAs include fish and fish products, dairy products, meat and meat products and fermented products (SHALABY, 1996). Reliable methods for evaluating BA production are important for preventing food-borne intoxication, maintaining good control of the production chain and checking safety quality. High performance liquid chromatography methods are reliable and highly sensitive techniques for the simultaneous detection and quantification of different BAs (EFSA, 2011). Table 1 shows a summary of some chromatography methods to detect and quantify BAs in different food matrices.

Milk and dairy products

Milk and dairy products are good examples to demonstrate the undesirable increase of histamine content during improper food processing. Whereas fresh milk normally contains very low levels of histamine, commercially available pasteurized or UHT milk already shows slightly higher histamine content. Upon fermentation of milk, a considerable increase of histamine content often occurs, leading to contents of up to 7 ppm histamine in sour cream and even slightly higher levels in yoghurt. Finally, in cheese production a rather drastic increase of histamine content often occurs, leading to maximum levels of histamine of up to 2500 ppm in aged cheese (BODMER; IMARK; KNEUBÜHL, 1999).

Milk and milk products are very important in human nutrition and, among them, cheese is considered a good source of proteins, vitamins and minerals. However, cheese is one of the most fermented foods commonly associated with BA contamination (LOIZZO et al.,

Table 1 - Different chromatographic methods to biogenic amine determination in foods of animal origin (Continues)

Food Sample	Biogenic amine	Extraction	Stationary phase	Mobile phase/flow rate	Derivatization/detector	Ref.
Meat and meat products	Tyr, His, Phm, Put, Cad, Trp, Agm, Spm, Spd	7.5% TCA	Cation-exchange	A: potassium phosphate buffer B: 5% potassium chloride, 4% 2-propanol, 0.9% potassium phosphate dibasic, 0.3% acetic acid, 89.8% in H ₂ O (pH 5.63) Gradient elution: 0.8mL/min	OPA/Fluorescence (Ex: 330nm; Em: 465nm)	Triki et al. (2012)
Fermented meat	Spm, Spd, Cad, Put, Phm, Tyr, His, Trp	0.4 M HClO ₄	C18	A: MeOH:ACN:H ₂ O (12.5:37.5:50) B: MeOH:ACN (25:75) Gradient elution: 1mL/min	Dbs-Cl/UV (450nm)	De Mey et al. (2012)
Meat and meat products	His, Tyr, Phm, Put, Cad	0.1mol/L MSA	Cation-exchange	MSA Gradient elution: 0.38mL/min	No derivative step/UV (276nm), MS	Saccani et al. (2005)
Meat	Trp, Put, Cad, Tyr, Spd, Spm	0.4 M HClO ₄	C18	A: 0.1M ammonium acetate B: ACN Gradient elution: 1.2 mL/min	Dns-Cl/UV (254nm)	Vinci; Antonelli (2002)
Meat products	His, Tyr, Trp, Put, Cad, Spd, Spm	5% TCA	C8 (OPA), C18 (Dns-Cl)	OPA: acetate buffer:ACN. Gradient elution: 0.6mL/min Dansyl: H ₂ O:ACN Gradient elution: 0.8mL/min	Dns-Cl/UV (254nm) OPA/Fluorescence (Ex: 330nm; Em: 440nm)	Smelá et al. (2002)
Meat and meat products	Tyr, Trp, His, Phm, Put, Cad, Agm, Spm, Spd	0.6M HClO ₄	C18	ACN:H ₂ O Gradient elution: 1.5mL/min	OPA/Fluorescence (Ex: 340nm; Em: 445nm)	Hernández-Jover et al. (1997)
Chicken meat	Tyr, Put, Cad, Spd, Spm	5% HClO ₄	C18	ACN:H ₂ O (42:58) Isocratic elution: 1mL/min	Bnz-Cl/DAD (198nm)	Lázaro et al (2012a,b; 2013)
Chicken meat	Put, Cad, Spm, Spd, Tyr, His	6% TCA	C18	A: 0.40M SDS (pH 3.0) B: 0.02M phosphate buffer solution:ACN Gradient elution: 1.1mL/min	Bnz-Cl/UV (254nm)	Balamatsia et al. (2006) 2013)
Chicken meat	Trp, Phm, Put, Cad, His, Tyr, Spm, Spd	0.4M HClO ₄	C18	0.1M ammonium acetate:ACN (1:1) Gradient elution: 0.9mL/min	Dns-Cl/UV (254nm)	Rokka et al. (2004)
Chicken meat	Put, Cad, Spd, Spm, His, Tyr	5% TCA	C18	A: 0.2M sodium acetate + 10mM 1-octanesulfonic acid sodium salt (pH 5.0) B: MeOH:ACN:10mM 1-octanesulfonic acid sodium salt (1:9:1) Gradient elution: 0.6mL/min	OPA (Fluorecence, Ex:340 nm; Em:445 nm)	Silva and Gloria (2002)
Chicken meat	Trp, Put, Cad, His, Tyr, Spd, Spm	0.4 M HClO ₄	C18	H ₂ O:MeOH Gradient elution: 2mL/min	Dns-Cl/Fluorescence (Ex: 350nm; Em: 520nm)	Tamim et al. (2002)
Fish meat	Put, Cad	5% HClO ₄	C18	ACN:H ₂ O (42:58) Isocratic elution: 1mL/min	Bnz-Cl/UV (198nm)	Rodrigues et al. (2013)
Fish meat	Spm, Spd, Cad, Put, His, Tyr, Phm, Trp	5% TCA	C18	A: Ammonium formate 15 mM + formic acid in H ₂ O (pH 3.3) B: MeOH Gradient elution: 0.5 mL/min	LC-ESI- MS/MS	Sagratiini et al. (2012)
Fish meat	Put, His, Cad, Trp	5% TCA	C18	A: ACN/potassium dihydrogen (50:50) B: MeOH/H ₂ O (50:50) Gradient elution: 2.5mL/min	Bnz-Cl/UV (254 nm) OPA/Fluorecence (Ex:320 nm; Em:523 nm)	Tahmouzi; Khaksar; Ghasemlou (2011)

Table 1 - Different chromatographic methods to biogenic amine determination in foods of animal origin (Continuation)

Food Sample	Biogenic amine	Extraction	Stationary phase	Mobile phase/flow rate	Derivatization/detector	Ref.
Fish products	Agm, His, Phm, Put, Trp, Tyr	MSPD	C18	A: ammonium B: ACN Gradient elution: 0.75ml/min	APCI-MS	Self; Wu; Marks (2011)
Fish and meat products	Spd, Put, His, Trp, Tyr	5% TCA	C18	ACN:H ₂ O (67:33) Isocratic elution: 1.2 mL/min	Dns-Cl/UV (254nm)	Saaïd et al. (2009)
Fish, calamari and salami	Agm, Cad, His, Put, Spd, Spm, Tyr	0.6 M HClO ₄	C18	A: 100 mmol ammonium formate and 200 µL formic acid in H ₂ O (pH ~ 4) B: ACN Gradient elution: 0.45 mL/min.	SFP/ESI-MS	Bomke et al. (2009)
Fish meat	His	1M HClO ₄	C18	A: 85% buffer solution (pH 6.9), 15% MeOH B: ACN Isocratic elution: 1mL/min	No derivative step/ DAD (214nm)	Cinquina et al. (2004)
Fish and fishery products	Put, Cad, Spd, His, Tyr	5% TCA	HPLC: C18 TLC: Silica gel plate	HPLC: Gradient elution- MeOH/water TLC: chloroform:triethylamine (100:25)	HPLC: Dns-Cl/UV (254nm) TLC: isopropanol: triethanolamine (8:2)/ UV (365 nm)	Jeya Shakila; Vasundhara; Kumudavally (2001)
Milk	Put, Spd, Spm, Agm, Cad, His, Tyr, Trp, Phm	SSA	C18	A: 0.2 mol/L sodium acetate and 15 mmol/L 1-octanesulphonic acid sodium salt B: ACN Gradient elution: 0.8ml/min	OPA/Fluorescence (Ex:340 nm; Em:445 nm)	Gloria et al. (2011)
Milk	Put, Spd, Spm, Agm, Cad, His, Tyr, Trp, Phm	70% HClO ₄	C18	A: 0.1 M sodium acetate and 10 mM sodium octanesulfonate (pH 5.30) B: B: ACN (6.6:3.4). Solvent B consisted of 0.2 M sodium acetate and 10 mM sodium octanesulfonate (pH 4.50) Gradient elution: 1mL/min	OPA/Fluorescence (Ex: 340 nm; Em:445 nm)	Novella-Rodriguez et al. (2000)
Kefir	Cad, Trp, Spd, Spm, Tyr, Agm	0.2M HCl	C18	A: 0.05M acetate buffer: MeOH (60:40) B: MeOH Gradient elution: 1mL/min	Bnz-Cl/UV (254 nm)	Özdestan; Üren (2010)
Cheese	Spm, Spd, Put, His, Tyr, Cad, Agm, Phm	SPE	Cation-exchange	A: ACN/H ₂ O (20/80) + 0.05% TFA B: ACN/H ₂ O (20/80) + 0.35% TFA Gradient elution: 0.7mL/min	No derivative step/ELSD	Spizzirri et al. (2013)
Cheese and sausage	Put, Cad, His, Tyr, Spd	0.1M HCl	C18	A: 0.1% formic acid in H ₂ O B: 0.1% formic acid in ACN Gradient elution: 0.2 mL/min	Dns-Cl/ESI-QToF-MS	Jia et al. (2011)
Cheese	Spm, Spd, Put, His, Tyr	SPE	Cation-exchange	A: ACN/H ₂ O (20/80) + 0.05% TFA B: ACN/H ₂ O (20/80) + 0.35% TFA Gradient elution: 0.7mL/min	No derivative step/ELSD	Restuccia et al. (2011)
Cheese	Tyr, His, Cad	5% TCA	C18	A: ACN B: Water Gradient elution: 0.8 mL/min	Dns-Cl/UV (254nm)	Ibrahim and Amer (2010)
Cheese	Agm, His, Tyr, Put, Cad, Trp, Spd, Spm	0.6N HClO ₄	C18	A: 50mM sodium acetate in 1% tetrahydrofuran in H ₂ O B: MeOH HPLC Gradient elution: 1mL/min UPLC Gradient elution: 0.4mL/min	AQC/UV (254 nm) Fluorescence (Ex: 250nm; Em: 395nm)	Mayer; Fiechter; Fischer (2010)

Table 1 - Different chromatographic methods to biogenic amine determination in foods of animal origin (Continuation)

Food Sample	Biogenic amine	Extraction	Stationary phase	Mobile phase/flow rate	Derivatization/detector	Ref.
Cheese	Cad, Put, Tyr, Trp, Phm, His	0.4M HClO ₄	C18	A: 0.1 M ammonium acetate B: ACN Gradient elution: 1 mL/min	Dns-Cl/DAD (254nm)	Andic; Genccelep; Kose (2010)
Cheese, clams, salami	Cad, His, Tyr, Trp	0.1M HCl	C18	A: ACN B: ammonium Gradient elution: 1mL/min	Dns-Cl/UV (254nm) ESI-MS APCI-MS	Mazzucco et al. (2010)
Cheese	His, Tyr, Put, Cad, Spd	1 M HClO ₄ 0.5M SSA 1M HCl 1M TCA	C18	A: ACN:0.36 M sodium acetate: H ₂ O (10:5:85) B: MeOH:0.36 M sodium acetate: H ₂ O (55:8:37) C: ACN:0.36 M sodium acetate: H ₂ O (55:5:40) D: ACN Gradient elution: 1.8mL/min	OPA-ET-FMOC/Fluorecence (Ex: 337nm; Em: 454 nm)	Kőrös; Varga; Molnár-Perl (2008)
Cheese	His, Tyr	MSPD	C18	A: 0.1% TFA (v/v) B: MeOH Gradient elution: 0.2mL/min	ESI-MS	Calbiani et al. (2005)
Cheese	Tyr	5% HClO ₄	C18	MeOH:H ₂ O Isocratic elution: 1 mL/min	NBD-Cl/UV (458 nm)	Yigit; Ersoy (2003)
Honey	His, Put, Cad, Tyr, Agm	---	C18	A: 0.05M sodium acetate + 5% MeOH B: MeOH:ACN (70:30) Gradient elution: 0.5mL/min	OPA/Fluorescence (Ex: 335nm; Em: 440nm)	Kelly; Blaise; Larroque (2010)
Honey	His, Tyr, Trp, Cad	---	C18	A: 1% tetrahydrofuran, 8% MeOH and 91% phosphate buffer B: 80% MeOH + 20% phosphate buffer Gradient elution: 1mL/min	OPA/Fluorescence, Ex: 330nm; Em: 440nm)	Pereira et al. (2008)

Biogenic amine: Tyramine (Tyr), cadaverine (Cad), putrescine (Put), histamine (His), tryptamine (Trm), agmatine (Agm), spermidine (Spd), spermine (Spm), phenylethylamine (Phm).

Extraction procedures/reagents: matrix solid-phase dispersion (MSPD), solid-phase extraction (SPE), trichloroacetic acid (TCA), perchloric acid (HClO₄), sulphosalicylic acid (SSA), chlorhidric acid (HCl), methanesulfonic acid (MSA).

Derivative reagents: benzoyl chloride (Bnz-Cl), o-orthophthalaldehyde (OPA), ethanethiol (ET), 9-fluorenylmethyl chloroformate (FMOC), Dabsyl chloride (Dbs-Cl), Dansyl chloride (Dns-Cl), 4-chloro-7-nitrobenzofurazan (NBD-Cl), 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate (AQC), Succinimidylferrocenyl propionate (SFP)

Mobile phase: Methanol (MeOH), trifluoroacetic acid (TFA), acetonitrile (ACN), sodium dodecyl sulphate (SDS).

Chromatography/detectors: Electrospray ionization (ESI), Atmospheric-pressure chemical ionization (APCI), Diode-Array Detection (DAD), Evaporative light scattering detector (ELSD), Quadrupole time-of-flight (QToF), thin layer chromatography (TLC), mass spectrometry (MS).

2013). The BA content of different types of cheese varies. Indeed, it can also vary within the same type of cheese and even between different sections of the same cheese (NOVELLA-RODRÍGUEZ et al., 2003). On the other hand, the effect of the hygienic quality of milk on changes in BA content was evaluated during ripening of goat cheeses manufactured from pasteurized and raw milk. Spermidine and spermine were the main amines in raw milk, while they were minor amines in cheeses. Other amines increased markedly during

ripening, tyramine being the main amine in cheese made from raw milk and cadaverine and putrescine in those produced from pasteurized milk. Raw milk cheese showed remarkably higher BA levels compared with pasteurized milk cheeses. These differences can be attributed to the reduction of microbial counts (NOVELLA-RODRÍGUEZ et al., 2004).

Calbiani et al. (2005) developed a new rapid and sensitive method based on MSPD followed by LC-ESI/MS for the determination of BAs at trace levels

in cheese samples. The method required 0.25 g of sample, CN bonded silica as a dispersant sorbent, and a formic acid aqueous solution/methanol mixture as an eluting solvent. Extraction recoveries from soft cheese products were calculated between 98 to 110% range. Results in the 0.05-0.25 mg kg⁻¹ range were obtained for limits of detection for histamine, tyramine, and β -phenylethylamine and linearity was established over two orders of magnitude. Excellent precision in terms of intra-day repeatability was calculated (RSD% < 5).

Kőrös, Varga and Molnár-Perl (2008) described a HPLC with combined diode array and fluorescence detection of BAs in various cheese samples. The proposal is based on acidic deproteinization, derivatization and gradient optimization studies, resulting in the identification and quantification of nine amines from a single solution, by one injection. The optimized and simple protocol consists of deproteinization (1M perchloric acid), centrifugation, filtration and the subsequent derivatization with the o-phthalaldehyde-ethanethiol-9-fluorenylmethyl chloroformate (OPA-ET-FMOC) reagent. The method can be characterized with a linearity of wide concentration range (6.25–1000 pM/injection), a good chromatographic reproducibility (average: 2.69% RSD) and an excellent recovery (average: 100.2%; average 3.84% RSD).

Mayer, Fiechter and Fischer (2010) explored a fast and reliable ultra-performance liquid chromatography (UPLC) method to detection of ethanolamine, methylamine, agmatine, histamine, dimethylamine, ethylamine, octopamine, pyrrolidine, dopamine, isopropylamine, propylamine, tyramine, putrescine, butylamine, cadaverine, tryptamine, 2-phenylethylamine, 3-methylbutylamine, spermidine, spermine in cheese samples. After pre-column derivatization with AQC, 20 primary and secondary BAs were separated within 9 min. Limits of detection (mg/100 g cheese) ranged from 0.04 (ethanolamine) to 1.62 (spermine), and limits of quantification were between 0.16 (ethanolamine) and 6.09 (spermine). The UPLC

method was applied to the analysis of 58 cheese samples sold in Austria. About 13.8% of samples showed a histamine level above 10 mg/100 g, and 22.4% had tyramine content above 10 mg/100 g. Moreover, 8.6% of samples had a putrescine or cadaverine content higher than 10 mg/100 g. The total concentration of BA in two cheese samples was about 194 mg/100 g.

Andic, Genccelep and Kose (2010) determined the BA profile by HPLC of Herby cheese, a semi-hard texture and a salty taste cheese produced in Turkey. They found tyramine (range 18.0–1125.5 mg kg⁻¹) and cadaverine (range not detected to 1844.5 mg kg⁻¹) were the most important BAs. Histamine content was found higher than 100 mg kg⁻¹. The concentration of amines in some cheeses was much higher than the toxic dose limits. Linares et al. (2011) made a extensive review of BAs contained in different dairy products. In milk, polyamines are the most abundant. However, tyramine, histamine, putrescine, cadaverine, and, at lower concentrations, β -phenylethylamine and tryptamine, are all detected.

Fish, shellfish and fish products

Histamine intoxication is probably the principal sanitary problem associated with the high content of BAs in fish. Scombroid fish species, such as tuna, bonito, saury, and mackerel, as well as non-scombroid species, such as mahi-mahi, sardines, pilchards, anchovies, herring, marlin, salmon, amberjack, and bluefish have high levels of histidine in their flesh (RICHARD et al., 2008). However, some cases of food poisoning from fish with low contents of histamine indicate that other substances, as toxicity potentiators, might be involved. Veciana-Nogués, Mariné-Font and Vidal-Carou (1997) evaluated changes in 10 BAs throughout tuna storage. Histamine was the prevailing BA throughout storage. However, a great increase in cadaverine and tyramine and a slight increase in putrescine were also observed. These researchers proposed the index of BAs from the sum of histamine, tyramine, cadaverine, and putrescine which showed

good correlations with time of storage.

Cinquina et al. (2004) compared and validated a capillary electrophoresis with HPLC method with diode arrays detection for determining histamine in tuna samples. Both techniques gave excellent results in terms of accuracy, precision, linear range and reproducibility. For both techniques, different columns, capillaries and batches of reagent were tested and the robustness of the method demonstrated.

Prester (2011) related the application of chromatography for BA detection in cephalopods, crustaceans and bivalves. These shellfish contained lower amounts of both histamine and tyramine than fish species. On the other hand, fish products, especially those produced in all Southeast Asian countries had considerable amount of BAs. Products such as sauces, smoked-dried, canned and packed seafood are commonly indicated as a potential risk for BA intoxication.

Rodrigues et al. (2013) explored the potential use of BAs as a quality indicator for rainbow trout (*Oncorhynchus mykiss*) and found a significant increase in putrescine and cadaverine levels over the 15-day storage. On the other hand, Cunha et al. (2013) evaluated levels of BAs in tilapia packaged in modified atmosphere and irradiated during refrigerated storage with a HPLC method and showed an extension of shelf life in irradiated tilapia.

Meat and meat products

BA content in meat can be considered a freshness marker or a bad conservation marker. In particular, the study of BA quantities in meat as a function of conservation time could be a useful tool to control meat spoilage. In fact, the formation of some amines and concentration increase of those already existing in meat are due to degrading processes in food (VINCI; ANTONELLI, 2002).

High amounts of BAs can be found in fermented foods derived from raw material with high protein content, such as dry and semi-dry fermented

sausages. Dry fermented sausages can potentially support the accumulation of BAs due to the presence of significant levels of spermidine and spermine but also for microbial growth. Nevertheless, a great variability characterizes the BA content in fermented meat products (SUZZI; GARDINI, 2003).

BAs levels of sucuk (Turkish dry fermented sausage) were determined by using HPLC method with diode array detector after pre-column derivatization with dansyl. Levels of putrescine and cadaverine were detected as 93% and 87% of the samples, respectively. Spermine and spermidine were detected in ranges from not detected to 16.4 and from not detected to 10.7 mg kg⁻¹, respectively. Histamine was found to be between 50 and 100 mg kg⁻¹ as 17% of the samples. Tryptamine was detected in the range of 1.2–82.3 mg kg⁻¹. Tyramine contents of all samples were within the acceptable level. Phenylethylamine was found in 17 of the 30 samples and levels in all detected samples were found to be lower than 25 mg kg (GENÇCELEP et al., 2008).

There are numerous studies on the determination of biogenic amines in dry and semi-dry fermented sausages. Mazzucco et al. (2010) developed an HPLC-UV method to simultaneous determination of BAs and their precursor amino acids after a precolumn derivatization with dansyl chloride. The HPLC-UV method was validated and applied to the analysis of salami and other foods. All matrices showed recoveries always >92% and relative standard deviation always <5%. On the other hand, Silva et al. (2013) reviewed BAs and fermented sausages and concluded that these products had conditions for BAs production principally for the use of culture starter cultures and spoilage bacteria, reaffirming the need for the meat industry to pay special attention to the use of microorganisms and specific control of all processes.

Chicken meat

Many authors had reported several methodologies to determinate these substances in chicken. Vinci and Antonelli (2002) developed an HPLC-UV method to

detect dansyl chloride derivatives with good precision, recovery values > 93%, relative standard deviation between 1.47% and 2.94% and detection limits for all amines, and confirmed that very low quantities of BAs could be detected in real samples.

Lázaro et al. (2013) validated a HPLC method to determine tyramine, putrescine, cadaverine, spermidine and spermine in chicken using perchloric acid (5%) extraction and 40µL benzoyl chloride, followed by homogenization in vortex for 15 sec and kept at room temperature ($25 \pm 2^\circ\text{C}$) for 20 min. The biogenic amines were collected through liquid partitioning with 1000 µL of diethyl ether, which proceeded twice. The ether layers containing amines were evaporated to dryness under nitrogen stream, resuspended in 1000µL of mobile phase (acetonitrile:water) and stored at $4 \pm 1^\circ\text{C}$. Separation was performed in C18 column, in isocratic condition of water:Acetonitrile 42:58 (v/v). The chromatography conditions were: flow rate of $1 \text{ mL}\cdot\text{min}^{-1}$, injection volume of 20µL, column temperature of 20°C , detector wavelength set at 198 nm and total run time of 15 min.

Baston et al. (2008) used a similar technique but with some changes: gradient system, 254nm and internal standard (1,7-diaminoheptan). Chicken-based products such as mortadella, frankfurters, sausage, meatballs, hamburger, and nuggets contain bioactive amines. In general, these products had lower BA levels and were considered unlikely to elicit direct adverse effects in consumers (SORIANO-SANTOS, 2010).

Honey

Pereira et al. (2008) proposed a simple HPLC analytical method for the simultaneous analysis of amino acids and BAs in liquid food matrices: a pre-column derivatization with OPA in the presence of 2-mercaptoethanol, performed in the sample injection loop, and fluorescence detection. Only residual levels of BAs were detected in the analyzed samples.

Kelly, Blaise and Larroque (2010) reported a new, simple, rapid and economical method for routine

determination of 24 amino acids and BAs in honey. The method was validated in the range 0.25–10 mg/L; repeatability was less than 3% RSD and the intermediate precision ranged from 2 to 7% RSD. The method was shown to be linear by the 'lack of fit' test and the accuracy was between 97 and 101%. The LOQ was 100µg/L for putrescine and cadaverine.

Conclusions

The production of BAs in foods of animal origin is complex due to several parameters and interactions in each product. The choice of an adequate method depends on the complexity of the sample matrix and levels of BAs present in the samples. For these reasons it is complicated to use a single method for all food matrices, even though in some foods several BA cannot be simultaneously determined. Reversed-phase HPLC is the usual method for the analysis of BAs in these kind of foods. In most cases, a derivatization step (o-orthophthalaldehyde or dansyl-chloride) is needed before the separation process and the most frequently-used detectors are ultraviolet or fluorescence. Even though some researchers proposed the application of a novel process of separation, no derivatization step and MS detection, the classical HPLC method is still the most-reported chromatography technique. Monitoring of raw materials at different points of the food chain (production, distribution and storage) must be implemented by the food industry, especially in foods such as fish, fermented meat products and cheese with high risk of BA formation.

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