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Biogenic amines in Brazilian cheeses

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The levels of biogenic amines in Brazilian cheeses were investigated for the first time. Ninety-two samples of 10 types of cheese were purchased at retail stores. The amines were extracted using hydrochloric acid, partitioned into diethyl ether, separated through reversed-phase ion-pair chromatography and quantified fluorimetrically after postcolumn derivatization with *o*-phthaldehyde. Overall, spermine was the most prevalent amine (93%), followed by histamine (65%), 2-phenylethylamine (62%), spermidine (61%), putrescine (60%), cadaverine (59%), serotonin (44%), agmatine (38%), tyramine (37%) and tryptamine (29%). Spermine, agmatine, 2-phenylethylamine, serotonin, spermidine and tryptamine were detected at low levels (<4.10 mg/100 g). Cadaverine, tyramine, histamine and putrescine were present at levels up to 111.00, 21.25, 19.65 and 17.37 mg/100 g, respectively. There was variability on the type and levels of amine in each kind of cheese suggesting that amine formation and accumulation in cheese could be prevented. Efforts should be made to understand amine formation in cheese in order to optimize technology and secure low amine levels. Susceptible individuals should be advised to consume cheeses with low biogenic amines contents.

INTRODUCTION

Biogenic amines are aliphatic, alicyclic or heterocyclic organic bases of low molecular weight which arise as a consequence of metabolic process in animals, plants and microorganisms. These amines are found in a variety of foods and beverages whose elaboration includes a ripening or fermentation process. The formation of biogenic amines is believed to result primarily from the enzymatic decarboxylation of free amino acids (Rice *et al.*, 1976; Izquierdo-Pulido *et al.*, 1993; Halász *et al.*, 1994).

Cheeses represent an ideal environment for amine production (Edwards and Sandine, 1981; Chang *et al.*, 1985). The major factors that govern the formation, accumulation and type of amines are probably the availability of amino acids (and hence proteolysis of cheese) and the presence of bacteria able to decarboxylate amino acids (Van Boekel and Arentsen-Stasse, 1987). Several factors may also contribute, such as pH, salt concentration, water availability, temperature and duration of ripening and storage, bacterial density, and the presence of cofactor and amine catabolism (Rice *et al.*, 1976; Edwards and Sandine, 1981; Chang *et al.*, 1985; Stratton *et al.*, 1992). According to Edwards and Sandine (1981), the pH of cheese is appropriate for amine production, generally between 5.0 and 6.5, depending on age and type. Cheeses were observed to contain ample pyridoxal phosphate which is required for amino acid decarboxylase activity (Shahani *et al.*, 1962). Amine catabolism by means of mono- and diamine oxidase activity was absent in several cheeses (Voigt and Eitenmiller, 1977). Amines such as histamine accumulate in cheese during aging (Antila *et al.*, 1984; Stratton *et al.*, 1991; Simon-Sarkadi *et al.*, 1995). Numerous bacteria, both intentional and adventitious, have been reported as being capable of amine production. These are *Escherichia*, *Enterobacter*, *Salmonella*, *Shigella*, *Clostridium perfringens*, *Streptococcus*, *Lactobacillus* and *Leuconostoc* (Edwards and Sandine, 1981; Chang *et al.*, 1985; Stratton *et al.*, 1991). *Lactobacilli* appear to play a major role in histamine, tyramine and putrescine accumulation (Joosten and Northolt, 1987; Stratton *et al.*, 1991). *Enterococci* are considered to be notorious tyramine formers. Representatives of the Enterobacteriaceae can cause cadaverine and putrescine build-up even at low densities (Joosten and Northolt, 1987). Therefore, biogenic amines might be useful indicators of spoilage (Halász *et al.*, 1994).

The presence of low levels of biogenic amines in cheeses and other foods is not considered a serious risk. However, if normal routes of amine catabolism are

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inhibited or the amount consumed is large, various physiological effects may result (Koehler and Eitenmiller, 1978). Several outbreaks of histamine poisoning have occurred following the consumption of cheese, particularly Swiss and Cheddar, containing high levels of histamine (Taylor, 1985; Stratton *et al.*, 1991, 1992). "Cheese reaction", a hypertensive crisis usually accompanied by severe headache, has been observed after ingestion of foods rich in tyramine. Migraine headache has been observed after consumption of cheeses with high levels of tryptamine and 2-phenylethylamine. Biogenic amines may provoke hypertensive crises and even death from cerebral hemorrhage in patients treated with monoamine oxidase inhibitor (MAOI) drugs (Voigt *et al.*, 1974; Koehler and Eitenmiller, 1978; Edwards and Sandine, 1981; Reuvers *et al.*, 1986). Polyamines, such as putrescine, cadaverine, spermine and spermidine can potentiate histamine toxicity (Edwards and Sandine, 1981; Joosten, 1988; Halász *et al.*, 1994). Furthermore, in the presence of nitrite, these amines may form *N*-nitrosamines, some of which are known to be carcinogenic, mutagenic, teratogenic and embriophatic (Oliveira *et al.*, 1995). The exact toxic threshold of biogenic amines is difficult to determine due to its dependence on the efficiency of detoxification mechanisms of different individuals. However, according to Chang *et al.* (1985) and Halász *et al.* (1994), 10 mg of histamine in 100 g of sample can cause histamine poisoning; 10–80 mg of tyramine can cause "cheese reaction" (6 mg if patient is receiving MAOI); and 3 mg of 2-phenylethylamine can cause migraine headache.

No information was found on biogenic amines levels in Brazilian cheeses. The knowledge of biogenic amines levels in Brazilian cheese is necessary to make an assessment of the health hazard arising from the consumption of these products especially by susceptible individuals. Furthermore, it could provide information to improve cheese quality with respect to biogenic amines content. An ion-pair LC procedure followed by postcolumn derivatization with *o*-phthaldehyde and fluorometric detection has been developed recently for the simultaneous determination of 10 biogenic amines in cheese (Vale and Glória, 1997). In the present study, this procedure was used to determine the levels of biogenic amines in Brazilian cheeses.

MATERIALS AND METHODS

Materials

Cheese samples were purchased at retail stores in Belo Horizonte, Minas Gerais, Brazil between March and September 1996. The selection of cheese samples represented the different types commercially available and cheese production in the state of Minas Gerais. The cheeses were grated, homogenized thoroughly and analyzed immediately. Each analysis was performed in duplicate.

Methods

Samples were analyzed for biogenic amines according to the procedure described by Vale and Glória (1997). The amines were extracted from the cheese samples with 0.1 N HCl and partitioned into diethyl ether. The extract was evaporated and the residue diluted with 0.1 N HCl. The amines, histamine (HIM), tyramine (TYM), 2-phenylethylamine (PHM), tryptamine (TRM), serotonin (SER), cadaverine (CAD), putrescine (PUT), agmatine (AGM), spermine (SPM) and spermidine (SPD) were separated by ion-pair chromatography and quantified spectrofluorometrically after postcolumn derivatization with *o*-phthaldehyde (OPA).

Liquid chromatography was performed with a Shimadzu model LC-10AD system connected to a spectrofluorometric detector (Shimadzu model RF-551) at 340 and 445 nm of excitation and emission, respectively, and to a controller CBM-10AD (Shimadzu, Kyoto, Japan). A postcolumn derivatization unit was installed between column outlet and detector.

A reversed-phase μBondapak C_{18} column, 300 × 3.9 mm i.d., particle size 10 µm, was used with a μBondapak C_{18} guard-pak insert (Waters, Milford, MA). The mobile phases were: A, solution of 0.2 M sodium acetate and 10 mM 1-octanesulfonic acid sodium salt adjusted to pH 5.0 with acetic acid; and B, methanol-acetonitrile-10 mM 1-octanesulfonic acid sodium salt (1 + 9 + 1, v/v/v). The flow rate was set at 0.6 ml/min and the gradient was: 20 min at 12% B, 22 min at 13%, 35 min at 13%, 43 min at 26%, 66 min at 26%, 71 min at 12% and 80 min at 12%.

The post-column derivatization reagent was delivered at 0.4 ml/min. It consisted of 1.5 ml Brij-35, 1.5 ml mercaptoethanol and 0.2 g OPA dissolved in a 500 ml solution of 25 g boric acid and 22 g KOH (pH adjusted to 10.5 with 3% KOH). The column and the post-column reaction apparatus were at room temperature (23 ± 1°C).

Moisture and fat content, acidity (IAL, 1985) and pH (Lanara, 1981) were also determined.

Statistical analysis

Correlation coefficients among biogenic amines levels ($P \leq 0.001$) and among biogenic amines levels and quality parameters ($P \leq 0.05$) were determined by linear regression analysis of individual values.

RESULTS AND DISCUSSION

The types, percentage of samples containing the amines and levels of biogenic amines detected in the cheeses are indicated in Tables 1 and 2. Overall, spermine was the most prevalent amine, being found in 93% of the samples. It was followed by histamine (65%), 2-phenylethylamine (62%), spermidine (61%), putrescine

Table 1. Levels of biogenic amines in Minas, Gorgonzola, Prato, Tilsit and Gouda cheeses produced in Brazil

Cheeses	Biogenic amines (mg/100 g)									
	HIM	TYM	TRM	PHM	SER	PUT	CAD	SPM	SPD	AGM
Minas										
% positive	19	0	31	50	31	19	25	81	44	31
range	nd—2.50	nd	nd–0.72	nd–0.64	nd–0.31	nd–2.64	nd–0.30	0.07–2.58	nd–2.10	nd–0.04
mean ± SD	0.33 ± 0.77	0.0	0.08 ± 0.19	0.09 ± 0.18	0.05 ± 0.10	0.27 ± 0.69	0.03 ± 0.08	0.26 ± 0.66	0.20 ± 0.53	0.01 ± 0.01
Gorgonzola										
% positive	100	67	67	100	67	100	67	100	100	67
range	0.45–2.99	nd–1.07	nd–2.80	0.07–1.03	nd–1.81	0.17–0.80	nd–0.65	0.07–0.55	0.13–3.23	nd–1.79
mean ± SD	1.35 ± 1.42	0.39 ± 0.59	0.96 ± 1.59	0.43 ± 0.53	0.62 ± 1.03	0.41 ± 0.34	0.25 ± 0.35	0.25 ± 0.27	1.31 ± 1.68	0.64 ± 1.00
Prato										
% positive	80	27	33	67	53	53	40	100	80	27
range	nd–6.15	nd–1.75	nd–0.90	nd–1.19	nd–0.57	nd–3.53	nd–3.39	0.07–0.90	nd–2.69	nd–0.35
mean ± SD	1.60 ± 2.34	0.21 ± 0.48	0.10 ± 0.24	0.21 ± 0.32	0.13 ± 0.18	0.30 ± 0.90	0.26 ± 0.87	0.17 ± 0.23	0.44 ± 0.69	0.04 ± 0.10
Tilsit										
% positive	67	67	67	100	33	67	100	100	100	33
range	nd–4.82	nd–0.64	nd–0.48	0.07–1.03	nd–0.52	nd–3.39	0.07–1.83	0.07–2.55	0.07–1.08	nd–0.08
mean ± SD	1.61 ± 2.78	0.31 ± 0.32	0.20 ± 0.25	0.54 ± 0.48	0.17 ± 0.30	1.15 ± 1.94	1.06 ± 0.94	0.97 ± 1.38	0.51 ± 0.52	0.03 ± 0.04
Gouda										
% positive	67	56	33	67	44	67	78	67	56	56
range	nd–19.65	nd–2.47	nd–4.09	nd–1.92	nd–3.04	nd–17.37	nd–3.51	nd–1.13	nd–1.35	nd–1.34
mean ± SD	2.84 ± 6.35	0.70 ± 0.85	0.63 ± 1.40	0.25 ± 0.63	0.40 ± 1.01	2.33 ± 5.68	0.73 ± 1.10	0.27 ± 0.40	0.30 ± 0.47	0.24 ± 0.44

A total of 46 samples of cheese were analyzed in duplicate (16 Minas, 3 Gorgonzola, 15 Prato, 3 Tilsit and 9 Gouda).
Mean value ± standard deviation (SD) were calculated by using zero for not detected levels (HIM, PHM, PUT, CAD, SPD and SPM $\leq$0.07; TYM and TRM $\leq$0.12; SER $\leq$0.14; and AGM $\leq$0.15 mg/100 g).

Table 2. Levels of biogenic amines in Mozzarella, Provolone, Parmesan, grated Parmesan and grated cheeses produced in Brazil

Cheese	Biogenic amines (mg/100 g)									
	HIM	TYM	TRM	PHM	SER	PUT	CAD	SPM	SPD	AGM
Mozzarella										
% positive	69	39	31	54	31	62	62	100	62	15
range	nd–11.33	nd–1.56	nd–0.35	nd–0.26	nd–0.47	nd–1.37	nd–2.34	0.07–1.31	nd–1.06	nd–0.13
mean ± SD	1.57 ± 3.21	0.20 ± 0.43	0.05 ± 0.10	0.08 ± 0.10	0.07 ± 0.15	0.35 ± 0.47	0.23 ± 0.64	0.28 ± 0.40	0.19 ± 0.33	0.01 ± 0.04
Provolone										
% positive	60	33	13	60	47	60	53	100	67	67
range	nd–6.04	nd–0.44	nd–1.08	nd–1.40	nd–1.40	nd–8.17	nd–111	0.07–0.97	nd–2.38	nd–0.18
mean ± SD	1.04 ± 1.98	0.06 ± 0.14	0.08 ± 0.28	0.38 ± 0.55	0.15 ± 0.36	0.57 ± 2.10	7.44 ± 28.68	0.16 ± 0.27	0.31 ± 0.61	0.02 ± 0.05
Parmesan										
% positive	67	17	0	33	17	67	67	100	17	0
range	nd–0.87	nd–1.00	nd	nd–0.04	nd–0.23	nd–1.36	nd–0.25	0.07–0.09	nd–0.15	nd
mean ± SD	0.21 ± 0.34	0.17 ± 0.41	0.00	0.01 ± 0.02	0.04 ± 0.09	0.24 ± 0.55	0.07 ± 0.09	0.03 ± 0.04	0.03 ± 0.06	0.00
Grated Parmesan										
% positive	100	100	50	75	75	100	100	100	75	50
range	0.11–8.69	0.12–5.20	nd–0.34	nd–1.98	nd–1.96	0.08–6.30	0.07–13.42	0.07–0.80	nd–1.23	nd–1.41
mean ± SD	3.71 ± 3.39	2.86 ± 1.91	0.10 ± 0.15	0.55 ± 0.67	0.83 ± 0.72	1.55 ± 2.04	2.25 ± 4.56	0.24 ± 0.28	0.44 ± 0.45	0.23 ± 0.48
Grated cheese										
% positive	100	50	0	75	50	100	100	100	25	50
range	0.13–8.80	nd–21.25	nd	nd–1.71	nd–1.27	0.32–2.76	0.30–4.17	0.07–0.08	nd–0.36	nd–0.07
mean ± SD	2.88 ± 4.83	5.43 ± 12.27	0.00	0.47 ± 0.98	0.35 ± 0.73	1.41 ± 1.23	1.46 ± 2.23	0.07 ± 0.01	0.09 ± 0.21	0.02 ± 0.03

A total of 46 samples of cheese were analyzed in duplicate (13 Mozzarella, 15 Provolone, 6 Parmesan, 8 grated Parmesan and 4 grated cheese).
Mean value ± standard deviation (SD) were calculated by using zero for not detected levels (HIM, PHM, PUT, CAD, SPD and SPM $\leq$0.07; TYM and TRM $\leq$0.12; SER $\leq$0.14; and AGM $\leq$0.15 mg/100 g).

(60%), cadaverine (59%), serotonin (44%), agmatine (38%), tyramine (37%) and tryptamine (29%). In spite of being the most frequently detected amine, spermine was present at low levels, below 2.6 mg/100 g of cheese. Agmatine, 2-phenylethylamine, serotonin, spermidine and tryptamine were also detected at low levels (below 1.80, 1.99, 3.05, 3.24 and 4.10, respectively). However, cadaverine, tyramine, histamine and putrescine were detected at levels up to 111.00, 21.25, 19.65 and 17.37 mg/100 g, respectively.

Histamine was the second most prevalent amine. It was found in 100% of grated Parmesan, Gorgonzola and grated cheese, in 80% of Prato, 19% of Minas and 60–67% of the remaining cheeses. Higher mean levels were detected for grated Parmesan, grated and Gouda cheese (3.71, 2.88 and 2.84 mg/100 g, respectively). Histamine levels capable of causing histamine poisoning were detected in 11% of Gouda and 8% of Mozzarella cheese. However, taking into account the concomitant presence of polyamines, it is likely that a higher percentage of cheese samples could cause histamine poisoning.

Tyramine was present in 100% of grated Parmesan, 67% of Gorgonzola, 56% of Gouda, 50% of grated cheese and in 17 to 39% of the remaining types of cheese. No tyramine was detected in Minas cheese. Only grated cheese (25% of the samples) contained tyramine at levels capable of causing hypertensive crisis.

Overall, tryptamine was detected sporadically, at lower amounts compared to histamine and tyramine. Similar results were observed by Chang *et al.* (1985). It was present in 67% of Tilsit and Gorgonzola, 50% of grated Parmesan and in less than 33% of the remaining types of cheese. No tryptamine was detected in Parmesan and grated cheese. Higher mean tryptamine levels were observed in Gorgonzola and Gouda. The toxic threshold of tryptamine is not known (Joosten, 1988).

2-Phenylethylamine, another amine of health significance was detected in 100% of Gorgonzola and Tilsit, 75% of grated Parmesan, 67% of Gouda, Prato and grated cheese, 54% of Mozzarella, 50% of Minas and 33% of Prato cheese. The prevalence of this amine was high, however the levels detected were low ($\leq$1.98 mg/100 g), below its toxic threshold.

As shown in Table 3, higher total biogenic amines levels were detected in grated cheese, Provolone and Gouda cheese. According to Smith (1980-81), Sumner and Taylor (1989) and Halász *et al.* (1994), Gouda cheese, along with Swiss and Cheddar, contain high levels of biogenic amines and are the most frequently incriminated cheeses in histamine poisoning episodes. Provolone and Gouda cheese go through long aging period, which favors amine formation (Stratton *et al.*, 1991; Simon-Sarkadi *et al.*, 1995). Grated cheese is a product obtained from the mixture of different types of cheese, among them Prato, Edam, Sbrinz, Reino, Tilsit, Mozzarella and Provolone. Higher levels of amines in grated cheese could be due to the use of cheeses with defects or use of high amounts of cheese rinds, observed by Smith (1980–81) to contain particularly high levels of biogenic amines.

High variability in pH, acidity, moisture and fat content of the different types of cheese analyzed was observed. Several samples analyzed did not meet the standards of identity and quality established by Brazilian legislation (Brasil, 1996). Coefficients of variation up to 8% for pH in Prato cheese, 110% for acidity in grated cheese, 26% for moisture content in grated Parmesan cheese and 28% for fat content in Provolone cheese were observed. Such variation indicates need for better quality control during processing.

Regression analysis of the individual amines (Table 4) showed significant positive correlation ($P \leq 0.001$). The data in Table 4 suggest that the formation of some amines is influenced by the same mechanisms or conditions. With regard to quality parameters (Table 5), pH, moisture and fat contents and acidity correlated significantly ($P \leq 0.05$) with formation and accumulation of some amines. These results suggest that, among quality parameters evaluated, acidity influenced amine formation in several types of cheese. These results are supported by the theory that the formation of biogenic amines is a protective mechanism of bacteria against acidic environments (Eitenmiller *et al.*, 1981; Maijala, 1994).

Table 3. Total biogenic amines levels, pH, acidity, moisture and fat contents in Brazilian cheeses

Cheese	Samples analyzed	Biogenic amines (mg/100 g)	pH	Acidity[a] (g/l)	Content (g/100 g)	
					Moisture	Fat
Minas	16	1.32 ± 2.09	5.63 ± 0.22	1.06 ± 0.83	43.89 ± 3.33	25.82 ± 5.00
Gorgonzola	3	6.61 ± 6.00	5.77 ± 0.15	2.37 ± 0.87	39.94 ± 2.70	32.08 ± 3.66
Prato	15	3.44 ± 4.70	6.00 ± 0.50	0.79 ± 0.27	41.56 ± 2.39	27.20 ± 4.36
Tilsit	3	6.53 ± 8.27	5.80 ± 0.18	0.61 ± 0.06	40.63 ± 0.57	27.44 ± 2.15
Gouda	9	8.27 ± 18.42	6.03 ± 0.28	0.80 ± 0.36	38.47 ± 1.85	29.25 ± 2.60
Mozzarella	13	3.04 ± 4.20	5.81 ± 0.32	0.57 ± 0.28	45.82 ± 2.24	23.18 ± 2.57
Provolone	15	10.17 ± 33.04	5.43 ± 0.25	1.02 ± 0.52	35.56 ± 6.36	25.02 ± 7.07
Parmesan	6	0.79 ± 1.34	5.40 ± 0.22	1.76 ± 0.41	30.31 ± 2.75	31.57 ± 8.10
Grated Parmesan	8	12.76 ± 12.06	5.33 ± 0.08	2.19 ± 0.97	14.71 ± 3.92	34.83 ± 5.35
Grated cheese	4	12.13 ± 18.89	5.35 ± 0.02	1.30 ± 1.43	17.81 ± 1.46	35.55 ± 5.42

Mean value ± standard deviation.
[a] Acidity is expressed as lactic acid.

Table 4. Significant correlation ($P \leq 0.001$) observed in the regression analysis among biogenic amines in Brazilian cheeses

Amines	Cheeses with positive correlation at $P \leq 0.001$								
	HIM	TYM	TRM	PHM	SER	PUT	CAD	SPM	SPD
HIM									
TYM									
TRM	Minas Gouda	Prato							
PHM	Gouda		Gouda						
SER	Gouda		Gouda	Gouda Grated					
PUT	Gouda	Parmesan Prato	Gouda Prato	Gouda Minas	Gouda				
CAD	Prato Gouda Mozzarella	Prato Gouda	Gouda	Gouda	Gouda	Provolone Prato Gouda gr. Parmesan			
SPM		Gouda		Prato	Gouda Minas	Provolone	Gouda Provolone		
SPD		Grated	Gouda	Minas	Prato	Provolone	Gouda Provolone	Provolone	
AGM	Gouda Mozzarella	Gouda		Gouda	Provolone Prato Gouda	Minas Gouda gr. Parmesan	Gouda Mozzarella gr. Parmesan	Gouda	Prato

Table 5. Significant correlation ($P \leq 0.05$) observed in the regression analysis among biogenic amines and quality parameters

Parameter	Cheeses with significant correlation at $P \leq 0.05$								
	HIM	TYM	TRM	PHM	SER	PUT	CAD	SPM	AGM
pH		Mozzarella Provelone (−)	Tilsit		Minas	Minas			
Acidity	Gouda Grated Mozzarella	Gouda Grated Gorgonzola Mozzarella	Tilsit (−)	Grated	Grated	Gouda	Gouda	Gouda	Grated
Moisture				Gorgonzola		Gorgonzola		Gorgonzola	Tilsit (−)
Fat	Minas (−)	Tilsit			Parmesan				Parmesan

The fact that the amines were not detected in every sample and the high variability on amine levels among samples of the same type of cheese suggest that the presence of amine in cheeses can be prevented. Therefore, the sources and critical control points for amine formation during cheese manufacture should be determined in order to limit amine formation and accumulation in cheese. Moreover, susceptible individuals should be advised to consume cheeses with low biogenic amines contents.

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