

Critical Review

Tyramine in foods and monoamine oxidase inhibitor drugs: A crossroad where medicine, nutrition, pharmacy, and food industry converge

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Abstract

Since identification of the “cheese reaction” hypertensive crisis induced by dietary tyramine with monoamine oxidase inhibitors (MAOIs) drugs, numerous articles have addressed the biogenic amine (BA) content of foods. The objective of this review is to explain why many published analyses are no longer valid. Clinically significant BA levels from literature published between 1945 and 2003 were reviewed and compiled and are presented in common units. Clinical recommendations based on newer reports about foods and drugs are offered. Reliance on case reports without chemical analyses led to unnecessary dietary restrictions. Extrapolation of analysis from one food to a similar food led to lengthy lists of banned foods. Early analyses are no longer valid for several reasons: better methods to accurately identify these amines, better packaging methods, recognition of critical processing points in prevention of BA formation, better storage and handling procedures, and substitution of cultures less likely to form amines have reduced the risks of these Food–drug interactions. New generations of MAOIs and different administration routes allow smaller effective dosage and lower risks for interactions. This review of BAs illustrates variability of food components over time, progress of food industry toward a safer food supply, development of better drugs, and the necessity for medicine, nutrition, pharmacy, and food industry to work together. Published by Elsevier Inc.

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1. Introduction

Since the identification of the “cheese reaction” hypertensive crisis induced by dietary tyramine among individuals on monoamine oxidase inhibitor (MAOI) drugs (Davies, 1963; Asatoor et al., 1963; Blackwell, 1963), several hundred articles have addressed the biogenic amine (BA) content of foods. Compilation of values for BAs such as tyramine in foods differs from the usual compilation of food values in several ways. Most food composition analysis start with the initial analysis of a given food component and then consider loss over time. BAs, however, are not normally present in measurable amounts in fresh, wholesome foods but result from the degradation of amino acids present in aging or deteriorating foods. Thus, the measurement of BAs in foods increases in the

presence of poor hygiene, temperature abuse, or storage time abuse. Attention has been paid to developing more sensitive and specific detection methods for BAs, especially tyramine, as biosensors of freshness and of quality control (Nadon et al., 2001; Yano et al., 1995).

Analysis for the presence of these amines is seldom done for database purposes or even for clinical purposes. Most published data are in methodological papers aimed at assessing changes in the manufacturing processes for quality control purpose or for use of different microbial organism strains in production of foods such as cheese or fermented foods and are reported in different units (Komprda et al., 2001; Ordonez et al., 1997; Spicka et al., 2002; Baker et al., 1987; Moret and Conte, 1996). In these analyses, usually only one or two samples are purchased in local markets and, thus, are based on a convenience sample rather than representative samples (McCabe et al., 2003). The samples are sometimes deliberately subjected to both temperature and storage time abuse in order to assess the potential for BA formation.

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Attention has been paid to developing more sensitive and more specific detection methods with interest in BAs as biosensors of freshness and of quality control (Nadon et al., 2001; Yano et al., 1995; Shalaby, 1994). The handling of food in harvesting and in processing has been studied as a means of improving food quality and reducing the potential action of micro-organisms (Sivertsvik et al., 2002; Blixt and Borch, 2002; Silva and Gloria, 2002). The recognition of hazard analysis and critical control points (HACCP) in the prevention of BA formation during food harvesting, processing, storage, and preparation means that earlier values would not necessarily represent current values. Greater use of the “Best use by” or “Sell by” dates aid in identifying freshness of many prepared products. Improved manufacturing practices have led to better hygiene and to substitution of cultures less likely to produce decarboxylation (Silva and Gloria, 2002; Ayhan et al., 1999; Spicka et al., 2002). This paper reviews the literature, suggests why many published analyses may no longer be valid, and addresses the importance of BA tables for providing dietary advice for MAOI drugs or food-induced migraines.

2. Biogenic amines

BAs are organic bases usually produced by decarboxylation of amino acids (Shalaby, 1996). These amines are categorized primarily as either vasoactive or psychoactive. The action of vasoactive amines, largely tyramine, is the underlying cause of the hypertensive crisis that may occur in individuals on MAOI drugs. The physiological effects of tyramine include: peripheral vasoconstriction, increased cardiac output, increased respiration, elevated blood glucose, and release of norepinephrine (Shalaby, 1996). While the vasoactive amines are normally present in small amounts, the healthy gut readily detoxifies these through the action of monoamine oxidase. Two primary isoforms of monoamine oxidase selectively deaminate neurotransmitters, and one isoform will predominate in various body tissues. MAO-A deaminates serotonin in the central nervous system and dietary monoamines in the gastrointestinal system. MAO-B is found predominantly in liver and muscle and deaminates dopamine and phenylethylamine. Physiologic active amines of may also be deaminated by diamine oxidase (DAO) in the gut that provide protection from small amounts normally presented by foods. Conditions that lead to increased tyramine forma-

tion may also lead to increased level of other BAs (Mafra et al., 1999; Kaniou et al., 2001; Ansorena et al., 2002) and result in increased toxicity (Stratton et al., 1991).

3. MAOI drugs

MAOI drugs are used to inhibit the actions of monoamine oxidase, especially in the central nervous system, to serve as an antidepressant or as an anti-Parkinsonian agent (Facts and Comparisons, 2000; McCabe, 2004). These agents are considered as more effective than other types of antidepressants in some subgroups, e.g., people with anxiety depressions (Liebowitz et al., 1984; Robinson et al., 1985) and in older adults (Volz and Gleiter, 1998) that fail to respond to other antidepressants.

The first generation of MAOI drugs listed in Table 1 are nonspecific, inhibit both isoforms of MAO and the inhibition is considered irreversible. The second generations termed RIMA for reversible inhibitor monoamine, are selective in inhibition, reversible, and carry little risk of a hypertensive effect in low dosage as in the treatment of Parkinson Disease (Muller et al., 1988; Gieschke et al., 1988; Da Prada et al., 1988). To be effective in depression treatment, however, the higher dosage required begins to inhibit all isoforms and the potential for a hypertensive crisis increases. More recently, a transdermal patch form is being tested that appears to deliver an effective antidepressant level without the inhibition of the gut MAOs (Bodkin and Amsterdam, 2002). The first clinical trials using a tyramine-restricted diet are now being repeated without the dietary restrictions. Preliminary calculations using published dietary tyramine values suggest that risks may be quite low in the average American diet (McCabe and Gurley, 2003) (Table 2).

4. Challenges in use of tyramine analysis in dietary advice

Dietary advice on low tyramine diets have been based on case reports of hypertensive crisis with or without supporting analytic data (McCabe et al., 2003; McCabe, 1986). Additionally, case reports on consumption of the yeast extract “Marmite”[®], an actual byproduct of the brewing process, were erroneously used to ban brewer’s yeast supplements and food products made with baker’s yeast (McCabe and Tsuang, 1982). Actual analysis supported the presence of significant amounts of tyramine

Table 1
Monoamine oxidase inhibitor drugs currently on the United States market

Therapeutic classification	Generic name	Brand name	Type of inhibitor	Manufacturer
Antidepressants	Isocarboxazid	Marplan [®]	Nonselective irreversible	Oxford
	Phenelzine sulfate	Nardil [®]	Nonselective irreversible	Parke-Davis
	Tranylcypromine sulfate	Parnate [®]	Nonselective irreversible	GlaxoSmith & Kline
Anti-Parkinsonism	Selegiline	Eldepry [®]	Selective reversible	Somerset

Table 2

Products of decarboxylation conversion of free amino acids to vasoactive or psychoactive amines

Free amino acid	Primary action	Amine produced by decarboxylation
Histidine	Psychoactive amine	Histamine
Arginine		Putrescine
Lysine		Cadaverine
Ornithine		Putrescine
Phenylalanine	Vasoactive amine	Phenylethylamine, tyramine
Tyrosine		Tyramine
Tryptophan		Tryptamine

in the reclaimed yeast extract used as a spread or tea but not in brewer's yeast supplements (Shulman et al., 1989).

The portion of a food analyzed also is a challenge. A case report of an East Indian living in London who suffered a hypertensive crisis after consuming a whole stewed plantain (with the peel) was misinterpreted to exclude all banana products without recognizing that the actual analysis showing that BA content in the peel greatly exceeds that of the banana pulp (McCabe and Tsuang, 1982; Lovenberg, 1973; Walker et al., 1996). The sampling site of a food is another potential source of error. Aged cheeses are by far the most frequently reported food and most serious of the case reports. Tyramine produced in cheese aged in 50-lb wheels will vary with the outer rind samples having greater tyramine values than the center samples (Moret and Conte, 1996).

Most reports of tyramine analysis in foods are based on only one or two food samples. When multiple samples are used, there is frequently repeated sampling of the same food following storage and temperature abuse. A fresh sample will show little or no detectable amounts, but the same food sampled after abuse treatment develops detectable levels (Yen, 1992).

Early analysis of BAs in foods may have failed to distinguish among the various amines and may not represent tyramine content of today's foods (Walker et al., 1996; Da Prada et al., 1988). Until recently, the detection of and reliable quantification of amines in wine has been challenged by matrix interference caused by free amino acids and the low levels at which the amines are found (Mafra et al., 1999). Careful attention to appropriate procedures has allowed better detection of BA (Mafra et al., 1999; Alur et al., 1995).

5. Current assessment of biogenic potential by food group

Table 3 summarizes the percentage of published values of foods by categories that have been found to contain clinically significant levels of tyramine was compiled recently (McCabe et al., 2003). A definition of a clinically significant level relates to the severity of the blood pressure rise. The presence of 6 mg in one or two usual servings is thought to be sufficient to cause a mild adverse event while

Table 3

Percentage of foods analyzed for tyramine that had clinically significant (>6 mg) quantities in two servings

Food category	Total number of published values	Number with clinical significant levels	
		No.	%
Cheese	71	18	25
Asian dishes (fermented)	37	12	30
Vegetables/mushrooms ^a	28	9	32
Marmite [®] yeast extract	1	1	100
Meat/meat products	74	20	27
Sauces (fish, shrimp, soya)	21	5	24
Tap beers	34	4	12

^aFifteen samples of straw mushrooms were deliberately aged with storage extended to 9 days.

Table 4

Foods without clinically significant content (<6 mg) per serving of food published since 1981^a

Food group	Total number of reported samples	Range of mcg of tyramine
Bottled/canned beer	43	(ND–1292 mcg)
Dealcoholized beer	7	(3–511 mcg)
Distilled spirits	5	(ND–320 mcg)
Wine	28	
Red = 12		(ND–512 mcg)
Whites = 4		(ND–511 mcg)
Ports = 3		(ND–91 mcg)
Major chain store pizza	6	(0.0–653 mcg)
Fish/seafood	42	(ND–2450 mcg)
Fruit	11	(ND–2580 mcg)
Pate	3	(60–90 mcg)
Brewer's yeast	4	(ND–191 mcg)
Chocolate dishes	6	(6–98 mcg)
Yogurt	1	(ND)

^aLevels without clinical significance <6000 mcg or 6 mg in two typical servings.

10–25 mg will produce a severe adverse event in those using MAOI drugs (Horwitz et al., 1964; Stewart, 1977; Hedberg et al., 1966; Da Prada et al., 1988; Bieck and Antonin, 1988). For unmedicated adults, 200–800 mg of dietary tyramine is needed to induce a mild (30 mm Hg) rise in blood pressure (Bieck and Antonin, 1988). Only histamine has legal limits established for foods but 200–800 mg has been proposed as a limit level for tyramine in foods (Da Prada et al., 1988).

Table 4 presents foods exhibiting clinically insignificant levels of tyramine in a typical one or two serving size. The following section describes the studies from which values are drawn and the implications of the findings.

5.1. Cheese and other dairy products

The food industry has striven to develop new processes using different microbial strains to reduce the development of tyramine in cured or aged products such as cheese (Stratton et al., 1991; ten Brink et al., 1990). Numerous investigators have studied the formation of BAs by different micro-organisms during the ripening of many types of cheeses including Semicotto Caprino, feta, cheddar, and processed types (Joosten et al., 1995; Galgano et al., 2001; Leuschner and Hammes, 1998). Durlu-Ozkaya (2002) reported the BA content of Turkish cheeses. Cheeses made from pasteurized and pressurized milks are less likely to contain BAs (Novella-Rodriguez et al., 2002). Analyses of most fresh American and Canadian cheeses made from pasteurized milk have found little BA content unless aged or stored under adverse conditions (Shulman et al., 1989).

Aged foods, especially aged cheeses such as English Stilton, Cheshire, and Danish bleu, typically contain moderate to high BA level (McCabe et al., 2003; Shulman et al., 1989). Fresh types of cheese (e.g., cottage, ricotta) and soft processed cheeses (e.g., American cheese, cheese spreads) usually have little or no detectable levels of tyramine (Shulman et al., 1989; Mosnaim et al., 1996). The original quality of the milk and the length of “ripening” or storage appear to be dominant factors in the production of BAs in cheeses (Novella-Rodriguez et al., 2002).

Other milk products such as yogurt and kefir have little or no detectable levels of tyramine if made from pasteurized milk. A recent report compared the amino acids profiles of milk, yogurt, and kefir and found few differences (Guzel-Seydim et al., 2003) suggesting comparable risks of BA formation.

5.2. Meat and meat products

Starting with high quality fresh meat and using good manufacturing practices greatly reduces the risk of BA formation in processed meat products (Hernandez-Jover et al., 1996). Analysis for BAs is being proposed as a quality index for fresh meat (Vinci and Antonelli, 2002) and for the food and beverage industry in general (Mello and Kubota, 2002). Most case reports of tyramine in fresh meat have been from meats stored at or beyond the end of the recommended storage time (Boulton et al., 1970; Hedberg et al., 1966). Any protein-containing food not properly cleaned, stored, and prepared has the potential for tyramine formation from tyrosine and phenylalanine. Fresh ground beef and ground pork carries increased spoilage risks due to increased surface area, combining several cuts of meats, and potentially hides outdated or poor-quality meat (Mosnaim et al., 1996).

Newer forms of sealing and packaging of fresh meat products has lead to a longer-shelf life, but some BA formation can still occur (Krizek et al., 1995; Edwards et al., 1987; Vidal-Carou et al., 1990). While recommended storage time of fresh poultry is less than that for red meat,

several papers suggest that chicken meat products may undergo less change when properly processed and stored than red meat products (Vinci and Antonelli, 2002; Silva and Gloria, 2002; Geonaras et al., 1995; Nasser and Emam, 2002). Red (bovine) meat was found to be low in BA content until nine storage days after which levels rose sharply and continued to rise, but BA levels in chicken rose sharply by four storage days, the earlier rise being attributed to the shorter fibers in white (chicken) meat (Vinci and Antonelli, 2002). Methods to delay fish spoilage have been widely studied leading to increased use of freeze-stored fish, especially in fish harvested seasonally (Ben-Gurley et al., 1998; Crapo and Himelbloom, 1999; Sivertsvik et al., 2002; Veciana-Nogues et al., 1990; Serrar et al., 1995; Ashie et al., 1996). Histamine, rather than tyramine, has been the BA most closely associated with fish spoilage, but both can be found. (Baranowski et al., 1990; Kerr and Parke, 1998).

5.3. Fermented foods

Fermentation of foods leads to the formation of BAs during the aging or ripening process. Interestingly, no tyramine reactions have been published for fermented meat products such as dry summer sausages, but analyses from several countries have consistently shown the presence of tyramine (Shulman et al., 1989; Walker et al., 1996; ten Brink et al., 1990; Hernandez-Jover et al., 1996; Eerola et al., 1998). While sodium sulphite has been added to meat products as a preservative, its addition to sausages prior to ripening actually increased tyramine accumulation (Bover-Cid et al., 2001).

Fermented vegetables such as sauerkraut, Japanese pickled vegetables (urume-zuke) and Korean fermented cabbage (kim chee) do not consistently exhibit high levels of BAs (Ansorena et al., 2002; Trevino et al., 1996, 1997; Ayhan et al., 1999; Parente et al., 2001; Komprda et al., 2001; Walker et al., 1996; Shulman et al., 1989; Kalac et al., 1999). The inconsistency may be due to storage length as tyramine values rise with longer sauerkraut storage (Kalac et al., 2000) or to different microbial starters or conditions (Spicka et al., 2002).

5.4. Vegetables

Vegetables processed in brine from high-quality raw materials do not develop high levels of BAs unless contaminated or abused by temperature and storage time (Hornero-Mendez and Garrido-Fernandez, 1997). Studies of table olives have not found BAs (Garcia-Garcia et al., 2000; Cobo and Silva, 2000). Frozen spinach puree, ketchup, concentrated tomato paste, and frozen green peas have shown little or no BAs (Kalac et al., 2002). Chilled ready-to-eat meals containing minimally processed fresh vegetables contain little BA (Edgar and Aidoo, 2001). BA content of prepackaged salad mixtures and leafy greens

stored in excess of 5 days will increase 3–8-fold (Simon-Sarkadi et al., 1994).

Newer foods and dishes from Asian and Pacific origin represent another potentially high source of BAs and have been analyzed (Mower et al., 1989). Soy products such as tofu and soya sauce are fermented, and some contain significant BA levels. (Nout et al., 1993; Nout, 1994; Da Prada and Zurcher, 1992; Shulman et al., 1989; Walker et al., 1996; Shalaby, 2000). Recently, only one out of 23 soy sauces studied contained clinically significant levels of tyramine (Stute et al., 2002). Fish and shrimp sauces are potentially high sources of tyramine (Da Prada and Zurcher, 1992; Mower et al., 1989; Stute et al., 2002). A case report of a crisis involving use of long stored miso soup (Mexmer, 1987) directed attention to possible BA contamination of other Asian dishes.

5.5. Fruits

As a group, fruit is usually very low in BAs unless severe abuse has occurred or unless usually large amounts of a spoiled fruit are consumed. One case report of a hypertensive crisis arose from the consumption of a quart of guacamole salad being eaten at one setting by a patient on a MAOI regimen (Generali et al., 1981). A gift of very ripe avocados led to overconsumption of this homemade dish. The common restrictions of raisins, for example, have no supporting analysis and fresh grapes have nondetectable levels (Lovenberg, 1973).

5.6. Alcoholic beverages

5.6.1. Wine

Alcoholic beverages, particularly wine, have been counterindicated in MAOI regimens based on an early case report involving Chianti wine. Samples of wine analyzed in the United States and Canada show levels so low that consuming two servings would result in insignificant BA intake (Vidal-Carou et al., 1990; Gloria et al., 1998; Shulman et al., 1989; Ouch, 1971). No consistent differences have been found between red and white wines (Shulman, 1989). Spanish and Portuguese wines do not contain high levels of BAs when consumed in modest quantities (Vazquez-Lasa et al., 1998; Soufleros et al., 1998; Mafra et al., 1999).

5.6.2. Beer

Beers from around the world have been analyzed for BAs. American and Canadian bottled and canned beers (Shulman et al., 1989; Taylor et al., 1994) appear to contain small amounts of tyramine, but European and African beers (Taylor et al., 1994; Da Prada, 1992; Lasekan and Lasekan, 2000; Gloria and Izquierdo-Pulido, 1999; Izquierdo-Pulido et al., 2000; Fernandes et al., 2001; Kalac et al., 2003) have varied greatly. In general, ales may contain BAs in clinically significant levels as may tap beers (Taylor et al., 1994).

6. Conclusions

With nearly 300 foods and slightly over 100 alcoholic beverages samples analyzed and reported in the literature since 1981, sufficient BA data exist to offer insight into the types of dietary recommendations to be made to patients about to embark on an MAOI regimen. Any food with free amino acids, especially tyrosine and phenylalanine, are subject to BA formation if poor sanitation and low quality foods are used or if the food is subjected to temperature abuse or extended storage time. Most foods can be safely consumed if bought fresh, cooked fresh, and consumed fresh in modest quantities (1–2 servings of commonly used portions). Portion size is critical for assessing clinical significance of BA presence. A few foods such as aged cheeses should be absolutely banned for patients using MAOIs as the clinically significant tyramine level is present in one ounce or less. Overly strenuous restrictions may arise from failure to recognize how to extrapolate data to other foods, lack of knowledge of other cultures and cuisine, or failure to adjust recommendations for differing forms or newer generations of MAOIs. Simply banning a food based on a single case report without supporting analysis or consideration of the amount of the food or beverage consumed has led to unnecessary restrictions (McCabe and Tsuang, 1982; McCabe, 1986; Sullivan and Shulman, 1984; Sweet et al., 1995).

MAOI drugs are becoming safer for patients to use because of the interdisciplinary work of food scientists, pharmacologists, dietitians, physicians, nurses, and pharmacists. Each profession brings skills and knowledge to the science and its translation of food–drug interactions into patient care. Many BA values are published in specialized and international journals that may be difficult for busy health professionals to access. The compilation of tables of BAs and critical reviews of published case reports and food analyses are means by which the research of academia, food industry, and pharmaceutical industry can improve clinical decisions of practicing health-care professionals.

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