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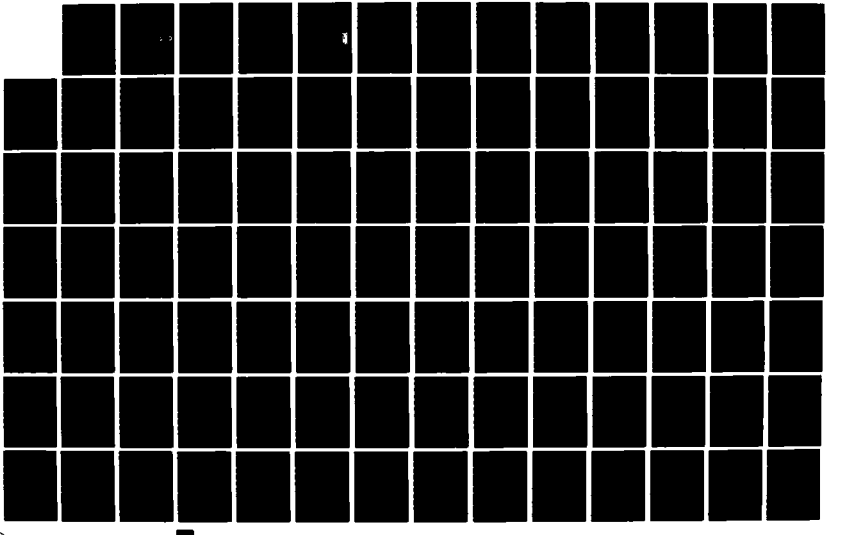

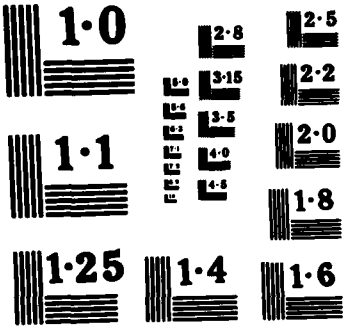

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HISTAMINE AND TYRAMINE IN FOOD

A Monograph

Presented to the Faculty of the Graduate School

of Cornell University

in Partial Fulfillment of the

Requirements for the Degree of

Masters of Professional Studies

by

Terry L. Baucom

May 1985

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ABSTRACT

Histamine and tyramine are normal constituents of many foods and have been found in cheese; sauerkraut; wine; fish; and putrid, aged or fermented meats. These low molecular weight organic bases do not represent any hazard to individuals unless large quantities are ingested or natural mechanisms for their catabolism are inhibited or genetically deficient. Tyramine and histamine which can arise from enzymatic decarboxylation of their corresponding amino acids are strongly vasoactive. Histamine, a capillary dilator, produces hypotensive effects while tyramine causes a rise in blood pressure. Tyramine has also been implicated in the onset of migraine headache. The physiological effects, the occurrence, mechanism of formation and catabolism, methods of detection and quantitation, and health and legal implications to food processors and restaurateurs are reviewed. Additionally, recommendations for reducing histamine and tyramine contents in food as well as reducing the health hazards and legal implications to restaurateurs and food processors are made.

ACKNOWLEDGMENTS

A sincere thanks to the United States Air Force for providing me with the opportunity to attend this educational program and to Professors Mary Tabacchi and John E. H. Sherry for their guidance and support in helping me complete this monograph.

BIOGRAPHICAL SKETCH

Terry Lamont Baucom was born on January 19, 1950 in Portsmouth Virginia. He graduated from Frank W. Cox High School, Virginia Beach, Virginia in 1968. In June 1972 he received a Bachelor of Science Degree in Biochemistry from the University of Georgia. In June 1983 he received a Master of Science Degree in Management from Troy State University, Troy, Alabama.

In June 1972 he was commissioned as a Second Lieutenant in the United States Air Force and entered active duty on September, 1974. Presently he is a Major and has been selected to become the Commander of the 3750th Services Squadron, Sheppard Air Force Base, Texas. His initial Air Force assignment was as a food-service officer and services operations officer at Homestead Air Force Base, Florida. This was followed by tours at Thule Air Base, Greenland; Brooks Aerospace Medical Division San Antonio, Texas; and Royal Air Force Base Alconbury, United Kingdom as Chief of Services. Finally he was selected by the Air Force Institute of Technology to attend the School of Hotel Administration, at Cornell University to obtain a Master of Professional Studies Degree.

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OVERVIEW

Biologically active amines, such as histamine and tyramine are normal constituents of many foods and have been found in cheese; sauerkraut; wine; fish; and putrid, aged, or fermented meats. These low molecular weight organic bases do not represent any hazard to individuals unless large quantities are ingested or natural mechanisms for their catabolism are inhibited or genetically deficient. Tyramine and histamine, which can arise from enzymatic decarboxylation of their corresponding amino acids, are strongly vasoactive. Histamine a capillary dilator produces hypotensive effects while tyramine causes a rise in blood pressure.

Although foods normally contain small amounts of tyramine and histamine, formation of large amounts of these amines has been reported only in aged, fermented products or products such as tuna fish that have undergone spoilage. Three factors govern the formation of amines. These include (1) the availability of free amino acids, (2) the presence of microorganisms that can decarboxylate the amino acids, and (3) favorable conditions for the growth of the microorganism

and for production of decarboxylase enzymes. From the hygienic point of view the presence of any one of these factors is extremely unfavorable and efforts need to be made to control them.

Under normal circumstances in man tyramine and histamine absorbed from food are rapidly detoxified by amine oxidase or by conjugation. Histamine is oxidatively deaminated by diamine oxidase (DAO) while tyramine is oxidized by a different enzyme known as monoamine oxidase (MAO).

As stated above, under most circumstances histamine and tyramine are oxidized by their specific enzymes to form harmless products. However, patients undergoing treatment for tuberculosis, asthma or depression are normally treated with monoamine oxidase inhibitory (MAOI) drugs. These drugs block the pathway for catabolism and inactivation of tyramine after ingestion and result in such symptoms as high blood pressure, headache, fever, forceful heatbeat and sometimes perspiration and vomiting. Under extreme conditions hemorrhage and heart failure can result. Symptoms of histamine reaction are facial flushing, nausea, vomiting, intense headache, swelling of the lips, burning sensations in the throat and thirst.

Many cases involving hypertensive crises in patients taking monoamine oxidase inhibitors were reported in the early 1960's and in at least one of these incidents the patient died as a result of the hypertension. The principle foods that have been implicated in these hypertensive attacks include cheese, yeast, pickled herring, beef and chicken liver.

A number of methods have been developed to detect and quantify histamine and tyramine in foods. These include both bioassays and chemical methods. Today chemical methods tend to be more widely used than the bioassay methods. This is primarily due to the fact that in dealing with live subjects provisions must be made for their care and the fact that their response is subject to individual variability. Additionally, chemical methods lend themselves to automation which decreases the amount of physical labor and time it takes to achieve results. Some of these methods that lend themselves to automation are fluorometric methods, ion exchange chromatographic methods using amino acid analyzers and high pressure liquid chromatography.

A survey of the literature available on histamine and tyramine in foods has produced evidence that certain foods

contain high levels of these amines. Of particular concern are ripened cheeses (Cheddar, Emmenthaler, Gruyere, Stilton, Brie and Camembert); yeast extracts, such as Bovril and Marmite; certain alcoholic beverages (mainly red wines); fermented sausages (fermented bolognas and salamis, pepperoni, and summer sausage); and fish that have been improperly refrigerated or allowed to ferment at room temperature. Because of their high amine content these foods should be avoided by patients being treated with monoamine oxidase inhibitory drugs.

Probably many more cases of histamine and tyramine poisoning have occurred than have been reported. This is probably due to the fact that the symptoms of histamine and tyramine poisoning are similar to those of other types of food poisoning. Because of this similarity of symptoms to other types of food poisoning less information has been provided to restaurateurs and food processors on what histamine and tyramine are, what symptoms they produce and how they can be prevented.

In addition to health implications there are also legal implications with regard to the histamine and tyramine contents of food. These legal implications arise out of the

restaurateur's and food processor's responsibilities to their customers. They revolve around three legal theories which form the background of liability law for the production and service of foods. These legal theories are the negligence theory, breach of warranty theory applied under the Uniform Commercial Code, and strict liability.

The negligence theory requires that the injured customer be able to prove that negligence on the part of the restaurateur or food processor resulted in the food being unfit and in turn resulted in the illness. Essentially the injured party has to show that the restaurateur or food processor did not exercise reasonable care in the storage, production or service of food.

The second theory is the breach of warranty as applied under the Uniform Commercial Code. Under breach of implied warranty the patron is not required to prove that the food service operator or food processor was negligent in the storage, preparation or service of the product but only that the product caused the illness and that the seller breached the contract by serving unfit food.

The final type of liability with which restaurateurs and food processors may be involved is strict liability. Strict

liability requires only that the patron prove that his or her illness was caused by ingestion of the food. Once this is proven, then the patron has legal grounds for recovery.

A final area of concern deals with the problem of serving foods not produced in this country. This problem centers around the fact that we know little about health and sanitation requirements in the countries from which we buy products. This is especially a problem for the restaurateur in this country since there is no way he/she can determine the quality of the food received. The restaurateur essentially has to rely on his/her purveyor to provide him or her with products which are free of defects. *If a restaurateur serves a patron food from a* another country which is high in histamine or tyramine and the patron becomes ill the restaurateur is open to a law suit. The restaurateur's only recourse is to bring suit against the purveyor who provided him or her with the food.

CHAPTER I

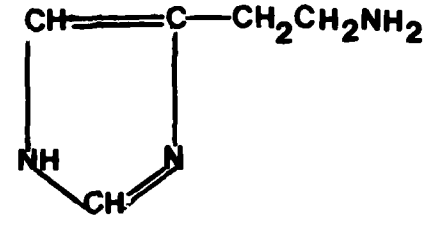
INTRODUCTION

Histamine and tyramine are biologically active amines which arise as a consequence of metabolic processes in animals, plants and micro-organisms. These amines are either pyschoactive or vasoactive. Pyschoactive amines act on the neural transmitters in the central nervous system, while vasoactive amines act, either directly or indirectly on the vascular system (1). Pressor amines are vasoactive amines that cause a rise in blood pressure. Barger and Walpole (2), in 1901, identified tyramine as the most active pressor amine in putrid meat. It is now known that tyramine causes a marked increase in blood pressure when injected intravenously into mammals (3). Histamine is also strongly vasoactive (1). Histamine, however, in contrast to tyramine is a strong capillary dilator and can produce hypotensive effects.

Tyramine and histamine fulfill important metabolic functions in man, especially in the nervous system and in the control of blood pressure. As mentioned earlier they occur widely in animals, plants, and bacteria and are frequently

found in high concentrations in food especially in that which has been subjected to deliberate or accidental bacterial contamination. Amino acid decarboxylation is the most common mode of synthesis of these amines, the structure of which is shown in Figure 1.

Under most circumstances in man tyramine and histamine absorbed from food are rapidly detoxified by amine oxidase or by conjugation. Histamine is oxidatively deaminated by diamine oxidase (DAO) while tyramine is oxidized by a different enzyme known as monoamine oxidase (MAO). Monoamine oxidase inhibitors (MAOI) are drugs that block the oxidative deamination of tyramine and certain other primary amines. These drugs have been primarily used for treatment of depression in psychiatric patients. Hypertensive attacks during treatment with monoamine oxidase inhibitors were first described by Ogilvie in 1955 (4). Six years later similar attacks were observed in five out of 212 patients treated for depression with nialamide (5), but it was not until the introduction of tranylcypromine that reports again appeared (6). Blackwell (7) first observed an association between hypertensive crises of patients on monoamine oxidase inhibitors and possible dietary precipitants



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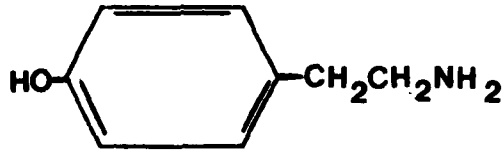

TYRAMINE

FIGURE 1.
STRUCTURE OF HISTAMINE AND TYRAMINE

(cheese). Asatoor et al (8) implicated tyramine in cheese as the primary causative agent. Many cases involving hypertensive crisis of patients taking monoamine oxidase inhibitors were reported in the literature during the early 1960's (9, 10, 11, 12) and in at least one of these incidents the patient died as a result of the hypertension (9). The principle foods implicated in these first attacks included cheese and yeast extract. Since then other foods have also been shown to cause similar hypertensive attacks. Pickled herring (13), beef (14), and chicken liver (15) have been shown to induce similar hypertensive crises attributable to tyramine. In addition to the reports of hypertensive crises in the literature there are reports connecting tyramine to migraine headaches (3). This area is currently being investigated.

Since Asatoor et al (8) associated tyramine in cheese as a primary causative agent in pressor attacks in monoamine oxidase patients, considerable research has been completed dealing with the appearance of biologically active amines in foods (3, 16, 17, 18, 19,). Especially comprehensive surveys of amines in food are given by Askar (20, 21), Maga (22) and Smith (23). The objective of this review is to present information on the

physiological effects of tyramine and histamine, to discuss the ways tyramine and histamine are formed and destroyed in foods, as well as the ways in which they are detected and quantified, to summarize the quantitative data that are available in the literature and to discuss the implications of tyramine and histamine to the food industry.

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CHAPTER II

FORMATION OF TYRAMINE AND HISTAMINE IN FOOD

Foods normally contain only small amounts of tyramine and histamine. However, large amounts of these amines have been found in aged, fermented products or products such as tuna fish that has undergone spoilage. Three factors normally govern formation of amines. These include: (1) availability of free amino acids; (2) presence of microorganisms that can decarboxylate the amino acids; and (3) favorable conditions for the growth of the microorganims and for production of decarboxylase enzymes. It is well known that during the ripening of cheese, amino acids are liberated. Dierick et al (1) observed a general increase in free amino acids with little change in the concentration of free tyrosine during sausage ripening. However, he later reported that there was an increase in the presence of tyramine during sausage ripening, indicating that although free tyrosine is produced it is decarboxylated to form tyramine. Microorganisms commonly found in sausage fermentations include Pediococcus, Lactobacillus, Streptococcus and Micrococcus (2).

Rodwell (3) investigated 34 strains of Lactobacillus for their ability to decarboxylate amino acids. He found that most of them showed no activity toward any amino acid with only Lactobacillus pentoacetius Rudensis showing slight tyrosine decarboxylase activity. Four of the 34 Lactobacillus strains had histidine decarboxylase activity. Lagerboard and Clapper (4) tested 33 strains of Lactobacillus and found that only three strains could produce CO_2 from tyrosine. One of the strains could produce CO_2 from histidine. Gale (5) studied production of tyramine by Streptococcus faecalis and found that six out of seven strains produced tyrosine decarboxylase. The optimal pH of the tyrosine decarboxylase in washed suspensions of the cells was reported to be pH 5.0. Additionally cultures grown at 27°C were found to have the same activity as cultures grown at 37°C. Other bacteria known to produce tyrosine decarboxylase include Betabacterium spp., Clostridium aerofoetidum, Clostridium sporogenes, Escherichia coli, Proteus mirabilis, and Pseudomonas reptilivora.

Yeast extracts have also been reported to contain large amounts of histamine and tyramine. This product is made by plasmolysis of brewer's yeast followed by autolysis in saline

solution at 36°C for 24 hours (pH 6.3-6-6) (6). These conditions are carefully controlled to permit maximum enzyme activity, and most of the protein is reduced to soluble form within 24 hours. It is possible that tyramine and histamine are formed by the yeast enzymes or by contaminating bacteria present in this ideal medium.

In the production of Cheddar cheese, the only microorganisms present known to have tyrosine decarboxylase activity are the coliforms and Streptococcus group D (S. faecalis, S. faecium, and S. durans) (7). Raw milk is often pasturized before acidification for fermentation. This step should kill the coliforms. However, it is possible that tyrosine or histidine decarboxylase may remain active following the heat treatment. It is also possible that further contamination may result from faulty sanitation.

Tyramine and histamine are also formed during the fermentation of cabbage in the production of sauerkraut (8, 9). Mayer et al (8) reported that sauerkraut with a low histamine and tyramine content could be produced by inhibiting growth of pediococci cerevisiae by early interruption of the fermentation just below pH 4.0. This results in a low-acid sauerkraut which can be pasteurized to achieve stability.

Mayer et al (9) observed that the histamine content of sauerkraut increased simultaneously with the appearance of Pediococcus cerevisiae.

Mossel (10) compiled a list of microorganisms that can produce histamine from histidine. These microorganisms include Betabacterium spp., Clostridium perfrigens, Enterobacter aerogenes, E. coli, Proteus morganii, P. reptilivora, and Ristella, Salmonella and Shigella species. Mossel reported that all of these organisms except Ristella are of frequent and numerous occurrence in foods and thus could be important in the production of histamine. Ferencik (11) implicated Hafnia strains, P. morganii and hemolytic E. coli in the formation of histamine in toxic samples of tuna fish. In addition to P. morganii, Ienistea (12) has mentioned that Achromobacter histaminum and Escherichia freundii have been isolated from fish containing large amounts of histamine. Okuzumi et al (13) have isolated a new histamine - forming bacteria which may be important for the problem of food hygiene. The bacteria's importance lies in the fact that it produces histamine at temperatures lower than previously thought possible. This bacteria which they have named "N-group bacteria" is both

psychrophic and halophilic. It grows at temperatures of 5°C but not at 35°C. Additionally it grew well in a medium with one to three percent NaCl but did not grow in the absence of NaCl. The fact that it grows at such low temperatures and at high salt concentrations makes it a potential hazard to the fishing industry.

It is thought that histamine is one of the primary toxicants in scromboid poisoning. Scombroid poisoning gets its name from the fact that the fish most often implicated in cases of poisoning, tuna and skipjack, belong to the suborder Scombroidei. These fish have a higher concentration of histidine than that found in the musculature of slaughtered animals and other fish (11). This may be an important factor in the formation of higher levels of histamine in the flesh. Since histidine decarboxylase is an inducible enzyme, the higher levels of free histidine will favor its induction. Also, increased levels of histidine favor the formation of histamine (11, 14). It appears that the limiting factor in the formation of histamine in fish muscle is the release of histidine from muscle proteins. Ferencik (11) stated that autolytic proteases are much more important in this respect

than the proteolytic enzymes of the contaminant bacteria. Autolytic proteases are enzymes which are activated upon the death of an organism. These autolytic enzymes break down proteins after the fish or any other animal is killed, thereby releasing free amino acids. Proteolytic enzymes, on the other hand, are found outside the organism generally in contaminating bacteria.

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CHAPTER III

DESTRUCTION OF TYRAMINE AND HISTAMINE IN FOODS AND IN MAN

The bacterial destruction of tyramine or histamine affects the amount of these amines in food (1). In comparison to data available on the formation of histamine and tyramine little information is available on the breakdown of these amines by bacteria. In man, tyramine may be catabolized by one of several different catabolic reactions (Figure 2). The oxidation of tyramine to para hydroxyphenylacetic acid by monoamine oxidase, is probably one of the more important catabolic pathways. In addition to tyramine, histamine also undergoes several different catabolic reactions of which deamination by diamine oxidase is the most significant pathway (Figure 3). Please note that any inhibition of MAO on DAO causes build-up of tyramine and histamine in the human or other biological organisms. Ienistea (1) has suggested that bacterial diamine oxidase could play an important role in foods containing high concentrations of histamine. He proposed that an equilibrium between histamine production and destruction

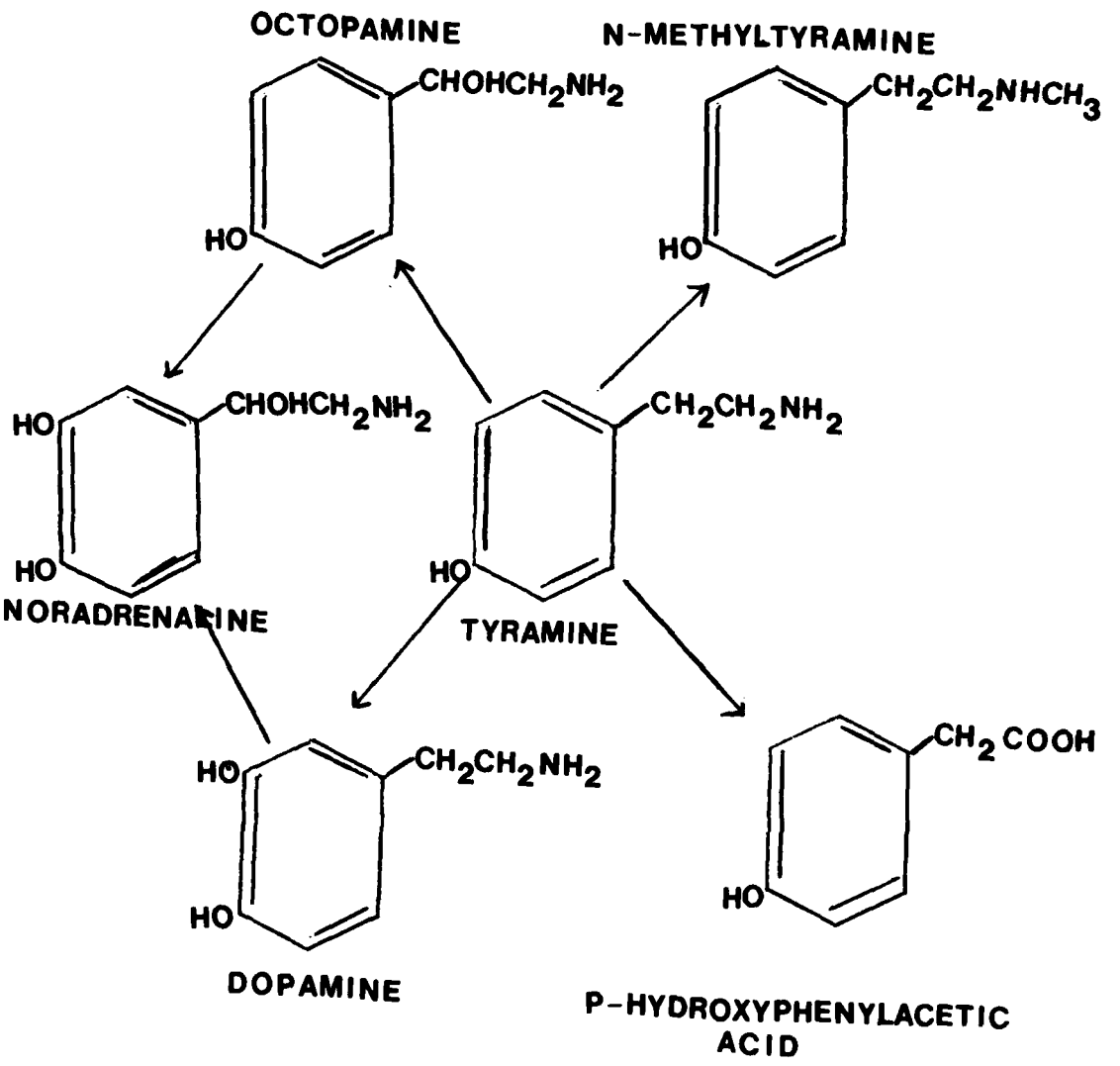

FIGURE 2.

TYRAMINE CATABOLIC ROUTES

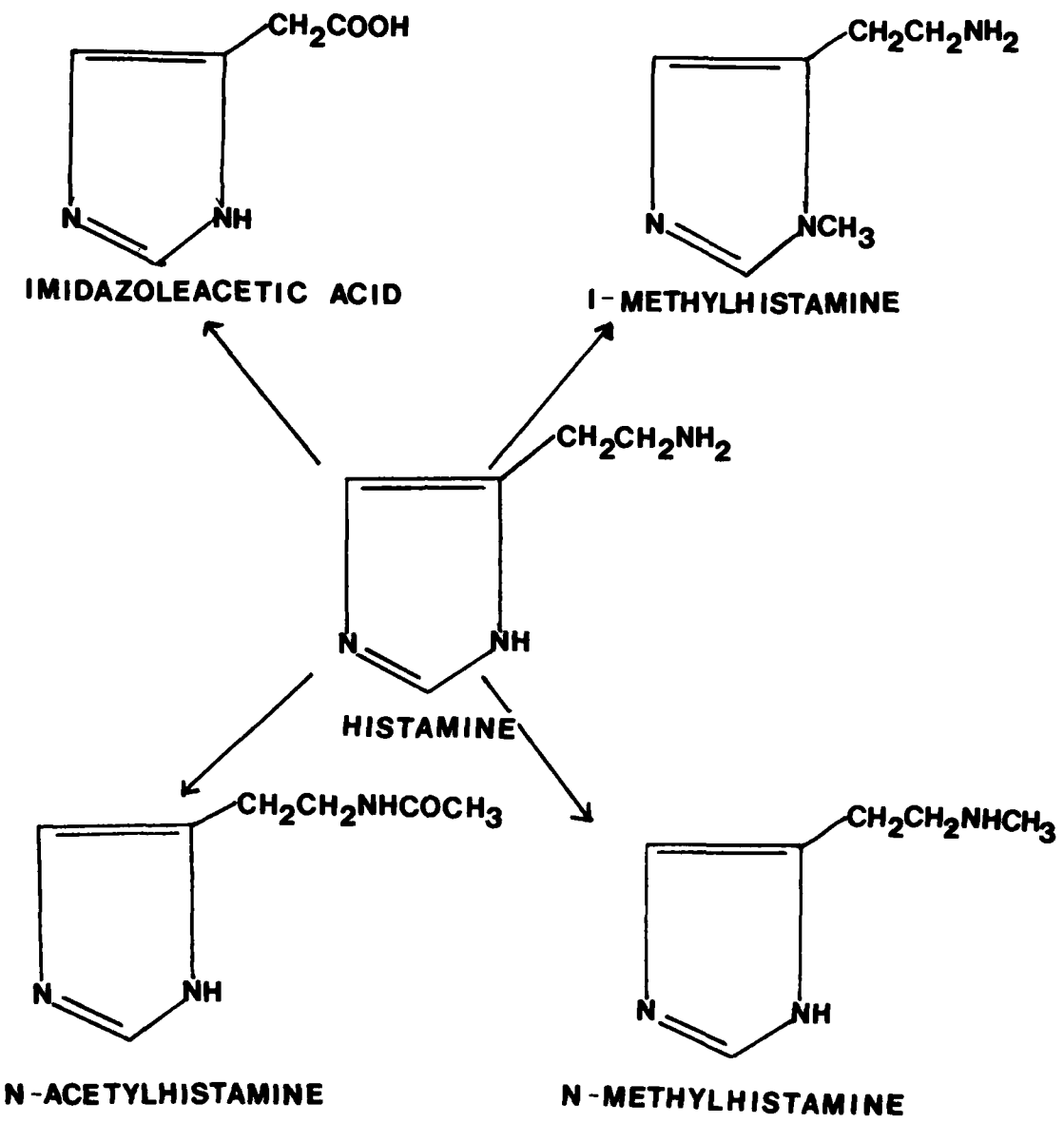

FIGURE 3. HISTAMINE CATABOLIC ROUTES

occurred in these foods. Many bacteria have been shown to possess either monoamine oxidase or diamine oxidase activity (2). Yamada et al (3) and Kumagai et al (4) have isolated, purified, and described the properties of a tyramine oxidase from Sarcina lutea. This enzyme oxidatively deaminates tyramine in the presence of oxygen and forms p-hydroxyphenyl-acetaldhyde, ammonia, and hydrogen peroxide. Large (5) has shown that both Aspergillus niger and Trichosporon sp. possess amine oxidases that oxidize a wide variety of primary amines.

Bacterial diamine oxidase activity has been detected in several types of bacteria including some species of Pseudomonas, Proteus, Escherichia, Vibrio, Clostridium, Serratia, and Klebsiella. It is possible that these bacteria when present in foods through contamination, or in the normal microflora, may carry out this reaction. Since several types of bacteria have the capability of degrading tyramine and histamine, this catabolism of amines by bacteria may play an important role in the final concentration of these amines in food.

END NOTES

(1) Ienistea, C. 1971. Bacterial Production and Destruction of Histamine in Food and Food Poisoning Caused by Histamine. die Nahrung. 109-113.

(2) Kapeller-Adler, R. 1970. Amine Oxidases and Methods for Their Study. Wiley-Interscience. New York. p. 139.

(3) Yamada, H., T. Uwajima, H. Kumagai, M. Watanabe, and K. Ogata. 1967. Bacterial Monoamine Oxidases. Part I. Purification and Crystallization of Tyramine Oxidase of Sarcina Lutea. Agric. Biol. Chem. 31:890-896.

(4) Kumagi, H., H. Matsui, K. Ogata, and H. Yamada. 1969. Properties of Crystalline Tyramine Oxidase from Sarcina Lutea. Biochim. Biophy. Acta. 171:1-8.

(5) Large, P. J. 1971. The Oxidative Cleavage of Alkyl-Nitrogen Bonds in Microorganisms. Xenobiotica 1:457-467.

CHAPTER IV

A SURVEY OF HISTAMINE AND TYRAMINE IN FOOD

Certain classes of amines, the catecholamines, indoleamines, and histamine fulfill important metabolic functions in man, especially in the nervous system and in the control of blood pressure. These amines occur widely in animals, plants and bacteria and they are frequently found in high concentrations in food especially that which has been subjected to deliberate or accidental bacterial contamination.

Tyramine, a catecholamine, causes a rise in blood pressure by constricting the vascular system and increasing the heart rate and force of contraction of the heart. By contrast histamine reduces the blood pressure by causing vasodilation.

Under normal circumstances in man, tyramine and histamine absorbed from food are rapidly detoxified by amine oxidases or conjugation. Histamine is oxidized by diamine oxidase while tyramine is oxidized by a different multiple enzyme system known as monoamine oxidase (MAO).

As stated above, under normal circumstances histamine and tyramine are oxidized by their specific enzymes. However, patients undergoing treatment for tuberculosis, asthma or depression are normally treated with monoamine oxidase inhibitory drugs. These drugs block the pathway for catabolism and inactivation of histamine and tyramine after their ingestion and result in the production of such symptoms as forceful heartbeat, severe headache, hypertension, flushing of the facial and neck area, and a feeling of heat and general discomfort. Not all these symptoms occur in every case.

Because of the increased use of monoamine oxidase inhibitory drugs in treating various illnesses the number of cases of histamine poisoning and hypertension attacks due to the ingestion of food containing tyramine have multiplied. It is therefore important that the food service industry be made aware of the potential problems regarding histamine and tyramine in foods. In an effort to do this a survey of various foodstuffs has been carried out and the results presented below.

A. Milk

The histamine and tyramine content in fresh milk is quite small. The average histamine and tyramine concentrations for

170 samples of dried milk products were respectively 1.31 and 0.42 ug/g (1). In yogurt the tyramine concentration was less than 0.2 ug/ml (2). Since the concentrations of tyramine and histamine in these products is so small it is extremely unlikely that these amines constitute a hazard to people.

B. Cheese

Tyramine and histamine are found in high concentrations in various cheeses, especially near the rind and in well matured cheeses like cheddar (Table 4-1). However, appearance is no guide to tyramine content and mild tasting cheese may contain a considerable amount of tyramine. According to Smith (3) tyramine is probably formed by aerobic bacteria and not by lactobacilli, added for cheese manufacture, which are anaerobes or facultative anaerobes.

The tyramine content of cheese is known to be variable ranging from almost nil to amounts approaching 3700 ug/g (2, 4, 5, 6). Histamine, while not found as frequently as tyramine, has been reported in cheddar (7, 8) in amounts up to 105 ug/g. Swiatek and Kisza (9) reported histamine amounts of 50-100 ug/g in samples of Trappisten, Tilsiter, and Roquefort cheese and a

TABLE 4-1
TYRAMINE AND HISTAMINE IN CHEESE
(ug/g)

CHEESE	HISTAMINE	TYRAMINE	REFERENCE
Cheddar			
Extra-Sharp	*ND-800	100-600	12
Sharp	ND-1300	ND-500	12
Medium	ND-900	ND-700	12
Mild	ND-1300	ND-500	12
Cheddar	-	136-1500	6
Cheddar			
Extra-Sharp	-	14-605	13
Sharp	-	57-1118	13
Medium	-	28-490	13
Mild	-	ND-187	13
Cheddar	-	130	14
Cheddar (mature)	-	775	15
Cheddar	37-265	350-1080	16
Roquefort	ND-2300	50-1100	12
Roquefort	-	656	15
Gouda	ND-450	80-670	12
Colby	ND-500	100-560	12
Camembert	ND-480	70-210	12
Sap Sago	2600	520	12
Swiss	187	ND-1800	10, 12
Provolone	20-235	-	17
Emmentaler	-	128	14
Emmentaler	-	225-1000	4
Cottage Cheese	ND	ND	12
Cottage Cheese	-	6-13	15

*ND=Not Detected

Swiss cheese that produced histamine intoxication aboard a U.S. nuclear submarine was found to contain 187 ug/g (10). Doeglas et al (11) reported a Gouda cheese that contained 850 ug/g histamine. This cheese produced a severe occipital headache

and generalized flushing in a sensitive subject. Formation of the histamine found in the Gouda cheese was traced to the presence of an unknown histidine decarboxylating lactobacillus contaminant in the rennet.

Voight et al (12) surveyed 85 Cheddar cheese samples for tyramine and histamine formation. Tyramine was found in measurable quantities in 81 of 85 samples examined. The average tyramine content was highest in the extra-sharp category (270 ug/g) and lowest in the mild category (90 ug/g). Histamine was present in measurable quantities in only 24 of the 85 Cheddar samples. The average histamine content for the Cheddar cheese samples varied from 210 ug/g for the extra-sharp cheeses to nondetectable levels in the processed samples. It was also noted that none of the processed Cheddar cheeses contained histamine. Voight et al (12) postulated that histamine might possibly be destroyed through pasturization of the processed cheese.

Forty-six samples of other types of cheese were also surveyed. Tyramine was present in detectable quantities in 42 of the samples. Tyramine was present in all varieties except in cottage cheese where amine build-up would not be expected to

occur. The highest tyramine level found was 1800 ug/g in a Swiss cheese sample.

Measurable quantities of histamine were found in only 9 of the 46 samples. The largest amount of histamine (2600 ug/g) was found in a sample of Sap-Sago cheese.

Table 4-2 presents data on the tyramine and histamine concentrations found in several varieties of imported cheeses. The tyramine levels in these cheeses were similar to the amounts found in the varieties listed in Table 4-1. None of these cheeses contained excessive amounts of tyramine, and the amine was present in measureable amounts in all but 2 of the samples assayed.

C. Yeast Extract

Yeast extract has been reported to contain large amounts of histamine and tyramine. This product is formed by the plasmolysis of brewer's yeast in saline solution at 36°C for 24 hours (pH 6.3-6.6) followed by autolysis. It is possible that tyramine and histamine are formed by the yeast enzymes or by contaminating bacteria present in this ideal medium. Hypertension can be induced in patients taking MAO inhibitors by ingesting about 4 gram of yeast extract (see Table 4-3).

TABLE 4-2
TYRAMINE AND HISTAMINE CONTENT OF VARIOUS IMPORTED CHEESES[a]
(ug/g)

CHEESE	HISTAMINE	TYRAMINE
Mimolette	ND[b]	280
Rehmkase	ND	270
Gourmandise (Fondu Blend)	ND-260	70-120
Gjetost	ND	120
German Blanco	280	100
Cheurotin	ND-500	ND-360
Danbo	ND	620
Tybo	980	660
Dofinio	ND	250
Graddoat	ND	120
Norweigian Jarlsberg	ND	ND
Port-Salut	ND	120-180
Reblochon	ND	220
Alpenjoi	ND	100
Stilton	ND	460
Muenster	ND	140
Boursault	ND	110
German Goldblock	ND	330
Brie	ND	40-260

[a]From Voight et al 1974.
[b]ND = Nondetectable

TABLE 4-3
TYRAMINE AND HISTAMINE IN YEAST EXTRACT
(ug/g)

	HISTAMINE	TYRAMINE	REFERENCE
English Yeast Extract	-	2100	6
Canadian Yeast Extract	-	84	6
Marmite (1)	2830	1640	18
Marmite (2)	1950	1440	18
Marmite (3)	980	1090	18
Marmite salt-free	1660	190	18
Vex	1340	510	18
Befit	270	420	18
Barmene	210	150	18
Yeastrel	260	100	18

D. Alcoholic Beverages

Both tyramine and histamine are found in wine and beer (see Tables 4-4 & 4-5). Although the concentrations are quite variable, Chianti appears to contain relatively high concentrations of tyramine (2, 6). It has been postulated that alcohol may potentiate the effect of tyramine and histamine present in wine or food by directly or indirectly inhibiting amine oxidase (26, 27, 28). Marquardt and Werringloer (26) have proposed an upper limit of 2 ug/ml histamine to achieve this inhibition. Early work done by Mayer et al (29) suggests that red wines have a greater histamine concentration than white wines (22, 29). The fact that red wines contain more

TABLE 4-4
TYRAMINE AND HISTAMINE IN ALCOHOLIC BEVERAGES
(ug/ml)

		HISTAMINE	TYRAMINE	REFERENCE
Sparkling Wine (Sekt, dry Germany)		5.1	1	95
Chianti		2.69	-	19
Chianti		-	2-12	6
Chianti		-	25	2
California Wines		0.2-13	-	20
Red Wine (Italy)		0.4-0.6	0.4 to 0.6	6
Red Wine		10	39	14, 21
White Wine		16	111	14, 21
Red Wines	Australia	2-3	-	96
	France	8	7	22
	Germany	-	-	22
	Italy	4	4	22
	Portugal	1	-	22
	Spain	6	4	22
	USA	7	9	22
	Canada	4	4	22
	Switzerland	0-15	0-20	97
White Wines:	Austria	7.4	-	95
	Australia	0	-	96
	France	4	7	22
	Germany	4	6	22
	Italy	1	1	22
	Portugal	1	4	22
	Spain	2	1	22
	USA	4	3	22
	Canada	2	-	22
	Switzerland	0-8	0-36	97
Bourgogne		0.4-21	-	23
Bourgogne		15.1	-	19
Bordeaux		15	-	24
Chambertin		30	-	24
Sake		-	0.51	25
Champagne		7.8	0.2-0.6	6, 95
Tokay Wine Hungary		1.1	-	95
Tokay Wine, dry Hungary		3.2	-	95
Whiskey		0	0	19
Cognac		0	0	19

histamine than white wines is well known and is particularly interesting. Contrary to the process in white wines, red wine vinification is usually carried out in the presence of grape pulp and thus brings about a higher amount of histidine in the must (24). Mayer et al (29) consider that histamine is formed by lactic acid cocci during maloactic fermentation. In addition, the free SO_2 content is higher in the finished white wines, thus inhibiting bacterial formation of amines from the corresponding amino acids (30).

Zee et al (22) in a study of biogenic amines in wine found an upper limit for histamine of 5.73 ug/ml and for tyramine 5.18 ug/ml. He postulated that it appeared unlikely that normal consumption of wine could precipitate hypertensive attacks. However, he did note that toxic effects may be increased manifold due to possible synergistic amine oxidase inhibition by a mono/diamine or by ethanol thus facilitating the amine absorption through the intestinal mucin, which acts as a primary neutralizing agent against toxic amines. A relationship has been found between toxicity of amines and some chronic illnesses, particularly those resulting from a large consumption of wine (31).

Zee et al (22) found that differences in amine contents among Canadian, American, and European wines were probably related to differences in the type of grapes used and in vinification practices. The different degree of grape maturity, the duration of maceration and bacterial contamination were all important factors in amine formation in wine.

According to Rivas-Gonzalo et al (91) one of the most important factors related to the amount of tyramine in wines is the hygienic status of the vinification process. It was even suggested that a wine fermented under optimal conditions from the point of view of hygiene should be practically free of amines (92). Nevertheless, Rivas-Gonzalo et al (91) found that tyramine was present in all the samples of wine they studied. This suggested to them that the amine up to a certain point, is a normal component appearing during the vinification process and was not the consequence of deficient hygiene conditions.

As compared to data available on amine products, less information is available concerning amine elimination. Cerutti and Colombo (93) have used bentonite to reduce histamine and tyramine contents in white wines. However, this has resulted

in a reduction in the color and organoleptic properties of the finished product. The effect of heat treatment on amines may also be of interest since histamine in certain foods has been reported to be heat labile or to coprecipitate with proteins during heat treatment.

Several analysis have been carried out to determine the amine content of beer (see Table 4-5). Chen et al (24) analyzed more than 200 Canadian, American and European beers.

TABLE 4-5

TYRAMINE AND HISTAMINE IN BEER AND ALE
(ug/g or ug/ml)

ORGIN	HISTAMINE	TYRAMINE	REFERENCE
Canadian Ale	0.108-0.410	9.0	6, 94
Canadian Lager	0.120-0.320	-	94
Canadian Malt Lager	0.215-0.495	-	94
Canadian Porter	0.345-0.545	-	94
Canadian Light Beer	0.078-0.160	-	94
Canadian Beer	-	6.46-11.22	6
Canadian Beer	1.57-5.10	13.32-53.40	97
Danish Beer	0.32-1.50	-	19
Swedish Beer	0.26-0.47	-	19
European Beer	0.095-0.298	-	94
United States Beer	0.083-0.193	-	94
Belgian Gueze	1.9	-	94
Japanese Beer		1.06-1.30	25

They found concentrations of histamine ranging from 0.20 to 0.30 ug per milliliter, depending on the type of beer. Among the Canadian beers Porter contained the highest amount of histamine, followed by malt liquor, ale, lager and low-alcohol beer in descending order. Unusually high amounts of histamine were found in some bacteria-infested beers. Granerus (19) determined the histamine content in various alcoholic drinks which are commercially available. Danish beer was found to have a histamine content ranging from 0.32 to 1.5 ug/ml while Swedish beer had a histamine concentration of from 0.26 to 0.47 ug/ml. These figures are similar to those reported by Chen et al (24).

Zee et al (97) studied the influence of malt and adjuncts as well as the various production stages on the amine content of beer. They found that malt and adjuncts (corn syrup, corn, wheat, barley and rice) contributed to amine content in beers. Tyramine concentrations in Canadian beers ranged from 13.32 to 53.40 ug/ml, while histamine concentrations ranged from 1.57 to 5.10 ug/ml. These results are much higher than those reported by other researchers (6, 19, 24, 94).

In general, when malt concentrations decreased amine contents of the beers also decreased. This was further

confirmed when increasing amounts of rice (20 and 40%) were substituted for malt and the amounts of amines were found to have decreased. Zee et al (97) concluded that the raw materials used in the production of the beers, especially malt, contributed to the high amine content in the beers.

E. Meat Products

Tyramine and histamine may accumulate in meat products due to bacterial decarboxylation of their corresponding amino acids, tyrosine and histidine (see Table 4-6). Although tyramine and histamine occur naturally in many foods, they seldom present any hazard unless large quantities are consumed or the normal routes of catabolism are inhibited or are genetically deficient. Little definitive information exists on the levels of histamine in meat products. Comminuted beef (32), beef-soy (33), pork (33), turkey (33) and cured hams (32,34) have low histamine concentrations. However, a preliminary survey of sausages indicated the occurrence of occasionally high histamine concentrations (33). Taylor et al (35) have pointed out the fact that fermentation may be important in the formation of histamine in certain types of sausages. During the fermentation of semi-dry sausages and dry

TABLE 4-6
TYRAMINE AND HISTAMINE IN MEAT PRODUCTS
(ug/g or ug/ml)

ITEM	TYRAMINE	HISTAMINE	REFERENCE
Chicken Liver	94-113	-	38
Chicken Skin		10-140	39
Meat Extract	95-304	-	6
Dry Sausage	ND-1240	0.74-7.81	32
Country Cured Ham	ND	0.82-2.7	32
Country Cured Ham	4.95	-	40
Salami	263	-	13
Cotte Salami	103	-	13
Lamb	3.70	-	40
Veal	1.19	-	40
Pork	11-22	11-45	34
Ham	2-8	4-5	34
Cooked Ham	4.9	-	40
Beef Liver	274	65	41
Semi-dry Sausages	-	3.1-36.3	35
Cooked Sausage	-	1	35
Dry Sausage	-	20.2	35
Dry Sausage	-	2-100	39
Dry Sausage	-	2-24.9	37

sausages the histamine concentration increases at least 10 fold during the first three days of ripening, while the concentration of histidine correspondingly decreases (36). The histamine concentration in a fermented sausage can be variable and dependent on the length of the ripening process (37).

Taylor et al (35) carried out a survey of histamine levels in sausages. They reported that cooked sausages normally had less than 1 mg/100g of sausage. These histamine concentrations were similar to those found in fresh comminuted meats which is not surprising since these products were not allowed to ferment.

Semi-dry sausages were reported to have slightly higher histamine concentrations than cooked sausages. Histamine concentrations ranged from 3.1 ug/g to 36.3 ug/g.

By comparison to cooked and semi-dry sausages, dry sausages have been reported to have larger and more variable histamine amounts. Rice et al (32) found the histamine content of dry sausage to range from 0.7 ug/g to 7.8 ug/g. Henry (39) reported levels of histamine ranging from 0.2 to 100 ug/g while Cantoni et al (37) reported concentrations ranging from 2 to 24.9 ug/g. These findings suggest that the conditions of fermentation may affect the amount of histamine produced.

Tyramine content of meat products has been surveyed by Celestino Santos-Buelga et al (40), Koehler and Eitenmiller (13), Rice et al (32) and Sen (6).

The tyramine contents of a number of meat products is given in Table 4-6. Rice et al (32) reported that tyramine was not detected in any of the country cured hams tested. This is in contrast to Cestintino Santos-Buelga et al (40) who reported tyramine concentrations up to 4.95 ug/g. Rice et al (42) reported the average tyramine concentration of dry sausage to be 244 ug/g and that for semi-dry sausages to be 85.5 ug/g. Highest tyramine concentrations found during the survey were in a Genoa salami (1237 ug/g).

Koehler and Eitenmiller (13) surveyed 13 samples of commercially prepared sausage. They found tyramine in 85% of the sausages surveyed. The average level of tyramine was 133 ug/g.

There are several factors that could contribute to the wide range of tyramine found in fermented sausages. The most important factors are (1) the number of organisms present that can decarboxylate tyrosine and (2) the availability of free tyrosine. Dierick et al (43) has shown that there is generally

an increase in free amino acids during sausage ripening. Variations in sausage processing may also account for differences in tyramine level.

F. Sauerkraut

Mayer et al (44) studied the effect of fermentation conditions on the formation of histamine and tyramine in sauerkeraut. They found that histamine could increase up to 160 ug/g after fermentation for 10 weeks. In an earlier study Mayer et al (45) also found between 50 and 75 ug/g of histamine in an analysis of sauerkraut juice. Taylor et al (46) found histamine in concentrations of up to 130 ug/g in 50 samples of sauerkraut. Mayer et al (45) reported that sauerkraut with a low histamine and tyramine content could be produced by inhibiting growth of pediococci by early interruption of the fermentation just below pH 4.0. This produces a mild low-acid sauerkraut which can be pasturized to achieve stability. Although Mayer and Pause (47) attributed a severe headache to the consumption of 200 g of sauerkraut, Taylor et al (46) now consider that the histamine levels in sauerkraut are unlikely to reach hazardous levels unless serious problems occur in the fermentation stage.

G. Fish

Scombroid poisoning is generally associated with consumption of spiney finned fish of the suborder Scombroidei which includes tuna, bonita, skipjack, mackerel and albacore. Histamine has been reported to be one of the principle compounds leading to scombroid poisoning. Histamine build-up is the result of growth of histidine decarboxylase positive bacteria under conditions favorable for enzyme synthesis and activity. Bacteria known to produce histidine decarboxylase include species of Proteus, Salmonella, Shigella, Clostridium and Escherichia (48).

Recent literature reviews on the subject of histamine toxicity and histamine formation in fish have been carried out by Arnold and Brown (49), Sinell (50) and Eitenmiller et al (51).

Although scombroid food poisoning is usually manifested as a discomfort for a period of hours and very rarely proves fatal, it is not to be taken lightly. World-wide incidences of scombroid food poisoning indicate the potential for a variety of foodstuffs to induce the intoxication. By the nature of its dissemination - often via commercial products - it is

frequently widespread before it can be arrested. During one well documented outbreak in the United States 254 persons in eight states were poisoned from the consumption of commercially canned tuna. Two lots of tuna constituting some 170,000 cans were recalled (52).

In addition to the United States, cases of scombroid poisoning have been reported in Japan, Indonesia and in European countries such as Czechoslovakia (53). The occurrence of this type of food poisoning is significant but is much lower on a per capita basis in the United States than in those countries that depend more on fish in their diet, yet rely less on refrigeration (51). Japan has been prone to many scombroid poisoning outbreaks. This is due to the consumption of certain dried products which are popular in Japan. Kawabata et al (54) described 14 outbreaks involving 1215 people during a four year period.

According to Eitenmiller et al (51) histamine is undoubtedly the major causative agent of scombroid food poisoning. Vomiting, abdominal pain, facial flushing, and headache are the most notable effects of scombroid fish poisoning. Onset is rapid but recovery is usually complete

within eight hours (55). Unlike tyramine, histamine is a powerful vasodilator and this accounts for the facial flushing in histamine toxicity. Fish with a histamine content above 1 mg/g is usually toxic (55). Early work on the occurrence of histamine in fish and other food is reviewed by Ienistea (56).

In addition to fish belonging to the suborder Scombroidei, sardines have also been implicated in apparent histamine poisoning episodes. Popovich et al (57) reported that out of 88 patients who ate sardines, 44 exhibited symptoms of headache, urticaria and subjective feelings of warmth.

Several aquatic species have been examined for their ability to support histamine formation (see Tables 4-7 & 4-8). Dabrowski et al (58) found no histamine in sterile Baltic herring muscle, but histamine was formed in muscle samples containing the normal microflora when stored at temperatures between 0-2^{o}C. Takagi et al (59) reported that histamine was not formed in the muscle of squid or octopus. In an examination of ocean mackerel Gheorghe et al (60) found that histamine concentration remained below toxic levels when the fish was stored at 8^{o}C for 11 days or for 8 months at -8^{o}C. Gheorghe et al (61) also reported that histamine never

TABLE 4-7

TYRAMINE AND HISTAMINE IN SEAFOOD
(ug/g)

ITEM	HISTAMINE	TYRAMINE	REFERENCE
Skipjack Tuna Spoiled	7140	-	66
Tuna Canned	20	-	67
Tuna Canned Decomposed	1180	-	67
Chunk Light Tuna Processed	12-280	0	68
Tuna	-	574.5	14
Trout	-	0	14
Bream	-	436.6	14
Pickled Herring	-	3030	65
Salted Cod	0	0	6
Salted Herring	-	470	6
Mackerel	10-315	-	68
Mackerel Stored 48 hr. at 24°C	238	28.3	63,98
Mackerel Stored 20 days at 10°C	1800	-	69
Mackerel Smoked	1480	0	55
Mullet Stored 48 hr. at 24°C	27.1	28.5	63,98
Squid & Octopus Stored 48 hr. at 25°C	0	0	59
Japanese Little Neck Clams stored 96 hr. at 25°C	0	238	64
Asiatic Hard Clams stored 48 hr. at 25°C	0	313	64
Giant Ezo Scallop stored 48 hr. at 25°C	0	trace	64
Sakhalin Surf Clam stored 48 hr. at 25°C	0	64.0	64
Speckled Trout Stored 48 hours at 24°C	1.67	119.2	63,98
Channel Catfish Stored 48 hours at 24°C	1.80	69.8	63,98
White Shrimp Stored 48 hours at 24°C	0.37	42.9	63,98

TABLE 4-8
HISTAMINE CONTENT OF FISH PRODUCTS
ON THE JAPANESE MARKET[a]

KIND OF PRODUCT		AMOUNT OF HISTAMINE (ug/g)
CANNED FISH	Oil Sardine	57.9
	Seasoned Sardine	13.1, 81.6
	Seasoned Mackerel	1.8, 49.3
	Seasoned Tuna	63.8, 99.8
	Seasoned Bonita	59.9, 156.9
	Seasoned Whale	11.3
	Pink Salmon	2.3
DRIED FISH	Sardine	124.3
	Herring	300.9
	Sand Eel	39.5
	Squid	26.0
	Shark Fin	1.8
SALTED FISH	Herring	98.3
	Trout	22.5
	Herring Roe	5.1
SALTED DRIED FISH	Mackerel Pike	297.8
	Gutted Cod	0.7
	Sardine	15.0
SEASONED DRIED FISH	Pressed Squid	10.2
	Globefish	2.4
	Broiled Sardine	398.9
FISH BROILED IN SOY SAUCE	Sand Eel	1.8
	Goby	5.3
SMOKED FISH	Herring	345.2
	Salmon	16.6
FISH CAKE	Kamaboko	0.4, 0.7

[a]From Kimata, 1961.(48)

exceeded 60 ug/g when the fish were stored at -10°C for 8 months. Takagi et al (62) investigated histamine formation in 21 aquatic species. After 24 and 48 hours of storage at 25°C highest histamine concentrations were found in Pacific Saury (2630 ug/g after 48 hours). Pacific mackerel reached a level of 2460 ug/g after the same storage period, and three other species reached concentrations exceeding 700 ppm. The remaining species never exceeded 100 ug/g and seven species were reported to remain histamine free. Takagi et al (62) concluded that the degree of histamine formation in marine products tended to be governed by the muscle histidine content but was not proportional to the loss of histidine.

Edmunds and Eitenmiller (63) concluded that histamine intoxication from mackerel was unlikely since the mackerel would have to reach an advanced stage of decomposition before the toxic concentration was reached. Arnold and Brown (49) believe that it is extremely unlikely that histamine acting alone is the sole factor responsible for scombroid poisoning. They believe that histamine together with some accompanying synergist or potentiating condition leads to the toxic syndrome.

Like histamine, tyramine in fish is produced by the bacterial decarboxylation of its corresponding amino acid.

Unlike histamine, however, much less work has been done on the study of tyramine content of seafood (see Table 4-7).

Takagi et al (59) reported that no tyramine was formed during the spoilage of squid and that only small amounts were formed during the spoilage of octopus. In another study Takagi et al (64) determined the tyramine content in the muscles of six species of shellfish. After 24, 48 and 72 hours of storage at 25°C highest tyramine concentrations were found in the Asiatic hard clam (516 ug/g after 72 hours). Japanese little neck clam reached a level of 346 ug/g after the same storage period. The remaining species never exceeded 170 ug/g.

Nuessle et al (65) found 3030 ug/g tyramine in pickled herring. This value is much higher than that reported by Sen (6) (470 ug/g). Tarjan and Janossy (14) detected 570 ug/g of tyramine in tuna and 436.6 ug/g in bream.

This author (98) determined the tyramine content in the muscle of five aquatic species. After 48 hours of storage at 24°C, highest tyramine concentration was found in speckled trout (119.2 ug/g). Channel catfish was found to have a concentration of 69.8 ug/g of tyramine followed by white shrimp

with 42.9 ug/g, mullet with 28.5 ug/g and Spanish mackerel with 28.3 ug/g. There appears to be little chance that these aquatic species would develop sufficient tyramine during spoilage to lead to a tyramine hypertensive attack.

H. Fruits and Vegetables and Their Products

The histamine and tyramine content of fruits, vegetables and their products is shown in Table 4-9. The fruits of avocado, lemon, and raspberry have been found to contain tyramine in moderate amounts. The banana itself also contains only moderate amounts of tyramine, however, its peel contains up to 65 ug/g of tyramine. Tarjan and Janossy (14) have reported tyramine concentrations of up to 69.1 ug/g in 16 samples of grapes tested. This is in contrast to Lovenberg et al (70) who could detect no tyramine in grape samples tested. The largest concentration of histamine was found in spinach (400 ug/g). It appears unlikely that tyramine or histamine in fruits or vegetables could precipitate hypertension attacks or intoxication syndromes unless large quantities of fruit or vegetables containing these amines are consumed.

TABLE 4-9

TYRAMINE AND HISTAMINE IN FRUITS, VEGETABLES, AND THEIR PRODUCTS (ug/g)

ITEM	HISTAMINE	TYRAMINE	REFERENCE
Apple	-	0	6
Avocado	-	23	78
Bananas	-	7	79, 80, 81, 82
Banana Peel	-	65	81
Barley	-	10	83
Beet	5.2	-	84
Egg Plant	-	3	81
Grape	-	69.1	14
Hops	30-40	-	3
Hop Extract	120-160	-	3
Lemon	-	25	85
Maize	-	1	86
Orange	-	1-10	6, 81, 87
Pineapple	-	0.4	6, 36, 80
Plum	-	6	81
Potato	-	1	81
Raspberries	-	8-93	80
Sauerkraut	6-200	20-95	47
Spinach	400	1	81, 88
Tangerine	-	1	89
Taro	-	34	89
Tomato	0.3-1	4	81,82
Cocoa based foods	-	3.4-11.5	77
Milk Chocolate	-	3.76-12.02	75
Drinking Chocolate	-	2	76
Dark Chocolate	-	0.7	90

Cocoa and its derivatives, especially chocolate, have been implicated with migraine; this has been attributed to the presence of tyramine in them. This has not been entirely confirmed, however, and other vasoactive amines have also been implicated, principally serotonin (71, 72) and phenylethylamine (73, 74).

The few studies appearing in the literature (75, 76, 77) report amounts of tyramine in cocoa derivatives ranging from undetectable to 14.6 ug/g; this is relatively low when compared with the amounts detected in cheese 3700 ug/g (4) or meat derivatives 1237 ug/g (32).

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CHAPTER V

HEALTH AND LEGAL IMPLICATIONS OF HISTAMINE AND TYRAMINE TO THE RESTAURANT AND FOOD INDUSTRIES

Numerous cases of histamine food poisoning and hypertensive attacks due to the ingestion of food containing tyramine have demonstrated the public health implications of biologically active amine formation in food. In addition to these public health implications there are also legal implications which concern both the restaurateur and the food processor. It is the purpose of this chapter to discuss some of these implications.

Although histamine and tyramine poisoning are usually manifested as a discomfort for a period of hours and very rarely proves fatal, they are not to be taken lightly. World-wide incidences of reactions to these amines indicate the potential for a variety of foodstuffs to induce histamine or tyramine intoxication. By the very nature of their dissemination - often via commercial products - they are frequently widespread before they can be arrested. During one

well documented outbreak in the United States 254 persons in eight states were poisoned from the consumption of commercially canned tuna. Two lots constituting some 170,000 cans were recalled (1, 2).

Although the number of cases of histamine and tyramine reactions have increased world-wide probably many more cases of histamine and tyramine poisoning remain unreported. This is probably due to the fact that the symptoms either are too mild or of too short duration to warrant the individual effected having to see a physician or the fact that the histamine or tyramine reactions are misdiagnosed since the symptoms are similar to those of other types of food poisoning. Because of this similarity of symptoms to other types of food poisoning restaurateurs and food processors, for the most part, have very little knowledge of what histamine and tyramine are, how they are produced, what symptoms they produce and how they can be prevented. This is the type of information that needs to be provided to both the restaurateur and to the food processor.

Essentially we know that histamine and tyramine fulfill important metabolic functions in man, especially in the nervous system and in the control of blood pressure. They are found in a wide variety of foods but normally not in high enough

concentrations to be harmful if ingested. Problems can arise, however, if bacteria are provided proper conditions for their growth. These conditions include: (1) the presence of free amino acids, (2) the presence of microorganisms that can decarboxylate the amino acids, and (3) favorable conditions for the growth of the microrganisms and for the production of the decarboxylase enzymes. From the hygienic point of view these conditions are considered to be extremely unfavorable and efforts must be made to prevent their occurrence. The major points that the food processors and restaurateurs need to be concerned with are (1) the speed with which microorganisms can form histamine and tyramine and (2) the fact that it is difficult to determine that a food product is high in one or both of these amines by sight or smell. Fish in particular, can look and smell fresh but can still contain hazardous levels of histamine or tyramine. Since odor and appearance do not reliably indicate the type of spoilage, consumers and food processing personnel often fail to be alerted and intoxication may occur.

Now the question is what can food processors and restaurateurs do to safeguard their customers? First,

processors must insure that food items, such as fish, have been held at low temperatures (0°C or below) and have remained at these temperatures until they are ready to be processed. Eitenmiller et al (3) have shown storage temperature to be the critical factor influencing the formation of histamine in tuna. By holding the food items at low temperatures microbial growth is slowed down which in turn inhibits the production of the decarboxylase enzymes which produces histamine and tyramine. In addition to storage at low temperatures processors can use antimicrobial agents, such as potassium sorbate, as an additional impediment to bacterial formation of histamine and tyramine (4). Finally processors can routinely test for these amines in items being processed. Items with too high a level of either amine should be discarded.

Other manufacturers such as cheese and wine makers should also be able to control the amounts of histamine and tyramine in their products. Price and Smith (5) found that tyramine was probably derived from aerobic bacteria which grew on the surface of the cheese. They postulated that it should therefore be relatively easy for manufacturers to produce tyramine-free cheese. Their findings are similar to those found in studies conducted on wine fermentation where tyramine

was also produced by aerobic bacteria. What this means is that by the use of specific starter cultures and by the use of good sanitation procedures the biogenic amine content of wine and cheese can be kept low.

Andreas Lembke, a Swiss researcher, has patented a process which uses microorganisms or enzymes obtained from these microorganisms to reduce the content of histamine and other biogenic amines in various foods. The process appears to be especially applicable to any industry involving fermentation (beer, wine, cheese, sauerkraut, etc.). The microorganism of preference can be a bacterium, perferably one of the class of micrococci, pseudomonas, or lactobacilli or it can be a fungus or yeast perferably a species of saccharomyces. The biogenic amine content of the food or beverage is reduced as a result of the microorganism's ability to deaminate or transaminate the amino acids which are normally converted into biogenic amines by decarboxylation. The deamination or transamination converts the amino acids into products which are not harmful to man.

Restaurateurs can do their part in protecting their patrons from consuming foods high in histamine or tyramine by (1) buying their food from reputable purveyors, (2) inspecting

the food when it is received, and (3) by refrigerating fresh food, particularly items such as fish and keeping it refrigerated until consumed. By doing this the restaurateur is denying microorganisms conditions favorable for their growth and thus inhibiting the production of histamine or tyramine. Additionally, restaurateurs need to realize that even though some foods are low in histamine or tyramine that they, when served in combination with other foods with similar histamine or tyramine content, may cause a reaction to some of their customers. They, therefore, need to make some effort in educating themselves on histamine and tyramine content of various foods. By doing this the restaurateur can hopefully lessen the chances of a histamine or tyramine reaction occurring in one of his or her patrons.

Finally as a result of all the studies done on hypertensive attacks, it is now routine for doctors to warn patients who are taking monoamine oxidase inhibitory drugs to avoid foods containing biogenic amines, and standard cards listing these foods are now issued to such patients (6).

Now in addition to the health implications stated above there are also some legal implications with regard to histamine

and tyramine in foods that are or should be of importance to both restaurateurs and food processors/manufacturers. According to Professor John E. H. Sherry, these legal implications arise out of the restaurateur's and the processor's responsibilities to their customers. These include liability for serving unfit foods (negligence), breach of implied warranty of fitness, strict liability and the consequences of dealing with foods from other countries (7, 8).

The liability of a restaurateur to his patron for serving unfit food is based on the principles of the law of torts and contracts. This means that a person is responsible for any injury or damage caused by his own negligence.

Negligence is generally defined as a failure to exercise reasonable care. Thus if a restaurateur purchased fish from a reputable purveyor, inspected the fish when it was received, kept it under proper storage conditions and then prepared it and served it to the guest the restaurateur would not be liable if the patron became ill due to high histamine or tyramine content in the fish. The restaurateur had exercised reasonable care with regard to storage and preparation of the fish. There was no way the restaurant owner could have known about the

histamine or tyramine. If, however, the restaurateur had improperly stored or refrigerated the fish or if he accepted fish that was obviously spoiled he could be held liable. (9)

This same negligence theory applies to the processor/manufacturer in the same manner it applies to the restaurateur. The only difference is that the processor has more control over the final product since the processor can test for the histamine or tyramine in the final product. Thus they know just how much amine is present in the product and if too high a level is present the product should not be sold. If they don't test and the product is high in histamine or tyramine then they can be held liable for individuals who become sick due to ingestion of a contaminated product.

In the absence of negligence, a customer served unwholesome food can sue and try to recover on the basis of breach of implied warranty of fitness of the food. In order for there to be a warranty claim there must, however, be a sale. Under breach of implied warranty the patron is not required to prove that the foodservice operator or processor was negligent in the storage, preparation, or service of the product but only that the product caused the illness and the

seller breached the contract by serving unfit food. According to Sherry (8), an advantage of the breach of warranty theory to restaurateurs' is that they have recourse against the producer or packer of the food item if it was contaminated or unwholesome. For example, if a restauratuer bought fish from a reputable purveyor and the fish appeared and smelled fresh but actually had a high histamine or tyramine content and if it was consumed by a customer who became ill then the restaurateur would be liable for breach of warranty. The patron eating the fish could sue the restaurateur but the restaurateur could in turn sue the purveyor.

The final type of liability with which restaurateurs and food processors may be involved is strict liability. Strict liability does not require that negligence or breach of warranty be established, but only that it be proven that the unfit food caused the customer(s) to become ill. Once the injured party has shown that the food made him or her ill then they have legal grounds to recover.

Table 5-1 shows a number of cases of scombroid (histamine) poisoning which have resulted from canned fish which were not produced in this country. This points out a problem which we

TABLE 5-1

SCOMBROTOXIN (HISTAMINE) POISONING
FROM CANNED FISH

DATE	CANNED FISH INCRIMINATED	COUNTRY
March 1979	Mackerel	United Kingdom
May 1979	Sardines	Morocco
August 1979	Pilchard/Sardines	Morocco
October 1979	Mackerel	United Kingdom
January 1980	Pilchards	United Kingdom
February 1980	Bonita/Tuna	Thailand
April 1980	Tuna	Taiwan
April 1980	Tuna	Fiji
May 1980	Sardines	Morocco
May 1980	Mackerel	United Kingdom
May 1980	Tuna	Taiwan
May 1980	Sardines	Morocco
June 1980	Sardines	Morocco
October 1980	Tuna	Peru
November 1980	Tuna	Malaysia
November 1980	Tuna	Japan
November 1980	Skipjack Tuna	Japan
November 1980	Tuna	Taiwan
November 1980	Tuna	Taiwan
December 1980	Sardines	Morocco
December 1980	Anchovies	Spain
January 1981	Sardines	Morocco
January 1981	Tuna	Solomon Islands
February 1981	Tuna	Japan
February 1981	Tuna	Thailand
March 1981	Tuna	Philippines

From Murray et al (26).

currently have and which will probably get worse. This problem centers around the fact that we know little about health and sanitation requirements in the countries from which we buy products. (10) This especially poses problems for the restaurateur in this country since there is no way he/she can determine the quality of the food received. If a restaurateur serves a patron food from a foreign country which is high in histamine and the patron becomes ill the restaurateur is open to a law suit. The only recourse the restaurateur has is to sue the purveyor who provided the food or the producer of the food if he has a plant in this country. As stated earlier in this chapter it really behooves the restaurateur to ensure he is dealing with a purveyor who has a good reputation and has a good track record with regards to food quality.

Histamine and tyramine have both health and legal implications to restaurateurs and food processors. They are found in a variety of foods but don't normally constitute a health hazard unless large quantities of food containing them are ingested or the pathway for their catabolism in the body is inhibited or genetically deficient. The build up of these amines in foods is primarily due to microbial amino acid

decarboxylation. The critical factors in the formation of histamine and tyramine appear to be storage and sanitation. Since odor and appearance do not reliably indicate the type of spoilage, consumers and food processing personnel often fail to be alerted and histamine and tyramine intoxications may occur. Due to the increased number of cases of histamine poisoning in recent years histamine analysis has now become a routine quality control procedure in the tuna processing industry.

Restaurateurs can do their part in protecting their customers from consuming foods high in histamine or tyramine by buying their food from reputable purveyors, inspecting the food when it is received, and by refrigerating fresh food and keeping it refrigerated until it is consumed.

Food processors and manufacturers can reduce the possibility of histamine or tyramine formation in foods by ensuring that foods are kept at proper temperature and remain at proper temperatures until processed. Also foods being processed should be routinely tested for histamine and tyramine. Histamine and tyramine content of fermented products can be controlled through the use of proper sanitation to prevent contamination by aerobic bacteria that produce biogenic

amines and by the use of starter cultures that do not produce histamine or tyramine.

In addition to health implications there are also legal implications with regards to the histamine and tyramine contents of food. These legal implications arise out of the restaurateur's and food processor's responsibilities to their customers. They revolve around three legal theories which form the backbone of liability law for the production and service of foods. These legal theories are the negligence theory, breach of warranty theory applied under the Uniform Commerical Code and strict liability.

The negligence theory requires that the injured customer be able to prove that negligence on the part of the restaurateur or food processor resulted in the food being unfit and in turn resulted in the illness. Essentially the injured party has to show that the restaurateur or food processor did not exercise reasonable care in the storage, production or service of food.

The second theory is breach of warranty as applied under the Uniform Commercial Code. Under breach of implied warranty the patron is not required to prove that the food service

operator or food processor was negligent in the storage, preparation, or service of the product but only that the product caused the illness and the seller breached the contract by serving unfit food.

The final type of liability with which restaurateurs and food processors may be involved is strict liability. This law theory requires only that proof that the patron's illness was caused by ingestion of the food be shown. Once this is shown then the patron has legal grounds for recovery.

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CHAPTER VI

DETECTION AND DETERMINATION OF HISTAMINE AND TYRAMINE IN FOOD

A number of biological and chemical methods have been developed to detect and measure histamine and tyramine. Described in this chapter is a survey of some of the more common methods which have been developed.

A. Guinea Pig Ileum Contraction

Guinea pig ileum contraction is a bioassay method for the determination of histamine and is based on the fact that it will cause contraction of the guinea pig ileum.

The first application of this method to the analysis of histamine was carried out by Minard (1) and Guggenheim (2). Subsequently this method was applied to the analysis of histamine in fish tissue by Geiger (3). He and his fellow workers had earlier identified a biologically active substance in marine fish as histamine (4). He described how the method could be applied to fish and reported findings on histamine levels in raw and canned tuna and mackerel. He pointed out

that canning of these fish did not interfere with subsequent analysis for histamine, and demonstrated the practical application of histamine formation in canned tuna. The method was subsequently applied by Hillig (5) to several species of tuna at varying stages of decomposition while Sager and Horwitz (6) compared the bioassay with a chemical method based on coupling histamine with a diazonium compound. Formation of this diazonium compound was measured spectrophotometrically. They found that values with the bioassay were usually higher than those obtained by the chemical method. However, when they modified the extraction procedure used in the bioassay, they were able to obtain results with the modified bioassay that checked well with those obtained by the chemical method.

Work to 1956 is well summarized in a review by Code and McIntire (7) dealing with the quantitative determination of histamine; this review includes a detailed description of the guinea pig intestine assay as well as a summary of chemical methods developed at that time.

B. Other Bioassays

Although the use of the guinea pig ileum contraction technique is by far the most commonly used bioassay for the

detection of histamine other methods have been suggested. De Waart et al (8) evaluated a total of 32 biological systems, including 6 protozoa, 4 fish species, 5 insects, bull spermatozoa, 4 cell lines, 9 microorganisms, embryonated hen's eggs, Daphnia and Artemia for sensitivity to a variety of microbial toxins and histamine. As a result of his evaluation he suggested that the very small crustacean Daphnia magna might be used as a bioassay system for histamine since this organism reacts to minute concentrations of histamine in its aqueous environment. This organism is presently being used by an investigator at the University of California at Davis. (9) He found that the addition of histamine to water housing Daphnia caused the death of 90 to 100% of the animals in 20 to 50 minutes compared to a 0 - 4% effect in animals receiving an extract from good tuna. Daphnia are readily available and easy to house, with algae being a suitable food source.

C. Fluorometric Assays

Although accurate measurements may be made using bioassay techniques, such methods have numerous disadvantages. For example, in order to perform the guinea pig ileum contraction

bioassay, provisions must be made for the care and handling of guinea pigs. Additionally, the guinea pig ileum response is subject to individual variability. For this and other reasons, there has been increased interest in the development of suitable chemical means for histamine and tyramine determination.

The use of fluorometry has evolved as a major tool for the assay of tyramine and histamine. Shore et al (10) described a relatively simple fluorometric method that is supposedly precise and sensitive for histamine. The method involves extraction of histamine from alkalinized perchloric acid tissue extracts with n-butanol, and its ultimate condensation with O-phthalaldehyde to yield a stable and strongly fluorescing product. The authors noted that levels of histamine as low as 0.005ug/ml could be assayed.

Sen (11) modified the methods of Oates (12) and Spector et al (13) to determine the tyramine content of a number of foods. This method involves extraction of tyramine with ethyl acetate from an alkaline homogenate of food, the transfer of the tyramine to an acid phase by extracting the ethyl acetate layer with 0.2N HCl and then measuring tyramine

fluorometrically after its conversion to a fluoropher by reacting with ∝ nitroso-B-napthol.

Fluorometric assays have found broad application for the determination of histamine and tyramine in a variety of materials including cheese (14), wine (15, 16), sauerkraut (17), cocoa (18), meat extracts (19) and fish (20). A detailed description of the use of the fluorometric methods for the measurement of histamine is found in a review by Shore (21) which includes coverage of means of extraction of histamine from tissues together with a description of special purification procedures.

More recent developments in this field include development of the use of fluorescamine to react with amino acids, peptides, proteins and primary amines (22). Fluorescamine reacts rapidly at room temperature in aqueous media and yields highly fluorescent products. The reagent and its degradation products are nonfluorescent. Sensitivity of this chemical is in the picomole range.

Another chemical which has been used to react with amino acids, peptides, proteins, and primary amines is dansyl chloride (23). Although this reaction is not as rapid as that

of fluorescamine, it also yields highly fluorescent products and has a sensitivity in the picomole range.

Yamada and Wakabayashi (24) compared colorimetry, fluorometry and bioassay for measuring the increase in blood histamine following administration of certain antibiotics. They reported that fluorometry and bioassay were superior to the colorimetric determination and that the fluorometric procedure was the most simple of the three.

Lerke and Bell (25) have developed a method for determination of histamine in fish by fluorometry. Histamine is recovered from fish extracts by ion exchange chromatography and then derivatized with O-phythalaldehyde. Up to 12 samples per hour can be analyzed with this method. Recoveries of histamine added to extracts from acceptable quality fish ranged from 98-103%, and recoveries of 94-101% were demonstrated for histamine added to extracts of decomposed fish. This method is claimed to be as accurate as the Association of Official Analytical Chemistry's (AOAC) procedure and much simplier.

A simple automated fluorometric method for histamine released from mast cells has been reported by Kusner and Herzig (26). Histamine in the sample was coupled directly with

AD-A157 933 HISTAMINE AND TYRAMINE IN FOOD(U) AIR FORCE INST OF TECH WRIGHT-PATTERSON AFB OH T L BAUCOM MAY 85 AFIT/CI/NR-85-62T 2/2

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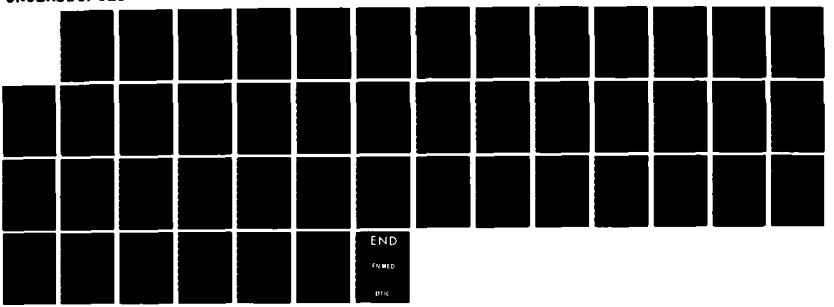

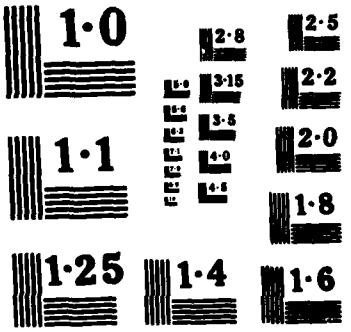

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MICROCOPY RESOLUTION TEST CHART

O-phthalaldehyde without protein precipitation and without isolating histamine. Up to 15 samples per hour could be analyzed with this method. Evans et al (27) have described an automated fluorometric assay for the rapid determination of histamine in biological fluids after protein precipitation. In Evan's automated method, histamine was extracted into N-butanol from an alkalinized sample solution, followed by several other extraction steps in order to eliminate interfering free amino acids and finally histamine was detected fluorometrically after the reaction with O-phthalaldehyde. Up to 30 samples per hour could be analyzed with a reproducibility greater than that of manual methods. An automated extraction and fluorometric detection procedure for the determination of histamine in fish products has been developed by Luten (28). In this method proteins are precipitated prior to automated extraction and fluorometric detection by adding trichloroacetic acid and sodium hydroxide followed by centrifugation. Using this method up to 80 pretreated samples could be analyzed automatically in one day by a skilled analytical chemist.

D. Gas-Liquid Chromatography

Histamine and tyramine can both be determined by gas-liquid chromatography. For example Sen (11) developed a very sensitive and specific gas chromatographic method whereby less than one nanogram of tyramine could be quantitatively measured. Kaplan et al (29) described a gas chromatographic method that could be used to detect tyramine in cheese. In this method tyramine hydrochloride was converted into its ON-bistrifluoroacetyl (TFA) derivative with a large excess of trifluoroacetic anhydride and determined by gas chromatography using ephedrine hydrochloride as an internal standard. Fales and Pisano (30) described a gas chromatographic method for the determination of histamine. This method employed a column containing 4% SE-30 siloxane polymer as the liquid phase. Navert (31) described a gas chromatographic procedure which is said to separate adequately histidine, histamine, and the naturally occurring methyl histamines. According to Arnold and Brown (32) although possibilities exist for the application of these techniques they have not achieved widespread use among investigators studying histamine or tyramine toxicity problems.

E. Colorimetric Assay

The color reaction between ∝ -nitroso - B-napthol and tyrosine was discovered by Gerngross, Voss and Herfeld (33). Despite its sensitivity and its specificity it was not used by these authors as a quantitative method because of the instability of the color formed. Attempts to find conditions which allowed stabilization of the red color were made by Thomas (39) and Giral (35), but under the conditions proposed by these authors, stability was far from satisfactory. Udenfriend and Cooper (36) proposed the transformation of the unstable red color into a stable yellow one, by heating in nitric acid solution and subsequently extracting the excess of reagent by ethylene dichloride. Good stabilization was obtained by this method. Ceriotti and Spandrio (37) conducted a systematic investigation of the different variables of the ∝ -nitroso-B-naphthol reaction with tyrosine. They found that it was possible to stabilize the red color and to use a simplified procedure which avoided extraction by ethylene dichloride. Rivas-Gonzalo et al (38) developed a method for the determination of tyramine in wine utilizing the reaction of ∝ nitroso-B-napthol with tyramine. Tyramine is determin-

ed in wine by sand column extraction in alkaline medium with anhydrous sodium sulfate. Tyramine is identified and quantitated by spectrofluorometry after the final extract is reacted with ∝ -nitroso-B-napthol. Average recovery with this method was 98.93%. Celestino Santos-Buelga et al (19) adapted the method of Rivas-Gonzalo et al (16) to determine the tyramine content of meat extracts, while Jalon et al (18) utilized the method to determine tyramine in cocoa and its derivatives.

Early chemical methods for the quantitative determination of histamine involved either coupling of histamine with a diazotized aromatic amine to produce an azo-dye, or the reaction of histamine with 2,4-dinitrofluorobenzene (DNFB). Both methods are discussed in detail by Code and McIntire in their review of chemical methods for measuring histamine. Code and McIntire concluded that DNFB was the better reagent of the two in that it yielded a much more stable colored histamine derivative, was more sensitive, and was potentially more specific than the azo-dye method.

Earlier studies on colorimetric assays involving histamine were carried out by Sager and Horowitz (6) and Ota (3).

Weissback et all (39) reported a method designed specifically for measuring both histamine and serotonin in the same extract. After protein precipitation, both compounds were extracted with butanol, and the butanol was then passed through a cotton-acid succinate column, which separated histamine from serotonin. Serotonin was assayed fluorometrically, while the histamine was reacted with DNFB for colorimetric determination.

A simple and rapid diazo method for the determination of histamine in fish samples was reported by Kawabata et al (40). Their method used a cationic exchange resin to achieve separation of histamine from interfering substances, including histidine, in a trichloroacetic acid extract of fish flesh. Samples of column eluates were coupled with Pauly's diazo reagent and the absorbance at 510 nm was determined by spectrophotometry. This method has been one of the most frequently employed by investigators and industry personnel involved with studying recent outbreaks of histamine poisoning.

F. Enzymatic Assay

Lerke et al (41) have described a rapid screening method for the detection of histamine in fish. The method uses a

two-step sequential enzyme system. First diamine oxidase catalyzes the breakdown of histamine with formation of hydrogen peroxide. Hydrogen peroxide is then detected by formation of crystal violet from the leuco base in the presence of peroxidase. The two reactions can be combined and peroxidase can be used to control the tightness of the screening. The method can be used for raw or heat-processed fish.

G. Thin-Layer Chromatography

Voight et al (42) described a thin-layer chromatographic method for the separation and quantification of tyramine, histamine and tryptamine in cheese. A chloroform-methanol-ammonium hydroxide solvent system was chosen because of its ability to efficiently separate the three amines. Quantitation of the amines was achieved by spraying the thin layer chromatographic plates with a 0.2% NBC-Cl (7 chloro-4-nitribenzofurazan) methanol solution and measuring fluorescence of the NBC-Cl derivatives. Lieber and Taylor (47) tested twelve solvent systems for their ability to separate histamine and histidine on a variety of thin layer coatings. They found that the methanol-ammonia (20:1) and the chloroform-methanol-ammonia

(2:2:1) systems, used with silica-gel plates, were the most promising for rapid preliminary screening of tuna fish extracts for histamine. Blackwell et al (44) determined the histamine and tyramine content of yeast extracts using either a butanol-acetic acid-water (4:1:5) or an ethanol-ammonia-water (8:1:1) solvent system. Chromatograms were sprayed with either a sulphanilic acid solution for histamine or with a ninhydrin solution for tyramine. For quantitative work the ethanol-ammonia solvent was found to be better.

Schwartzman (45) described a thin-layer chromatographic method for the separation of histamine, methylhistamine, acetylhistamine, and imidazoleacetic acid. His method used a butanol-glacial acetic acid-water system and produced fluorescent compounds of the five amines which were quantitated by absorption or fluorescence. Schwartzman and Halliwell (46) later described application of a thin-layer chromatographic assay to determination of histamine and its metabolites in urine. Although these two methods are accurate they take four to five hours for thin-layer chromatographic development.

In recent years, researchers interested in the problem of scombroid toxicity have developed several methods that also

utilize thin-layer chromatography. These methods are claimed to be more rapid than those suggested by Schwartzman (45) and Schwartzman and Halliwell (46). In one of these new methods, Lin et al (47), ground and mixed fish is extracted with methanol, the extract is filtered and subjected to thin-layer chromatography. Plates are developed with a methanol-ammonium hydroxide solvent for 70 minutes, dried for 8 minutes and the histamine spot developed with Ninhydrin. The amount of histamine present is determined by densitometry. This method does not require preliminary column purification of the extract and is a quick and simple method for the determination of histamine in fish. A similar method was used by Taylor et al (48) to determine the histamine content of swiss cheese which was implicated in the histamine poisoning of six individuals on the nuclear submarine USS Benjamin Franklin. This method involved the extraction of the sample with methanol in a sealed tube at $90^{o}C$. Following extraction the sample was spotted on a silica gel TLC plate with histamine standards and recovery extracts. After development in ammonia-water for approximately one hour, the histamine was visualized with a ninhydrin spray.

Another method which has been employed involves a technique in which samples of press juice or fish flesh are applied directly to thin-layer chromatographic plates (49). The plates are then developed with an acetone-ammonium hydroxide solution, and spots are visualized with ninhydrin or Pauly's reagent. Chromatographic separation of histamine is said to be readily achieved. This method is semi-quantitative, but should be quite suitable for routine screening of large numbers of samples.

H. Ion Exchange Chromatography

In order to study the amino acid and amine metabolism in the alimentary tract of pigs, Dierick et al (50) found it necessary to develop a convenient method for the quantitative analysis of several amines which are the primary decarboxylation products of amino acids. This sytem involved the use of a technicon amino acid analyzer with a 24 x 0.60 cm column packed with chromobead A. Separation of amines and amino acids was achieved using four buffers with a pH gradient of from 4.10 to 11.50.

A similar system was developed by Zee et al (51) to analyze mono and diamines in beer. This method involved using a column 0.5 x 30 cm adapted to the Technicon amino acid analyzer. For beer, this method required no precolumn cleaning and a 0.5 ml sample of beer was sufficient for analysis. Amines that could be separated by this method included 1,2-diamino propane, histamine, putrescine, cadaverine, tyramine, 5 hydroxy tryptamine, agmatine and tryptamine. This technique was later utilized to determine the amine content in various wines (52).

Sayem-El-Daher et al (53) have modified the method developed by Zee et al (52) and have been able to analyze fourteen biogenic amines in food. This system, like the others described above, utilizes the Technicon amino acid analyzer, however the buffer system and pH gradient have been changed. Sayem-EL-Daher et al's method provided good separation and detection of amines in several foodstuffs and appears to be sensitive enough to detect biogenic amines in any biological fluid or solid material.

I. High Pressure Liquid Chromatography

Koehler and Eitenmiller (54) developed a method using high pressure liquid chromatography in conjunction with paired-ion chromatography to provide a rapid, effective, and sensitive tool for studying biogenic amines in food products. In a survey of 61 cheeses, 13 sausages and 10 chocolate samples for tyramine, phenylethylamine and tryptamine, tyramine was found to be most prevalent and in generally higher concentration. Tyramine was present in 90% of the cheese and 85% of the sausage samples. Phenylethylamine was found in 38% of cheese and sausage samples while tryptamine occurred in only 18% of the cheeses and 38% of the sausages. None of the amines were detected in the chocolate samples.

A similar method was used by Briggs and Pargeter (55) as part of their investigation into the role of tyramine-containing foods and migraine. Samples were homogenized with perchloric acid, filtered, adjusted to pH 6.0 and absorbed onto Dowex 50W-X2 cation exchange resin. After elution with 4N HCl and adjustment of the extract to pH 5.0, the amines were resolved using reversed-phase high pressure liquid chromatography. Amines were determined by UV absorbance using dual cells set at 254 and 250 nm.

Karmas (56) utilized high pressure liquid chromatography to formulate a chemical index of decomposition for canned seafood. Biogenic amines in salmon were reacted with dansyl chloride to form their dansylated amine derivatives. The dansylated amine derivatives from salmon were then eluted by high pressure liquid chromatography and grouped into three sensory classes - acceptable, borderline, and unacceptable. Karmas concluded that the chemical index agreed well with the sensory evaluation scores and could be used as a quality indicator for raw and processed seafood.

As you can see from the information described above, a number of methods for detecting histamine and tyramine have been developed. These range from bioassays using guinea pig ileum or small crustacean, to methods using very expensive and accurate equipment which detect amines in the picomole range.

Although accurate measurements may be made using bioassay techniques, they do have several disadvantages. First, using live subjects requires you to make provisions for their care and handling. And second, the subject's response is prone to individual variability. For this and other reasons, there has been a shift away from bioassays towards chemical means for

detecting histamine and tyramine. Some of the chemical methods which have been developed include fluorometric methods, colorimetric assays, enzymatic assays, thin-layer chromatographic methods, ion-exchange chromatographic methods, gas chromatographic methods and high pressure liquid chromatographic methods. These chemical methods are not subject to the individual variabilities you have to deal with when using live subjects and are much more accurate. Additionally, some of these methods lend themselves to automation. This is particularly true of some of the fluorometric methods, the ion-exchange chromatographic methods and high pressure chromatographic methods. Automation of a system should increase the researcher's efficiency and allow more samples to be analyzed in a shorter time and at a lower cost. These automated systems are the type of systems more likely to be used by food processors when testing their product for histamine or tyramine.

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CHAPTER VII

RECOMMENDATIONS FOR FOOD PROCESSORS AND THE RESTAURANT INDUSTRY

Essentially we know that histamine and tyramine are found in a wide variety of foods but normally not in high enough concentrations to be harmful if ingested. Problems arise, however, if bacteria which produce these amines are provided proper conditions for their growth. This unchecked growth can lead to hazardous levels of histamine and tyramine in food products. The major points that the food processors and restaurateurs need to be concerned with are: (1) the speed with which these hazardous levels of histamine and tyramine can be formed and (2) the fact that it is difficult to determine that a food product is high in histamine or tyramine by sight or smell. Fish in particular can smell and look fresh but can contain hazardous levels of histamine (1 mg/g). Since odor and appearance do not reliably indicate the type of spoilage, consumers and food processing personnel often fail to be alerted and intoxication may occur.

What can food processors and restaurateurs do to safeguard their patrons? Food processors can ensure that food items such as fish are stored at low temperatures (0°C or below). Eitenmiller et al (1) have shown storage temperature to be the critical factor influencing the formation of histamine in tuna. This evidence has been backed up by the number of cases of histamine poisoning caused by improper refrigeration (2,3,4). In addition to storage of food items such as fish at low temperatures, the use of antimicrobial agents can provide an additional impediment to bacterial formation of histamine and tyramine (5). Finally, processors can routinely test foods being processed for tyramine and histamine. As a result of a mass outbreak of histamine poisoning in 1973 (254 cases in eight states) histamine analysis is now a routine quality control procedure in the tuna fish processing industry.

Other industries such as cheese manufacturers and wine producers should also be able to control the amount of histamine and tyramine in their products. Through the use of proper sanitation and the use of specific starter cultures the histamine and tyramine content of wines and cheeses can be kept low.

Andreas Lembke (6), a Swiss researcher, has patented a process which appears to be applicable to any industry involving fermentation (beer, wine, cheese, sauerkraut, etc.). The process uses microorganisms or enzymes obtained from these microorganisms to reduce the content of histamine and tyramine in various foods and beverages. The microorganisms of preference can be a bacterium, perferably one of the class of micrococci, pseudomonas, or lactobacilli or it can be a fungus or yeast perferably a species of saccharomyces. The biogenic amine content of the food or beverage is reduced as a result of the microorganism's ability to deaminate or transaminate the amino acid precursors of histamine and tyramine. The deamination or transamination converts the amino acids into products which are not harmful to man.

Restaurateurs can do their part to safeguard their patrons by buying their food products from reputable purveyors and by inspecting these items when received. All items (such as fish) requiring refrigeration should be refrigerated immediately and kept refrigerated until consumed. Items that appear spoiled or smell bad should, obviously, be rejected.

Another way that restaurateur's and food processors can reduce the possibility of their customers obtaining food with high histamine or tyramine content is to try to get the United States government to establish maximum allowable quantities of histamine and tyramine in foods. At the present time Sweden is the only country that has passed laws establishing the maximum permitted amount of histamine in fish. This level has been established at a maximum of 200 mg/kg of histamine in fish products. (7)

Finally because of the increased use of monoamine oxidase inhibitory drugs in treating asthma, tuberculosis, and depression doctors need to warn their patients to avoid foods containing high amounts of histamine or tyramine and to issue standard cards listing these foods. Foods to be avoided include aged cheese of all kinds, yeast extracts, game foods, certain alcoholic beverages (red wines) fermented sausage and meat products and fish that have not been properly stored.

In conclusion, I would like to once again reinterate some of the problems that restaurateurs face with regards to histamine and tyramine in food. First, histamine and tyramine

are formed by the action of microorganisms. Unless the growth of these microorganisms can be stopped, or at least retarded, hazardous levels of histamine and tyramine can be formed. Since it has been shown that storage temperature is the critical factor influencing the formation of these amines in foods it behooves the restaurateur to keep his food items stored at proper temperatures. Second, it is difficult to determine that a food product is high in one or both of these amines by sight or smell. Fish in particular, can look and smell fresh but can still contain hazardous levels of histamine or tyramine. Since odor and appearance do not reliably indicate the type of spoilage, consumers often fail to be alerted and intoxication may occur. Third, restaurateurs need to realize that even though some foods are low in histamine or tyramine that they, when served in combination with other foods with similar histamine or tyramine content, may cause a reaction in some of their customers. Fourth, restaurateurs should be aware that certain foods contain high levels of histamine and tyramine. Of particular concern are ripened cheeses (Cheddar, Emmenthaler, Gruyere, Stilton, Brie and Camembert); yeast

extracts such as Bovril and Marmite; certain alcoholic beverages (mainly red wines); fermented sausages (fermented bolognas and salamis, pepperoni, and summer sausage); and fish that have been improperly stored or refrigerated. Fifth, because of the similarity of symptoms of histamine and tyramine poisoning to other types of food poisoning restaurateurs have been provided very little information on what histamine and tyramine are, what symptoms they produce and how they can be prevented. Finally, in addition to all of these health related problems, there are also legal implications concerning histamine and tyramine in foods. By the nature of his or her operation the restaurateur is operating under an implied warranty that his or her food is fit for human consumption. If a customer consumes food prepared in the restaurant, becomes sick and can prove that the food caused the illness, than the customer can sue the restaurateur. Thus the restaurateur is faced not only with immediate financial loss due to the lawsuit but also with future financial loss due to bad publicity. Finally the restaurateur has to be concerned with the problem of serving foods not produced in the United States. This

problem centers around the fact that we know little about health and sanitation requirements in the countries from which we buy products. This is particularly a problem for the restaurateur in this country since there is no way he or she can determine the quality of the food received. The restaurateur essentially has to rely on his or her purveyor to provide him or her with products which are free of defect.

It is my hope that by recognizing some of these problems restaurateurs can take action to prevent or at least alleviate some of the consequences of histamine and tyramine in food.

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